Frontal and parietal contributions to the modulation of somatosensory cortex by relevance and modality

by

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Author's Declaration

I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

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Abstract

Afferent somatosensory inputs ascend from the periphery to the cortex carrying information about touch that is critical for planning motor responses. At the cortical level, this information is subject to modulation from its earliest arrival in somatosensory cortex where factors such as task-relevance begin to shape how the sensory signals are processed. The goal of such modulation is largely to facilitate the extraction of relevant sensory information (and suppression of irrelevant signals) early in the processing stream, and these functions are in part carried out by top-down influences from cortical and sub-cortical structures. Efforts to understand the mechanisms contributing to modulation of sensory-specific cortex have revealed that crossmodal signals (i.e. simultaneously presented stimuli from a different modality) can also influence early sensory processing, but the precise nature of this modulation and what may drive it is largely unknown. It is the purpose of this thesis to investigate the modulation of somatosensory cortex, specifically how task-relevant modulation of somatosensory cortex might be influenced by crossmodal (visual) stimuli, and whether specific task requirements have any bearing on SI excitability. The studies comprising this thesis aim to address these gaps in our mechanistic understanding of the networks involved in modulating somatosensory cortex. Studies 1 and 2 employed functional magnetic resonance imaging (fMRI) and electroencephalography (EEG) to investigate how task-relevant visual and vibrotactile stimuli modulate somatosensory cortex and to probe the role of a frontoparietal network in mediating this modulation. Studies 3 and 4 also used EEG to determine how manipulating the relevance of the stimuli affects the modulation of somatosensory event-related potentials (ERPs), and to probe how task-specific sensory-motor requirements mediate excitability in somatosensory cortex as well as frontal and parietal regions. The results of this thesis provide insight into the factors that modulate somatosensory cortex and the role of a fronto-parietal network in subserving these modulations.

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List of Abbreviations

SI	Primary somatosensory cortex
SII	Secondary somatosensory cortex
ERP	Event-related potential
fMRI	Functional magnetic resonance imaging
EEG	Electroencephalography
PET	Positron emission topography
BOLD	Blood oxygen level dependent
EP	Evoked potential
SEP	Somatosensory evoked potential
TRN	Thalamic reticular nucleus
MFG	Middle frontal gyrus
VAC	Visual association cortex
DLPFC	Dorsolateral prefrontal cortex
PFC	Prefrontal cortex
TPJ	Temporoparietal junction
SMG	Supramarginal gyrus
STG	Superior temporal gyrus
ANOVA	Analysis of variance
BA	Brodmann area
NE	Norepinephrine

Chapter 1 – Introduction

1.1 Overview of thesis

Chapter 1 outlines the general objectives of the thesis, followed by a review of relevant literature pertaining to the anatomy and physiology of somatosensory cortex and the modulating roles of task-relevance and crossmodal influences. For the purposes of this thesis, the terms crossmodal effects or influences are meant to represent the role that simultaneous visual and tactile stimuli have on modulating somatosensory cortex. Chapters 2 through 4 detail the rationale, hypotheses, methods, results and discussion of the research studies contributing to the thesis. Chapter 5 includes a general discussion of the findings of the thesis, its limitations, and future directions for study.

1.2 General objective of thesis

The general objective of this thesis is to probe the role of crossmodality interactions in the task-relevant modulation of somatosensory cortex. On a larger scale, investigating the factors that modulate activity in somatosensory cortex is important to understanding deficits in somatosensation, which are often associated with abnormal patterns of cortical excitability. Somatosensory deficits are commonly observed as a consequence of stroke and are typically coupled with motor deficits, although the precise link between these deficits has yet to be defined. Studies in the stroke population have shown that patients with somatosensory and motor impairments take longer to regain motor function and are less likely to make a complete recovery compared to those with motor deficits alone (Patel et al., 2000). With this in mind, understanding the mechanisms that contribute to modulation of somatosensory cortex is an important step in determining how to best inform rehabilitative strategies aimed at recovering somatic and motor function.

Previous studies have shown that primary somatosensory cortex (SI) is sensitive to attentional manipulations and is upregulated when tactile stimuli are made relevant to the performance of a task (Johansen-Berg et al., 2000; Nelson et al., 2004; Staines et al., 2002; Steinmetz et al., 2000a). The mechanisms behind this facilitation are still unclear but may involve bottom-up processes that bias the processing of relevant incoming sensory signals (Desimone, 1998; Kastner and Ungerleider, 2001), and could also be subject to selective enhancement and suppression of sensory inputs mediated by the prefrontal cortex and the thalamic reticular nucleus (Gazzaley et al., 2007; Knight et al., 1999; Staines et al., 2002; Yamaguchi and Knight, 1990). Regardless of the mechanisms involved, the upregulation of relevant sensory information, perhaps more importantly the concomitant suppression of irrelevant signals, play important roles in modulating the excitability of somatosensory cortex.

The role of crossmodal interactions in modulating somatosensory cortex is somewhat less clear; evidence of crossmodal modulation in sensory-specific cortex exists for visual and auditory modalities (Foxe et al., 2002; Ghazanfar et al., 2005; Kayser et al., 2008; Macaluso et al., 2000; Martuzzi et al., 2007; Molholm et al., 2002; Murray et al., 2005; Schroeder and Foxe, 2005), but reports of effects in SI are not as abundant. In terms of understanding the link between somatosensory function and motor deficits, the interaction of vision and touch is of particular interest since information from these modalities is often used to guide motor behaviour. Effects of vision on somatosensory event-related potential (ERP) components suggest that vision may modulate excitability in SI (as inferred by modulation of somatosensory ERP components) during a tactile acuity task, and that this modulation is associated with an improvement in acuity (Taylor-Clarke et al., 2002). It is not yet known whether a similar modulation would be seen in a sensory to motor integration task, and whether this facilitation can be manipulated by stimulus relevance.

1.3 Background research

1.3.1 Somatosensory cortex

The somatosensory cortex can be divided into primary (SI) and secondary (SII) cortices and comprises the postcentral gyrus of the parietal lobe, with SII making up the most lateral portion adjacent to the sylvian fissure. SI is somatotopically organized with representations of the feet lying most medial and the face most lateral. SI is further divided into four Brodmann areas: 3a, 3b, 1 and 2, progressing from anterior to posterior along the postcentral gyrus. These areas receive inputs from the dorsal column-medial lemniscal system via thalamic sensory nuclei. Areas 3b and 1 receive independent thalamocortical inputs generated by different classes of cutaneous afferents, whereas 3a and 2 receive proprioceptive inputs from peripheral muscle and joint afferents. There is a sharp gradient in dominance of thalamocortical input in 3b to mixed thalamocortical and cortico-cortical projections from 3b in areas 1 & 2. Lesion studies in monkeys have shown that damage to these areas creates different deficits; lesions in area 1 impair texture discrimination, damage to area 2 produces deficits in recognizing contours, and 3b lesions produce more global somatic deficits because it is the main gateway for cutaneous information to areas 1 and 2 (Carlson, 1981; Randolph and Semmes, 1974).

SII is located on the upper bank of the Sylvian fissure, a region also known as the parietal operculum. It receives thalamocortical projections from thalamic somatosensory nuclei as well as dense cortico-cortical projections from postcentral somatosensory areas. Evidence from electrophysiological and tracing studies in a variety of species shows that the SII region can be subdivided into several distinct areas, each with its own somatotopic map (Burton et al. 1995, Huffman et al. 1999, Slutsky et al. 2000). In nonhuman primates, secondary somatosensory cortex is most often divided into the parietal ventral area (PV), which is immediately ventral to SI, followed caudally by area SII, and medial to SII and PV lying in the Sylvian fissure is the ventral somatosensory area (VS). SII and PV both contain complete somatotopic maps while the map in VS is less detailed (Krubitzer and Calford, 1992, Burton et al., 1995). Homologous subdivisions of SII in humans have also been proposed, and histological examination of postmortem brains has identified 4 distinct cytoarchitectonic areas on the human parietal operculum, labeled OP 1-4 (Eickhoff et al. 2006). Based on topography and comparison of somatotopic maps, OP 4 corresponds to primate PV and OP1 to area SII, OP 3 aligns with area VS, and OP 2 is in fact not part of the secondary somatosensory cortex but instead corresponds to the parietal-insular vestibular cortex in nonhuman primates (Eickhoff et al., 2006, 2007). Functionally speaking, SII has been implicated in carrying out higher-order somatosensory functions such as stimulus recognition and discrimination, tactile memory and learning, and somatosensory engagement of the motor system at the cortical level (Burton et al., 1997; Fujiwara et al., 2002; Johansen-Berg et al., 2000; Mima et al., 1998). SII often shows bilateral activity during somatosensory stimulation, although responses are typically larger contralateral to the stimulated site (Johansen-Berg et al., 2000; Nelson et al., 2004).

1.3.2 Cortical somatosensory processing

Mechanoreceptive afferent fibres innervating the skin project through parallel channels of the lemniscal system to corresponding neurons in the postcentral gyrus, preserving their properties of place and mode and serving selective aspects of mechanoreceptive sensation. In humans there are four types of cutaneous afferent fibers, and they are classified according to how they adapt to constant skin indentation (Vallbo and Johansson, 1984). Slowly-adapting (SA) fibers are associated with receptors of the same type (Merkel cells and Ruffini endings) and they exhibit sustained discharge during constant skin indentation increasing their firing rate during increased indentation. Rapidly-adapting fibers are associated with Meissner and Pacinian mechanoreceptors, which respond most strongly to onset and offset of indentation. Although all of these fibers respond to stimulation of the skin, they are selective for different spatiotemporal features of the stimulus (Mountcastle et al., 1972; Talbot et al., 1968). Sensory signals transduced from these receptors travel via afferent nerve fibers to the dorsal root ganglion neurons in the dorsal root of spinal nerves. At this point the large diameter axons mediating touch and proprioception diverge from smaller diameter afferents subserving temperature pain and follow different pathways to the cortex. Tactile and proprioceptive information is transmitted to the cortex via the central axons of dorsal root ganglion cells that enter the spinal cord and ascend directly to the medulla via the ipsilateral dorsal columns as part of the dorsal column-medial lemniscal system, with axons from proprioceptors located more ventrally than axons from tactile receptors. After synapsing in the medulla somatosensory afferents decussate and ascend as part of the medial lemniscus to the ventral posterior lateral (VPL) nucleus of the thalamus. Thalamic neurons receiving these inputs send axons to the somatic sensory areas, with most of the thalamic input terminating in 3a and 3b, which then project to 1 and 2, although there are some sparse but direct connections between the thalamus and areas 1 and 2.

Neurons in SI can also be classified as RA or SA as they exhibit firing patterns similar to that of the corresponding cutaneous afferents (Mountcastle et al., 1972; Talbot et al., 1968). The functional organization of SI is characterized by columns of neurons with specificity for location and mode of peripheral stimulation, which maintains the integrity of somatic signals as they travel from receptor to cortex (Mountcastle, 1997) Intracortical projections link columns with similar functional properties. SI sends cortico-cortical projections to posterior parietal, temporal, and frontal lobes but these regions receive no direct thalamocortical projections from thalamic somatosensory nuclei. Each of the 4 somatosensory areas contains a separate representation of the body form, with a direct relationship between peripheral innervation density of a body part and the area of cortex in which it is represented. Modality and spatial specificity declines and convergence increases beyond the first cortical representations in SI, with area 3b having the most specificity and area 2 the least.

1.3.3 Cortical networks involved in task-relevant modulation

Posner & Peterson (1990) subdivide the broad concept of attention into three processes of attention with different functions: 1) orienting to sensory events, 2) detecting signals for conscious processing, and 3) maintaining a vigilant or alert state. Similarly, Corbetta & Shulman (2002) discuss these processes within the framework of two interrelated systems: a top-down, goal-directed system that selects stimuli for further processing, and a bottom-up, stimulus-driven system that detects behaviourally relevant stimuli and acts to focus the top-down system on the most salient events. Top-down processes, which can also be described as endogenous or selective attention are known to recruit a network involving the intraparietal cortex and superior frontal cortex, and thus has been termed the dorsal attention system. Activity in this network is observed in tasks that require cognitive selection of stimuli and actions, task switching, and stimulus-response associations (Corbetta and Shulman, 2002). Bottom-up processes, which are also referred to as exogenous attention are associated with a right-hemisphere lateralized network that includes the inferior frontal cortex and temporoparietal cortex and is known as the ventral attention system. In particular, the prefrontal cortex has been implicated in evaluating the novelty of stimuli while the temporoparietal junction (TPJ) detects the behavioural valence of those sensory signals (Corbetta and Shulman, 2002; Kincade et al., 2005). As this network is involved in orienting attention to unexpected sensory events, lesions to the right prefrontal cortex impair detection of low-frequency events.

While top-down and bottom-up processes carry out specific attentional functions, they are interrelated and work together to efficiently achieve behavioural goals. Orienting to the spatial location of a stimulus improves the efficiency with which it is processed, and these bottom-up orienting responses are associated with increased neural activity in the primary sensory cortex and thalamic nuclei corresponding to the stimulus modality, as well as the posterior parietal cortex (Posner and Peterson, 1990). Further to this, damage to the posterior parietal cortex produces deficits in the ability to disengage attention from targets in the contralesional space, which suggests that the parietal lobe plays an important role in spatial attention, a process that is critical in orienting to sensory events. The posterior parietal lobe is highly interconnected with regions of the lateral and medial frontal cortex (Goldman-Rakic, 1988), and these anatomical connections form the basis of the top-down (meaning cognitively-driven) attentional orienting network that subserves detection of stimuli. Posner (1980) showed that detecting a target interferes with the performance of other cognitive functions, whereas simply monitoring locations and modalities for stimuli does not produce the same interference until a target occurs. This finding distinguishes between a state of general alertness and a state of orienting and focusing attention and suggests that this state of selective attention to a stimulus of interest occurs on a supramodal level (Duncan, 1980). Studies of cerebral blood flow provide evidence that selective top-down attentional processes are associated with increased blood flow in lateral superior and midline frontal areas, in what has been called an anterior attention system (Posner et al., 1988; Roland, 1985).

The third attentional process delineated by Posner (1990) is the alerting system, referred to above as the system that sustains an alert and vigilant state in the absence of a sensory target. This state of sustained attention allows for more rapid responding to targets when they do occur, but can also be associated with a higher error rate at high levels of alertness (Posner et al., 1988). Studies investigating sustained attention have shown that the ability to maintain a vigilant state is heavily dependent on the integrity of the right cerebral hemisphere (Corbetta and Shulman, 2002; Heilman et al., 1985; Milner and McIntosh, 2005; Pardo et al., 1991). Interestingly, the norepinephrine (NE) neuromodulatory system has been shown to play a critical role in maintaining an alert state and animal studies have shown that lesions of the right cerebral hemisphere but not the left lead to depletion of NE in both hemispheres (Aston-Jones et al., 1984). The observation that damage to the right parietal lobe frequently produces neglect, which affects spatial attention processes, provides an example of the interrelated nature of the different attention systems (Posner et al., 1984).

1.3.4 Prefrontal cortex & task-relevant sensory modulation

The prefrontal cortex (PFC) can be divided into three regions: lateral, medial, and orbitofrontal (Kandel et al., 1991). All receive extensive afferent inputs from the mediodorsal thalamic nucleus. The orbitofrontal and medial prefrontal regions have direct connections with limbic structures and are typically involved in executive functions such as error monitoring, response selection, and evaluating the consequences of actions (Fuster, 1993). In order to achieve this, the PFC relies on incoming sensory information to determine the appropriate behavioural response.

PFC neurons are particularly active during delayed response tasks, when there is a need to maintain information in working memory for a future response (Fuster 1990, Goldman-Rakic, 1990) . The lateral and mid-dorsal PFC are more closely associated with sensory-specific cortex than the ventromedial PFC. Many PFC areas receive converging inputs from at least two sensory modalities, for example dorsolateral and ventrolateral PFC both receive projections from visual, auditory, and somatosensory cortex (Chavis and Pandya, 1976; Jones and Powell, 1970). In addition the PFC is connected to cortical regions that are themselves sites of multisensory convergence, such as the superior temporal sulcus and the arcuate sulcus (Barnes and Pandya, 1992).

In addition to a well-known role in working memory, the prefrontal cortex has been implicated in the process of transforming incoming sensory information into meaningful behaviour, particularly when relevant and irrelevant inputs compete for attention. Thus the PFC is active during tasks that require selective attention, when the relevant stimulus is both present and absent. As outlined in the previous section, electrophysiology and neuroimaging studies provide evidence for task-relevant modulation of sensory cortex, and it has been suggested that this modulation might be mediated by inputs from other cortical regions that act to bias the processing of relevant stimuli over irrelevant ones (Knight et al., 1999). The PFC is a prime candidate to mediate these top-down effects given that it is sensitive to the relevancy of sensory inputs as they pertain to goal-directed behaviour. Such a role for the prefrontal cortex is also supported by axonal tract-tracing studies in monkeys, which have revealed extensive networks of reciprocal corticocortical connections between regions in the PFC and visual association areas (Rempel-Clower and Barbas, 2000; Ungerleider et al., 1989), as well as between dorsolateral prefrontal cortex and regions of both primary and secondary somatosensory cortex (Barbas et al., 1999).

Much of what is known about the role of the PFC in behaviour comes from studies of patients with lesions to this area. In general, patients with prefrontal damage show impairments in filtering out task-irrelevant stimuli and thus are more susceptible to distractors, and this has been seen across both auditory and somatosensory modalities (Chao and Knight, 1995; Knight et al., 1999). Interestingly, disinhibition of auditory and somatosensory evoked responses was only observed in patients with prefrontal lesions and not those with lesions to primary sensory cortex or the temporoparietal junction (Knight et al., 1999). Patients with prefrontal lesions also show deficits in sustained and transient attention such as detecting novel events (Gehring and Knight, 2002; Knight, 1984). Taken together, the inability to inhibit irrelevant sensory inputs and sustain attention to relevant ones are likely contributing factors to the behavioural deficits observed in prefrontal patients, including decision-making and response planning impairments (Goel and Grafman, 1995; Milner, 1982).

Early evidence for the role of PFC in regulating incoming sensory information comes from the use of cryogenic blockade to cool the PFC in cats, which revealed that suppression of this area increased the amplitudes of evoked responses recorded in primary sensory cortex (Skinner and Yingling, 1976). This suggests that the PFC normally exerts an inhibitory influence over the flow of information to primary sensory cortices. In contrast, stimulation of the thalamic reticular nucleus (TRN) produced a suppression in modality-specific primary sensory cortex. These results provide evidence for a prefrontal-thalamic inhibitory system that may function to suppress irrelevant inputs at an early stage of sensory processing. This system is modulated by an excitatory prefrontal projection to the TRN, which in turn sends inhibitory GABAergic projections to sensory relay nuclei. However, an evoked potentials (EPs) study in humans with prefrontal lesions provides evidence for direct inhibitory influences from DLPFC to SI as a disinhibition of the P27 SEP component (reflecting activity in area 1) was seen but the N20 component (reflecting the volley of information from the thalamus) was unaffected (Yamaguchi and Knight, 1990). In addition, Gehring & Knight (2002) reported that damage to the lateral PFC increases the effects of distractor stimuli, providing further evidence for prefrontal suppression of irrelevant information (Gehring and Knight, 2002).

Electrophysiological recordings in monkeys have shown that neurons in the PFC selectively encode task-relevant information (Sakagami and Niki, 1994). Some PFC cells code for task-irrelevant dimensions of stimuli that can be ignored (Lauwereyns et al., 2001; Rainer et al., 1998), but cells coding for relevant dimensions are more plentiful. Rao et al, (1997) showed that the same PFC neuron could code for either location or object properties depending on the task requirements (Rao et al., 1997). Cells in this region are also characterized by sustained firing during a delay period between stimulus presentation and a response made using the stimulus information to guide behaviour, and the firing pattern of this sustained activity is also modulated by task relevance (Chafee and Goldman-Rakic, 1998; Fuster and Alexander, 1971). Similar patterns of sustained task-related activity have also been observed with functional neuroimaging in humans (D'Esposito and Postle, 1999; D'Esposito et al., 2000; D'Esposito et al., 2006; Kimberg et al., 2000; Ranganath et al., 2000).

In a series of neuroimaging studies, Gazzaley et al. (2005, 2007) used a delayed memory-recall task to investigate the role of prefrontal cortex in task-relevant visual working memory. Subjects were shown interleaved sequences of pictures of either faces or places and given instructions about whether to pay attention to the faces, the places, both, or neither. After a delay period subjects were shown a probe stimulus and made a response to indicate whether that stimulus was present in the previously viewed sequence. PFC activity, reflected by a cluster in the middle frontal gyrus (MFG), was greater when stimuli had to be attended or ignored relative to passive viewing, with greater enhancement in the attend-to condition vs ignore. This is contrasted with activity in visual association cortex (VAC), where activity is enhanced in the attend-to condition, and suppressed in the ignore condition, relative to passive viewing. Functional connectivity analysis revealed greater connectivity between visual association areas & PFC when subjects were trying to remember scenes and less when they were attempting to ignore scenes relative to passive viewing. Interestingly, similar PFC-VAC networks were present for all 3 task conditions (remember, ignore, and passively view), and correlations between the VAC seed and MFG cluster were positive for all tasks, which suggests that enhancement and suppression of VAC activity reflects varying levels of excitatory modulatory influences from the PFC rather than excitatory and inhibitory modulatory influences (Gazzaley et al., 2005; Gazzaley et al., 2007). However, Rissman et al. (2008) found that increasing cognitive load with a task that requires overlapping resources disrupts the ability of subjects to suppress irrelevant information (Rissman et al., 2008). This is suggestive that suppression is an actively mediated control process and could still be reflected as an increase in BOLD activity. Also of interest, in the functional connectivity analysis performed by Gazzaley et al. the degree of connectivity between the PFC cluster and the stimulus selective VAC cluster correlated with the magnitude of attentional enhancement/suppression in the visual areas. This may suggest that the prefrontal cortex biases activity in sensory-specific cortex by adjusting the strength of functional coupling in response to stimulus relevance.

1.3.5 Temporoparietal junction and task-relevance

Studies of endogenous and exogenous attention processes have revealed different cortical regions subserving these processes. In neuroimaging studies, top-down orienting processes tend to activate a bilateral frontoparietal network, whereas stimulus-driven detection typically activates a ventral frontoparietal network that is lateralized to the right hemisphere (Corbetta et al., 2000; Corbetta and Shulman, 2002; Kincade et al., 2005). In particular the temporoparietal junction (TPJ), which includes the supramarginal gyrus (SMG) and posterior portion of the superior temporal gyrus (STG), appears to play a specific role in stimulus-driven shifts of attention (Corbetta and Shulman, 2002). Kincade et al. (2005) reported that while the TPJ was strongly modulated by stimulus-driven shifts in attention to behaviourally relevant stimuli, it was not active in response to stimuli that were task-irrelevant. This suggests that the TPJ is not driven solely by stimulus salience and that task relevance modulates activity in this region (Kincade et al., 2005). These findings are consistent with those of Downar et al. (2001) who also found that the responsiveness of TPJ to changes in a sensory stimulus increases when the stimulus is behaviourally relevant, and that this is true regardless of the modality of the stimulus. A role for TPJ in stimulus-orienting behaviour is further supported by patients with lesions affecting the right TPJ who often present with spatial neglect and/or sensory extinction, impairments that are suspected to bias attention to the right hemispace while neglecting the left (Brozzoli et al., 2006; Driver and Mattingley, 1998; Driver and Vuilleumier, 2001; Milner and McIntosh, 2005).

1.3.6 Task-relevant modulation of sensory cortex

Monkey neurophysiology and human electrophysiology as well as neuroimaging data converge on the idea that attention to a modality is associated with enhanced activity in corresponding modality-specific regions. Single cell studies in monkeys have found robust attentional effects on activity of SII neurons, and smaller effects on neurons in SI (Hsiao et al., 1993; Hyvarinen et al., 1980). Hsiao et al. (1993) trained monkeys to switch between two tasks: a tactile task that required detecting the pattern of an embossed letter passively rotated against the finger tip that matched a visual analog, and a visual task that involved detecting one of three dimmed LED displays while ignoring continuous tactile stimulation with the same raised letter pattern. Most cells in SI had enhanced firing rates during the tactile task compared to responses to the same tactile stimuli during the visual task, when the tactile stimuli were irrelevant, thus providing evidence for task-relevant modulation in SI.

In humans, PET studies have shown that compared to passive tactile stimulation, directing attention toward attributes of somatosensory stimuli in the context of performing a discrimination task increases blood flow in the contralateral postcentral gyrus (Meyer et al., 1991; Pardo et al., 1991; Roland, 1981), and that activity in SI is enhanced even in the context of expecting an impending tactile stimulus (Drevets et al., 1995). Further evidence of task-relevant modulation of somatosensory cortex comes from somatosensory evoked potentials (SEPs), a measure of excitability in the somatosensory cortex. Under passive stimulation conditions SEP components are attenuated during movement, a phenomenon termed movement-related gating (Cheron and Borenstein, 1991; Jones et al., 1989). This gating effect is partially lifted when the incoming somatosensory information is relevant to the performance of a task (Staines et al., 1997; Staines et al., 2000). Neuroimaging studies provide further evidence for enhanced activity in SI when tactile stimuli are relevant compared to irrelevant (Burton et al., 1999; Johansen-Berg et al., 2000; Staines et al., 2002) although the temporal resolution of the hemodynamic response limits the ability to discern whether these modulations occur during initial sensory processing or at longer latencies mediated by re-entrant signals from higher-order areas.

Evidence of early task-relevant modulation in SI is sparse in studies using both event-related potentials and evoked potentials, with some studies showing no effect of attention on very early SEP components such as the N20 (Desmedt and Robertson, 1977), which is thought to reflect the first synapse of information from the thalamus to SI, particularly area 3b. However other studies have observed attention effects on the N80 component (Michie et al., 1987) that may still reflect processing within primary somatosensory cortex. More often, effects of attention to somatosensory stimuli are observed later in the processing stream and typically in the tactile N140, a large negative deflection that is associated with attending to a tactile stimulus (Eimer and Forster, 2003; Garcia-Larrea et al., 1995) but with generators outside primary sensory cortex. In terms of behaviour, it has been suggested that such enhancements might be associated with improvements in task performance, and it has been shown that directing attention to tactile stimuli can facilitate both accuracy and speed of responses (Sathian and Burton, 1991; Spence et al., 2000).

A number of mechanisms have been proposed to explain the modulatory role of attention in somatosensory cortex. One possibility is that neural responses are amplified for selected and relevant stimuli, such that responses to attended stimuli are stronger and more selective resulting in an improved signal-to-noise ratio, with the goal of improving detection of task-relevant events (Corbetta et al., 1990; Hillyard et al., 1998; Posner and Driver, 1992). Similarly, the suppression of non-essential cortical areas may play a role in tactile attention, since it has been shown that attending to tasks that involve non-tactile modalities decreases blood flow in SI (Fiez et al., 1996; Haxby et al., 1994; Kawashima et al., 1995), and similar effects can be seen within SI when attention is directed to a different body part (Drevets et al., 1995). At the neuronal population level, attention has been shown to increase synchronous firing patterns across populations of neurons, and this may expand the pool of responsive neurons via enhanced synaptic efficacy, produced by temporal summation (Roy et al., 2007; Steinmetz et al., 2000). The outcome is a further propagation of neural signals in response to stimulation at an attended location, which has been supported by imaging studies showing that attention enhances the spatial extent of activated regions (Vannini et al., 2004). This suggests that attention can also amplify neural signals by recruiting responses from a greater population of neurons.

1.3.7 Crossmodal interactions in sensory-specific cortex

The possibility of crossmodal attention effects in primary sensory cortex has been raised by previous observations of such effects on early modality-specific event-related potential (ERP) components (Eimer, 2001; Eimer and van Velzen, 2005; Kennett et al., 2001; McDonald et al., 2001; Murray et al., 2005; Teder-Salejarvi et al., 2002). Schurmann et al. (2002) found a facilitation of EP components over midline and ipsilateral electrode sites beginning at 75 ms when visual stimuli were presented simultaneously with electrical median nerve stimulation, and similar results were found by Murray et al. (2005), who observed enhancement of auditory evoked responses as early as 50 ms after a somatosensory stimulus was applied to the hand (Murray et al., 2005). Further evidence of early multisensory interactions comes from functional imaging of monkey auditory cortex, revealing regions that show response enhancement to visual plus auditory stimulation, and somatosensory plus auditory stimulation (Kayser et al., 2005; Kayser et al., 2007). Also in monkeys, Ghazanfar et al. (2005) demonstrated facilitation of neurons in auditory cortex when visual stimuli were presented in addition to auditory stimuli, as well as some cells that responded to the visual stimulus alone (Ghazanfar et al., 2005). Using functional imaging in humans, Schurmann et al. (2006) found that passive vibrotactile stimuli enhanced BOLD activity in auditory cortex, both during auditory stimulation and in isolation (Schurmann et al., 2006). In contrast, when information from one modality is irrelevant to the task cross-modal suppression can be observed. For example a decrease in blood flow to SI was found during tasks requiring visual processing (Haxby et al., 1991) or auditory discrimination (Fiez et al., 1996).

1.3.8 Crossmodal interactions and task-relevance in somatosensory cortex

The literature discussed above pertaining to the modulation of excitability in somatosensory cortex reveals that it is subject to both task-relevant (i.e. attentional) modulation and cross-modality influences (Desmedt and Robertson, 1977, Drevets et al., 1995, Eimer and Forster, 2003, Hotting et al., 2003, Hyvarinen et al., 1980, Johansen-Berg et al., 2000, Meehan and Staines, 2007, Meyer et al., 1991, Michie et al., 1987, Mima et al., 1998, Schurmann et al., 2002, Spence 2002) . However there is a gap in the understanding of how these two factors interact, and thus the general objective of this thesis is to understand how task-relevant modulation of primary somatosensory cortex is influenced by cross-modal interactions. The studies comprising this thesis aim to first determine how the combination of visual and tactile stimuli modulates somatosensory cortex when both stimuli are relevant to task performance. The next step will be to probe how manipulating the relevance of the visual and tactile stimuli affects the modulation of SI. Lastly, the contribution of motor response requirements to the modulation of somatosensory cortex will be considered.

1.4 Specific research objectives

1.4.1 Research Objective 1

To determine how crossmodal interactions between visual and tactile information modulate activity in somatosensory cortex.

Previous research has shown that crossmodal stimuli can influence excitability within primary sensory cortex (Kayser and Logothetis, 2007, Ghazanfar et al., 2005, Foxe et al., 2002). There is some evidence to suggest that somatosensory cortex is sensitive to crossmodal interactions when visual and tactile stimuli are presented simultaneously, but in previous studies only one modality was relevant to behaviour (Meehan and Staines, 2007). Research Objective 1 sets out to determine the effects of simultaneous visual and tactile stimuli on somatosensory cortex, in the context of a behavioural task requiring attention to both modalities. Given that somatosensory cortex is sensitive to the task-relevance of stimuli, it is hypothesized that combining visual and tactile stimuli in the context of a sensory-guided motor response will be associated with increased SI excitability, compared to tactile stimuli alone. Study 1 tests this hypothesis using functional magnetic resonance imaging (fMRI) to contrast BOLD activity in SI during crossmodal and unimodal tasks. Study 2 employs electroencephalography (EEG) to test the same hypothesis with more precise temporal resolution by comparing event-related potentials (ERPs) generated by vibrotactile stimuli in crossmodal and unimodal task conditions.

1.4.2 Research Objective 2

To investigate how visual-tactile crossmodal effects interact with task-relevant modulation in somatosensory cortex.

Results from the first study in this thesis suggest that excitability in somatosensory cortex appears to be modulated by the presence of visual and tactile stimuli when both modalities are relevant to performing a sensory-motor task (Dionne et al., 2010). Neuroimaging evidence reveals that this modulation within primary somatosensory cortex is associated with activity in a fronto-parietal network involving the dorsolateral prefrontal cortex (DLPFC) and the temporoparietal junction (TPJ), however this network is active when stimuli are both unimodal and crossmodal. ERP findings echo the neuroimaging data, suggesting that crossmodal effects occur within sensory-specific cortex and early in the processing stream. It is unclear whether this modulation is being driven by top-down cognitive mechanisms or by bottom-up low-level connections between visual and somatosensory cortex. Thus the goal of Research Objective 2 was to determine if crossmodal effects in somatosensory cortex are contingent upon the task-relevance of the stimuli, based on the assumption that if such modulation is a product of top-down processes, it will only occur when both modalities are relevant and attended to. Conversely, if crossmodal modulation of SI is mediated by bottom-up mechanisms, the relevance of the stimuli to behaviour should not influence crossmodal effects in SI. Study 3 set out to test the hypothesis that crossmodal enhancement in SI will only be observed when both visual and tactile stimuli are task-relevant. It is also hypothesized that contributions of prefrontal and parietal regions to mid-latency components will be differentiated by stimulus relevance. Specifically it is predicted that an effect of relevancy will be seen at frontal sites and not at parietal sites.

1.4.3 Research Objective 3

To probe the contribution of motor task requirements to the interaction of task-relevance and crossmodal influences in somatosensory cortex.

The first two studies of this thesis clearly show that in the context of a sensory-guided motor task, somatosensory cortex is sensitive to crossmodal stimuli. The third study revealed that this modulation is contingent on the relevancy of the stimuli to the motor task, such that modality-specific ERP components are enhanced when both visual and tactile stimuli are relevant to the task, but not when one is irrelevant. The final study set out to determine whether the specific motor task requirements, specifically the degree to which the behavioural response relies on the sensory information, influence somatosensory ERP components. It is hypothesized that crossmodal enhancement of task-relevant stimuli will be dependent on the specific motor task demands and will be greater in a graded motor task compared to detection and discrimination tasks.

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Chapter 2 – Study 1: Crossmodal influences in somatosensory cortex: interaction of vision and touch.

Adapted from:

Dionne JK, Meehan SK, Legon W, & Staines WR. Crossmodal influences in somatosensory cortex: interaction of vision and touch. Human Brain Mapping. 2010: 31:14-25.

2.1 Overview

Directing attention to tactile stimuli is associated with an upregulation of neural activity in somatosensory cortex (Johansen-Berg and Lloyd, 2000; Steinmetz et al., 2000). This modulation is likely subject to attenuation and facilitation by a number of factors but it is not yet clear how crossmodal stimuli might influence the task-relevant modulation of SI, and this study aims to address this gap.

Previous research has shown that information from one sensory modality has the potential to influence activity in a different modality, and these crossmodal interactions can occur early in the cortical sensory processing stream within sensory-specific cortex. In addition, it has been shown that when sensory information is relevant to the performance of a task there is an upregulation of sensory cortex. This study sought to investigate the effects of simultaneous bimodal (visual and vibrotactile) stimulation on the modulation of primary somatosensory cortex (SI), in the context of a delayed sensory-to-motor task when both stimuli are task-relevant. It was hypothesized that the requirement to combine visual and vibrotactile stimuli would be associated with an increase in SI activity compared to vibrotactile stimuli alone. Functional magnetic resonance imaging (fMRI) was performed on healthy subjects using a 3T scanner. During the scanning session subjects performed a sensory-guided motor task while receiving visual, vibrotactile, or both types of stimuli. An event-related design was used to examine cortical activity related to the stimulus onset and the motor response. A region of interest (ROI) analysis was performed on right somatosensory cortex and revealed an increase in percent BOLD signal change in the bimodal (visual + tactile) task compared to the unimodal tasks. Results of the whole-brain analysis revealed a common fronto-parietal network that was active across both the bimodal and unimodal task conditions, suggesting that these regions are sensitive to the attentional and motor planning aspects of the task rather than the unimodal or bimodal nature of the stimuli.

2.2 Introduction

Previous studies suggest that a number of factors can modulate neural activity in modality-specific sensory cortex, including attention (Johansen-Berg et al., 2000; Steinmetz et al., 2000) and cross-modal influences (Burton et al., 1997; Macaluso et al., 2000). More recently the interaction between these two factors has emerged as a promising area of research for understanding how sensory information is processed in the cortex (Spence, 2002; Driver and Spence, 1998; Eimer and Driver, 2000). Presumably the goal of these interactions is to facilitate the extraction of relevant sensory information early in the processing stream to ensure task-relevant information is passed on for further processing in higher-order cortical areas. Evidence for attentional modulation is most abundant in studies of visual (Andersen et al., 2008; Corbetta et al., 1991; Gazzaley et al., 2007; Moran and Desimone, 1985; Watanabe et al., 1998) and auditory (Jancke et al., 1999; Petkov et al., 2004; Sussman et al., 2005; Woldorff et al., 1993) modalities, however similar findings are emerging within primary somatosensory cortex (SI). For example, some studies have reported that attending to a relevant tactile stimulus increases activity in SI relative to ignoring an irrelevant tactile stimulus (Johansen-Berg et al., 2000; Staines et al., 2002; Van de Winckel et al., 2005), but other studies have not found a task-relevant modulation within SI (Burton et al., 2008; Fujiwara et al., 2002; Mima et al., 1998). Further to this discrepancy, Meehan & Staines (2007) found that the requirement to perform a continuous motor–tracking task in the presence of bimodal (visual and vibrotactile) stimuli produced differential modulation of activity in contralateral SI when the vibrotactile stimulus was relevant to the task compared to when it was irrelevant to the task, such that the volume of activity in SI decreased when subjects attended to the vibrotactile stimulus compared to when they ignored it and tracked the visual stimulus. These results suggest that the specific requirements of the task may determine the nature of SI modulation; in this case the continuous motor task and the presence of a crossmodal distractor may have been mitigating factors in the observed suppression of SI.

The possibility of crossmodal attention effects in primary sensory cortex has been raised by previous observations of such effects on early modality-specific event-related potential (ERP) components (Eimer, 2001; Eimer and van Velzen, 2005; Kennett et al., 2001; McDonald et al., 2001; Murray et al., 2005; Teder-Salejarvi et al., 2002). For example, Ghazanfar et al. (2005) demonstrated facilitation of neurons in auditory cortex when visual stimuli were presented in addition to auditory stimuli, as well as some cells that responded to the visual stimulus alone. Similar results were found for somatosensory stimuli by Murray et al. (2005), who observed enhancement of auditory evoked responses as early as 50 ms after a somatosensory stimulus was applied to the hand. Using evoked potentials (EPs), Schurmann et al. (2002) found a facilitation of EP components over midline and ipsilateral electrode sites beginning at 75 ms when visual stimuli were presented simultaneously with electrical median nerve stimulation. Further evidence of early multisensory interactions comes from functional imaging of monkey auditory cortex, revealing regions that show response enhancement to visual plus auditory stimulation, and somatosensory plus auditory stimulation (Kayser et al., 2005; Kayser and Logothetis, 2007). In humans, Schurmann et al. (2006) found that passive vibrotactile stimuli enhanced BOLD activity in auditory cortex, both during auditory stimulation and in isolation. In contrast, when information from one modality is irrelevant to the task cross-modal suppression can be observed, for example a decrease in blood flow to SI was found during tasks requiring visual processing (Haxby et al., 1991) or auditory discrimination (Fiez et al., 1996).

Taken together, the findings of task-relevant and cross-modal modulation of primary sensory cortex suggest that both relevance and modality of stimuli can affect the excitability of sensory cortex. It remains unclear how these two factors interact to modulate incoming sensory information, and thus the goal of the present study was to determine whether bimodal (visual and tactile) sensory stimulation differentially modulates primary somatosensory cortex compared to unimodal stimulation when task-relevancy requirements are held constant. To investigate whether activity in SI is modulated by bimodal sensory stimulation, we employed a task that required subjects to extract sensory information either within or across modalities and use this information to plan and execute an accurate motor response. Based on the growing body of evidence suggesting that information from different modalities interacts within primary sensory cortex, we hypothesized that the requirement to process both visual and tactile stimuli would enhance activity in SI compared to using visual or tactile stimuli alone.

Our secondary hypothesis was targeted at gaining insight into what may drive this facilitation if observed. In functional MRI studies, multisensory tasks are often associated with increased BOLD activity in higher-order frontal and parietal association regions, including dorsolateral prefrontal cortex (DLPFC), temporoparietal junction, superior temporal sulcus, and inferior parietal sulcus (Beauchamp et al., 2004; Beauchamp et al., 2008; Calvert, 2001; Downar et al., 2001; McDonald et al., 2001). In particular, DLPFC appears to be a strong candidate for top-down modulation of multisensory information. Johnson & Zatorre (2006) found increased signal change in left DLPFC when attention was divided between auditory and visual stimuli compared to passive bimodal stimulation and selective attention to either modality. Given the connections between frontal heteromodal areas and sensory cortex, it is possible that activity in areas like DLPFC may modulate activity in primary sensory cortex in a top-down manner to enhance the extraction and processing of relevant sensory information (Knight et al., 1999; Yamaguchi and Knight, 1990). Support for the role of parietal associative regions in the processing of task-relevant information comes from studies of visual and tactile attention, which suggest that these processes are mediated by a fronto-parietal network that is involved in selecting behaviourally-relevant stimuli for further processing (Burton et al., 1997; Burton et al., 1999; Corbetta et al., 1998; Corbetta, 1998; Mesulam, 1990; Posner and Petersen, 1990). In particular, the posterior parietal cortex has been implicated in mediating attention to sensory information in different modalities (Andersen et al., 1997; Nakashita et al., 2008; Rushworth and Taylor, 2006). Thus we hypothesized that frontal and parietal associative regions would show increased BOLD activation when visual and tactile stimuli are presented together compared to presentation of visual or tactile stimuli alone, and that this would be associated with an upregulation of activity in primary somatosensory cortex.

2.3 Methods

2.3.1 Subjects

Functional magnetic resonance imaging was performed on 10 healthy participants (mean age = 25, range = 22-37, 5 females). Experimental procedures were approved by the Sunnybrook Health Sciences Centre Ethics Committee and the University of Waterloo Office of Research Ethics. All subjects provided informed written consent.

2.3.2 Behavioural task

The experimental task required participants to judge the amplitude of two stimuli, either visual, tactile, or both, and make a graded motor response to represent the sum of these amplitudes by squeezing a pressure-sensitive bulb with their right hand. Prior to the functional scans participants underwent a 7-minute training session with visual feedback to learn the relationship between the amplitudes of the stimuli and the corresponding force required to apply to the bulb. During training, a horizontal target bar appeared on the visual display and subjects were instructed to squeeze the pressure-sensitive bulb with enough force to raise another visual horizontal bar to the same level as the target bar. At the same time, as subjects applied force to the bulb with their right hand a vibrotactile device vibrated against the volar surface of their left index finger with corresponding changes in amplitude, i.e. as they squeezed harder on the bulb the amplitude of the vibration increased proportionately. Subjects were instructed to pay attention to these changes in amplitude as they related to the force they were applying to the bulb, and in this way subjects became familiar with the relationship between the vibrotactile stimulus amplitude and the corresponding force applied to the bulb. To control for force-related trial-to-trial differences, stimulus amplitudes were scaled such that no single stimulus required a squeeze of more than 25% of an individual's maximum force, thus the response for adding two stimuli was never more than 50% of an individual's maximum force.

Stimulus presentation was manipulated in two ways: timing and modality. Stimuli were presented either sequentially for two seconds each, or simultaneously for four seconds, such that in both cases the total stimulation period was four seconds. Pairs of stimuli were either unimodal (two visual or two tactile stimuli) and sequentially presented, or bimodal (one visual and one tactile stimuli) and presented simultaneously for a total of 3 experimental conditions: 2 unimodal conditions, visual and tactile, and 1 bimodal condition, visual + tactile.

2.3.3 Experimental design

An event-related design was used to investigate changes in the hemodynamic response at different stages of the sensorimotor integration process. Stimuli were presented for four seconds followed by a four second delay, at which point a brief (500ms) cue was given to signal participants to make their motor response during a two second window, followed by ten seconds of rest prior to the start of the next trial, for a total of 20 seconds per trial. This design yielded 3 event-related time periods (stimulus, delay, response) with the remainder of each trial serving as the baseline (off). For the purposes of addressing the hypotheses of this study, the stimulus period was the primary time point of interest and all analyses were performed on the volumes corresponding to the stimulus presentation period. Each task condition was performed in a block of 15 trials with each block lasting 5 minutes.

2.3.4 Stimuli

Visual stimuli consisted of a centrally-presented horizontal bar at varying heights representing different amplitudes. Visual stimuli were back-projected onto a white screen placed over the subjects' feet that was visible to subjects via an angled mirror in the head coil. Vibrotactile stimuli consisted of discrete vibrations at a constant frequency of 25 Hz, delivered by a custom MRI-compatible device (Graham et al., 2001) applied to the volar surface of the left index finger. Vibrotactile stimulation was controlled by converting digitally generated waveforms to an analog signal (DAQCard 6024E, National Instruments, Austin, Texas) and then amplifying the signal (Bryston 2B-LP, Peterborough, Ontario) using a custom program written in LabVIEW (version 7.1, National Instruments, Austin, Texas). Varying the amplitude of the driving voltage to the vibrotactile device produced proportional changes in vibration of the device on the finger in the MR environment (Graham et al., 2001). The amplitude of each discrete vibration was constant within a trial and varied between trials. The average stimulus amplitude across all 15 trials of a run did not differ between the experimental conditions. The frequency of the vibration was held constant at 25 Hz. Output from the computer was routed through a penetration panel to the magnet room using a filtered 9-pin D sub-connector and shielded cable to ensure that no perceptible torque was produced by currents induced by radio-frequency transmit pulses or time-varying magnetic field gradients during imaging.

2.3.5 Data acquisition & scanning parameters

Functional and anatomical images were collected at Sunnybrook Health Sciences Centre on a 3T MRI scanner (GE HealthCare, Milwaukee, Wisconsin) using a standard birdcage head coil. Prior to the functional scans, high-resolution anatomical scans were acquired for each subject (TR = 12.4ms, TE = 5.4ms, flip angle $\theta = 35°$, FOV = 20 x 16.5, 124 slices, slice thickness = 1.4mm) for later co-registration with functional maps. Blood oxygenation level dependent (BOLD) images were acquired using gradient echo imaging with single-shot spiral in-out readout (TR=2000ms, TE = 30ms, flip angle $\theta = 70°$, FOV = 20, 26 slices, slice thickness = 5mm). Total scan time for each subject was approximately 60 minutes.

2.3.6 Data analysis

Raw data was reconstructed offline and a time series of 154 images per slice was generated for each functional scan. The resulting time courses were analyzed using BrainVoyager QX 1.9 software (Brain Innovation, Mastricht, The Netherlands). The first 4 volumes of each time series were excluded to prevent artifact from transient signal changes as the brain reached a steady magnetized state. Prior to co-registration, the functional data was pre-processed by linear trend removal, temporal high pass filtering to remove non-linear low frequency drift, and 3-dimensional motion correction using trilinear interpolation to detect and correct for small head movements during the scan by spatially realigning all subsequent volumes to the fifth volume. Estimated translation and rotation measures were visually inspected and never exceeded 1 mm and 1 degree, respectively. The functional data sets were transformed into Talairach space (Talairach and Tournoux, 1988) by coregistering the functional data with the anatomical data for each subject. The resulting volume time courses were filtered using a 6mm Gaussian kernel at full-width half-maximum.

A multiple regression analysis was used to determine the statistical differences across the three experimental conditions (visual-visual, tactile-tactile, visual + tactile) for the stimulus presentation period as well as the delay and response periods for a total of 5 predictors, with the 10 s of “off” in each condition serving as the baseline. The event of interest for this study was the stimulus presentation period, thus three stimulation protocols were applied using dummy-predictors for those predictors not present in a given scan. The protocols were convolved with a boxcar hemodynamic response function (Boynton et al., 1996) to account for the expected response and temporal delay of the changes in blood flow. The resulting reference functions served as the model for the response time course functions used in the general linear model.

Two different general linear models were used to carry out a region-of-interest (ROI) analysis on the right primary somatosensory cortex (SI) and a whole-brain analysis.

ROI analysis

Given that the primary hypothesis of the study focused on changes in primary somatosensory cortex, a region of interest (ROI) analysis was used to assess the effects of the experimental manipulations on right SI (contralateral to vibrotactile stimulation) in each subject. A mask of each subject's right SI was created using the following anatomical boundaries: the central sulcus anteriorly, the medial wall of the "hand knob" medially, the most lateral edge of the post-central gyrus laterally, and the post-central sulcus posteriorly (Nelson et al., 2004). After applying the general linear model using the mask restriction, any significant voxels that exceeded the Bonferroni corrected value of $p<0.05$ for the total number of voxels contained in the ROI and that were part of a cluster greater than three contiguous voxels were included in the ROI analyses. Task-related changes were quantified as changes in the intensity and volume of the activated clusters in the ROI. To quantify differences in intensity the individual time course data for all significantly activated voxels within a cluster were extracted and averaged across each subject and condition to produce one time series per subject per condition representing signal changes for the event relative to the off period for a given scan, thus BOLD signal changes are expressed as a percentage relative to the baseline off. To quantify volume of activation the total number of voxels reaching the significance threshold was represented as a percentage of the total number of voxels in each subject's SI mask. Volume measurements were analyzed using a paired t-test to assess differences between task conditions. A repeated-measures ANOVA was carried out using SPSS (v.17, SPSS Inc., Chicago, Illinois) to test for a main effect of task condition on percent signal change at the point of peak stimulus-related activity. Differences in signal change between the three task conditions (visual, tactile and visual + tactile) were assessed using Tukey post-hoc tests.

Whole-brain analysis

A random effects analysis was used to investigate regions that were sensitive to the experimental manipulations. Contrast maps were created using a voxel-based approach to show relative changes for stimulus vs off and response vs off. An additional *a priori* contrast was performed to compare tactile vs visual + tactile conditions. Activated voxels were considered significant if the threshold exceeded $p<0.001$ uncorrected and formed a cluster of 14 contiguous voxels, based on a cluster size threshold estimator simulation (BrainVoyager QX 1.9 software (Brain Innovation, Mastricht, The Netherlands), corresponding to a corrected threshold of $p<0.05$ (Forman et al., 1995). The center of gravity and t-statistics were extracted for each significant cluster. Event-related averaging was applied to each cluster to determine the BOLD response characteristics for each task condition and peak stimulus-related signal change was extracted and averaged across subjects.

Behavioural data analysis

Behavioural data was analyzed by summing the amplitudes of the two target stimuli and comparing this to the amplitude of the response. The force applied to the bulb forced air through a rubber tube in a closed system, inducing a change in pressure that was measured by a pressure sensor and converted to a voltage. There was a linear relationship between the pressure measurement and the voltage produced. The absolute percent difference between the summed target stimulus amplitude (i.e. the voltage of the 2 stimuli added together) and the actual response amplitude (in volts) was calculated and a repeated measures ANOVA was conducted to assess statistical differences across the experimental conditions.

2.4 Results

ROI analysis

Clusters of activation were found in the tactile and the visual + tactile task, but not surprisingly not for the visual task. This was true for all subjects except one who had no active voxels survive the thresholding criteria in any of the task conditions, thus ROI analyses were performed on the remaining 9 subjects. The results of the ROI analysis on right SI (contralateral to vibrotactile stimulation) are shown in Figure 2, which illustrates a significant increase in percent signal change in the tactile + visual condition compared to the tactile condition at the point of peak stimulus-related activity (8 seconds post-stimulus onset). This difference was confirmed by a significant main effect of task in a repeated measures ANOVA ($F_{2,16} = 36.4$, $p<0.001$). Post-hoc tests revealed significant differences between each task: tactile > visual ($p<0.001$), visual + tactile > visual ($p<0.001$), and most relevant to our hypothesis, visual + tactile > tactile ($p = 0.009$). No task-related difference was found for volume of activation between the tactile and visual + tactile conditions ($t_8= 0.471$, $p > 0.05$).

Whole brain analysis

Group activation maps for the stimulus and response periods contrasted vs baseline are displayed in Figures 3 and 4 respectively. For the stimulus presentation period, a common network of activation can be seen across all conditions, regardless of stimulus modality. This network includes the right medial frontal gyrus (BA 6), bilateral precentral and middle frontal gyri (BA 9), right superior temporal gyrus (BA 41), left inferior temporal gyrus (BA 37), and left inferior parietal lobule (BA 40). For a complete list of activations with center of gravity coordinates and t-statistics, see Table 1. Figure 3B depicts event-related average plots for clusters in the observed fronto-parietal network, illustrating the BOLD signal (represented as percent signal change relative to baseline) for each task condition. Time zero corresponds to the onset of the stimulus, with the stimulus-related activity peaking approximately 8 seconds later. The second peak in BOLD signal occurs around 16 seconds and corresponds to the motor response-related activity.

Event-related averages

To determine the stimulus-related BOLD response for each task condition, event-related averaging was performed on all significant ROIs from the whole brain analysis. Repeated measures ANOVAs with post-hoc tests were run on each peak to determine task-related differences and these results are shown in Table 1. Significant task effects were observed in the R premotor cortex (BA 6) ($F_{2,18}$=3.541 $p<0.05$) R inferior temporal gyrus (BA 37) ($F_{2,18}$=3.775 $p<0.05$, and L caudate ($F_{2,18}$=3.347 $p<0.05$). The visual task produced greater signal change in the R premotor cortex compared to the tactile and visual + tactile conditions. Similarly, in the R inferior temporal gyrus the visual task was also associated with greater signal change than the tactile and visual + tactile conditions, however the visual + tactile condition also showed greater peak signal change compared to the tactile task. Lastly in the L caudate the visual + tactile condition produced greater peak signal change than either the visual or tactile conditions. All post-hoc tests reported were significant at $p<0.05$.

Behavioural results

A one-way repeated measures ANOVA was performed on the error differences across all three conditions and yielded no main effect ($F_{2,20}=.070$, $p>0.05$). Thus all tasks were performed with equivalent accuracy as illustrated in Figure 5.

2.5 Discussion

This study sought to investigate how cross-modal information, in this case visual and somatosensory stimuli, interacts within primary somatosensory cortex for the purpose of performing a delayed sensory-to-motor task. Specifically we asked whether activity in SI is modulated by the requirement to use both visual and vibrotactile information to guide a motor response, and if so to identify regions that may contribute to or drive this modulation. Our first hypothesis that we would see a modulation of SI activity in the bimodal visual + tactile task relative to the unimodal visual and tactile tasks was supported by the results of our ROI analysis, which revealed an increase in peak percent BOLD signal change in the visual + tactile condition compared to the tactile-only and visual-only conditions. This finding of bimodal upregulation of SI aligns with similar observations made with fMRI of auditory-somatosensory convergence in early auditory cortex (Foxe et al., 2002; Kayser et al., 2005), and visual-auditory interactions in auditory cortex (Kayser et al., 2008; Miller and D'Esposito, 2005; van Atteveldt et al., 2004) as well as visual processing areas (Macaluso et al., 2000).

The SI modulation seen in the current study is also inline with ERP studies finding evidence of crossmodal interactions across auditory and somatosensory modalities less than 100 ms post-stimulus (Ghazanfar et al., 2005; Lakatos et al., 2007; Molholm et al., 2002; Murray et al., 2005; Teder-Salejarvi et al., 2005), a timeline that is consistent with processing within primary sensory cortex (Allison et al., 1992). Relatively few studies have specifically investigated the role of crossmodal effects in SI. Schurmann et al. (2002) combined visual evoked potentials (VEPs) and somatosensory evoked potentials (SEPs) and observed a bimodal enhancement at multiple electrode sites beginning at 75 ms, with a maximal effect at 225-275 ms. Zhou & Fuster (Zhou and Fuster, 2000) found that in monkeys trained to make visual-haptic or auditory-haptic associations, a subset of SI neurons responded to both the visual/auditory cue and the tactile stimulus. The present study provides further evidence for crossmodal interactions within sensory-specific cortex, and is the first to demonstrate an upregulation of somatosensory cortex with simultaneous visual and tactile stimulation using fMRI.

These findings diverge from those of Meehan & Staines (2007) who observed a decrease in volume of SI activity during bimodal visual and tactile stimulation when subjects tracked the tactile stimulus (and ignored the visual) compared to when they tracked the visual stimulus (and ignored the tactile). However, this discrepancy can likely be explained by differences in the nature of the task, the most salient being that in the current study both the visual and tactile stimuli were relevant to the performance of the motor task and thus both had to be attended to, as opposed to one stimulus being a target and the other a distractor. The latter requires selective intermodal attention. This difference in relevancy/attention has been shown to have an effect in both sensory modality-specific cortex (Eimer and van Velzen, 2005; Johnson and Zatorre, 2005; Kennett et al., 2001; Macaluso et al., 2002) and in heteromodal frontal and parietal areas (Downar et al., 2001). The disparity in findings between these two studies may also be accounted for by differences in the motor task such that in the previous study subjects were required to continuously track a fluctuating stimulus over a period of time whereas in the current study subjects made a discrete motor response after receiving two static stimuli. The continuous nature of the tracking task may have altered the attentional demands of the task, likely by requiring more sustained attention over a longer period of time.

Our secondary hypothesis that we would see differential patterns of activation in frontal and parietal regions between task conditions was not supported, and instead we observed a common fronto-parietal network, including the right precentral gyrus (BA 9), left middle frontal gyrus (BA 9), right medial frontal gyrus (BA 6), left inferior parietal lobule (BA 40), and right superior temporal gyrus (BA 41) that was active after the stimuli were presented for all three task conditions compared to rest. A comparable network of activation has often been observed in tasks that require shifts of attention (Corbetta, 1998; Mesulam, 1990; Rushworth et al., 2001), and this network has been implicated in the top-down modulation of relevant and irrelevant stimuli (Gazzaley et al., 2007; Ghatan et al., 1998; Miller and D'Esposito, 2005; Shulman et al., 1997; Staines et al., 2002). However, in the current study stimuli in all task conditions were always relevant to the performance of the motor task, which may account for why we observed relatively few task-related changes in frontal and parietal regions typically associated with top-down modulation. The event-related averaging plots did reveal some areas that were differentially sensitive to the task manipulation, including the right premotor cortex, left inferior temporal gyrus, and left caudate. The right premotor cortex showed greater peak signal change in response to the visual condition, and no difference between the tactile condition and the visual + tactile condition, suggesting that the premotor cortex is not sensitive to tactile stimuli or the combination of visual and tactile stimuli, but it does appear to show preferential activity for visual stimuli presented alone. There are two possible explanations for this observation: the first being that the visual processing demands are greater in the visual condition due to the presence of two visual cues and this drives an upregulation of premotor cortex. An alternative but not mutually exclusive explanation could be that the presence of tactile stimuli in the other two task conditions may have produced a relative suppression in this region compared to the visual condition. The similarity between the BOLD activity evoked by the cued response in all three conditions (the second peak in the signal plots in Figure 3B) supports the view that this is a stimulus-dependent effect rather than a difference in the motor requirements of the tasks.

In addition, the left inferior temporal gyrus showed preferential activity for visual stimuli such that peak signal change was greater for the visual + tactile condition than the tactile task, and greater still for the visual task. This region is thought to play a role in higher-level visual processing such as stimulus recognition and visual working memory (Axmacher et al., 2008; Ranganath and D'Esposito, 2005; Rissman et al., 2008), which may account for why we observed increased BOLD signal as the visual processing requirements increased across tasks. A task-related effect was also seen in the left caudate, which responded with greater peak signal change during the visual + tactile task compared to the unimodal tasks. While the caudate nucleus has been implicated in response selection for goal-directed action (Grahn et al., 2008), there is no evidence to date that it is sensitive to crossmodal stimuli, thus this study may be the first to demonstrate such an effect.

The results of the present study suggest that while a fronto-parietal network may be involved in the attentional and motor planning aspects of the task, which were equivalent across all conditions, such a network is not likely to be differentially involved in processing simultaneously presented visual and tactile stimuli. Given this observation, our secondary hypothesis that modulation of SI activity would coincide with increased activation in multimodal association regions such as the dorsolateral prefrontal cortex, temporal parietal junction and inferior parietal lobule was not supported by the data from the whole-brain analysis, and thus the crossmodal SI enhancement seen in this study was likely not driven by feedback from a higher-order multimodal area. An alternative explanation for the increase in BOLD signal in SI during the bimodal task may lie in the anatomical connectivity between visual and somatosensory processing areas. Evidence for these connections comes from a retrograde tracer study in marmosets, revealing projections from visual areas, specifically the ventral and dorsal fundus of the superior temporal area and middle temporal crescent (areas FST and MT) towards somatosensory areas 1 and 3b (Cappe and Barone, 2005). The existence of these connections supports the possibility that incoming visual and tactile information may interact in a bottom-up manner via low-level sensory to sensory connections. Evidence for feedforward crossmodal interactions has been reported in audio-visual modalities in ERP experiments, where interactions between these modalities have been observed as early as 40 ms post-stimulus over unisensory recording sites (Giard and Peronnet, 1999; Murray et al., 2005; Schroeder and Foxe, 2005), which is typically considered to be too early for feedback from higher-level cortical areas to reach these areas (Foxe and Schroeder, 2005; Giard and Peronnet, 1999). The present study is the first to find evidence of visual-somatosensory interactions within somatosensory cortex, but the precise mechanisms driving this interaction are not yet clear.

A similar but more frontally-focused network was observed related to the motor response, including bilateral middle frontal gyri (BA 9), bilateral medial frontal gyri (BA 6), right inferior frontal gyrus (BA 46), left superior frontal gyrus (BA 10), and left precentral and postcentral gyri (BA 4 & 2 respectively). Comparable networks of activation are often associated with movement preparation and execution (Deiber et al., 1996; Thoenissen et al., 2002; Toni et al., 2001; Toni et al., 2002), and in particular the frontal motor areas have been reported to show similar levels of activity regardless of the contribution of vision to motor planning (Deiber et al., 1996) thus we would not expect these areas to be differentially modulated by the modality of the stimulus. From a behavioural standpoint we also did not observe any difference in how well subjects performed the motor task across conditions. Previous studies of multisensory interactions have reported faster reaction times in multisensory conditions compared to unisensory conditions (Martuzzi et al., 2007; Molholm et al., 2002), however dual-task studies report decrements in task performance when subjects have to divide their attention between modalities (Alsius et al., 2005; Alsius et al., 2007; Spence and Read, 2003). Johnson & Zatorre (Johnson and Zatorre, 2006) found that splitting attention between modalities produced equivalent memory performance compared to attending to selective bimodal attention. In the present study accuracy was emphasized over speed of response. Also, given the high level of accuracy with which subjects performed the motor task it is possible that a ceiling effect may have limited the ability to detect task-related differences, but further studies are needed to more precisely determine the behavioural effects of crossmodal interactions.

Our findings extend the observation of multisensory interactions in sensory cortex to the visual-somatosensory domain and provide further evidence that the requirement to use information from different modalities can modulate sensory processing at early stages. It is important to note that the task used in this experiment was not designed to meet the requirements for multisensory integration across modalities, but instead was intended to explore how crossmodal stimuli interact within sensory-specific cortex. The strength of this task is that it allowed us to manipulate the modality of the stimuli while keeping the relevance of the stimuli and the motor requirements constant. Limitations of the present study include the temporal resolution of fMRI, which constrained our ability to investigate the precise timing of the observed crossmodal modulations, and the nature of the behavioural task within the fMRI environment may have limited the sensitivity of this measure. Future studies will be required to investigate the temporal nature of crossmodal interactions in sensory cortex and to determine the consequences of this modulation for sensory-guided movement.

2.6 Conclusion

Simultaneous visual and vibrotactile stimulation modulates activity in contralateral SI when both stimuli are relevant to performance of a sensorimotor task.

2.7 Figures & tables

Stimulus > baseline p<0.001 cluster threshold = 14					
Anatomical region/Brodmann area	x	y	z	t-statistic	Task-related difference (p<0.05)
R superior temporal gyrus (BA 41)	44	-35	13	5.77	n.s.
R precentral gyrus (BA 9)	40	20	36	5.66	n.s.
R medial frontal gyrus (BA 6)	18	2	58	5.84	v>t, v>vt
R caudate	9	11	10	5.19	n.s.
R claustrum	34	-3	-9	5.65	n.s.
L superior frontal gyrus (BA 8)	-4	16	50	5.23	n.s.
L inferior parietal lobule (BA 40)	-38	-34	45	5.78	n.s.
L middle frontal gyrus (BA 9)	-40	43	27	5.39	n.s.
	-49	8	34	6.12	n.s.
L inferior temporal gyrus (BA 37)	-50	-48	-4	5.45	v>t v>vt vt>t
L caudate	-15	17	8	5.32	vt>v, vt>t
L insula (BA 13)	-31	25	13	5.96	n.s.

Table 1: Regions demonstrating stimulus-related activity > baseline

Response > baseline p<0.001 cluster threshold = 14				
Anatomical region/Brodmann area	x	y	z	t-statistic
R precentral gyrus (BA 6)	52	-9	39	7.23
R inferior frontal gyrus (BA 46)	47	35	10	6.69
R middle frontal gyrus (BA 6)	45	8	43	6.58
R middle frontal gyrus (BA 9)	46	19	31	6.91
R superior frontal gyrus (BA 9)	35	46	31	7.07
R medial frontal gyrus (BA 6)	9	4	63	7.01
L superior frontal gyrus (BA 10)	-39	51	24	7.61
L medial frontal gyrus (BA 6)	-9	5	51	6.76
L precentral gyrus (BA 4)	-41	-24	53	7.89
L postcentral gyrus (BA 2)	-51	-21	29	6.93
L middle frontal gyrus (BA 9)	-55	9	34	7.07
L insula (BA 13)	-37	3	6	6.60

Table 2: Regions demonstrating motor response-related activity > baseline

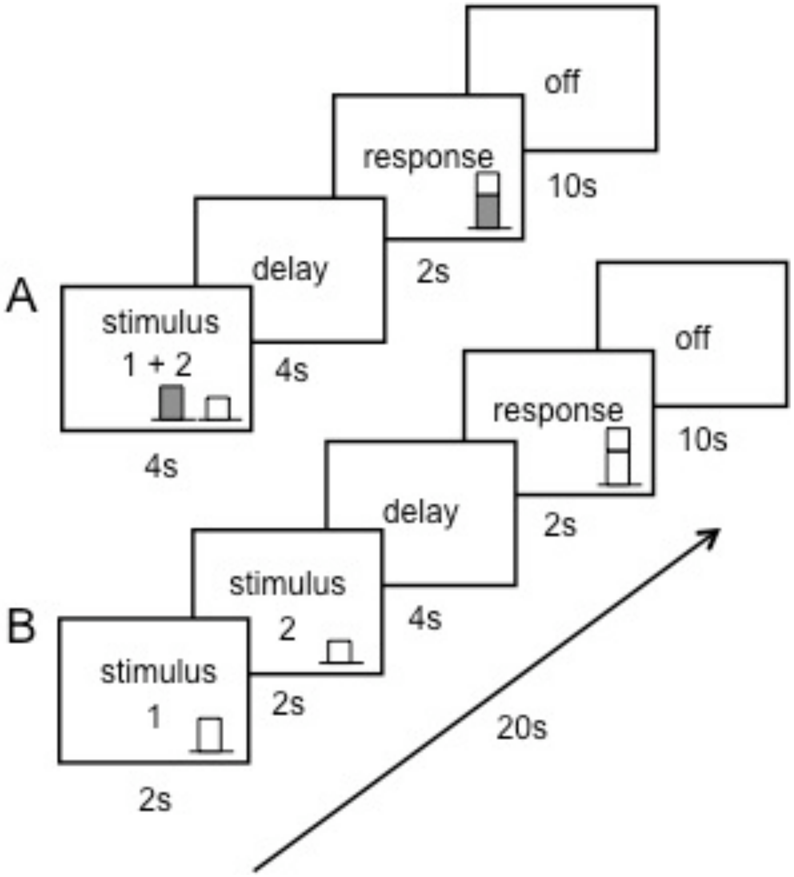


Figure 1
Timing of experimental task. A shows timing for the bimodal visual + tactile condition; B depicts the timing for trials in the unimodal task conditions

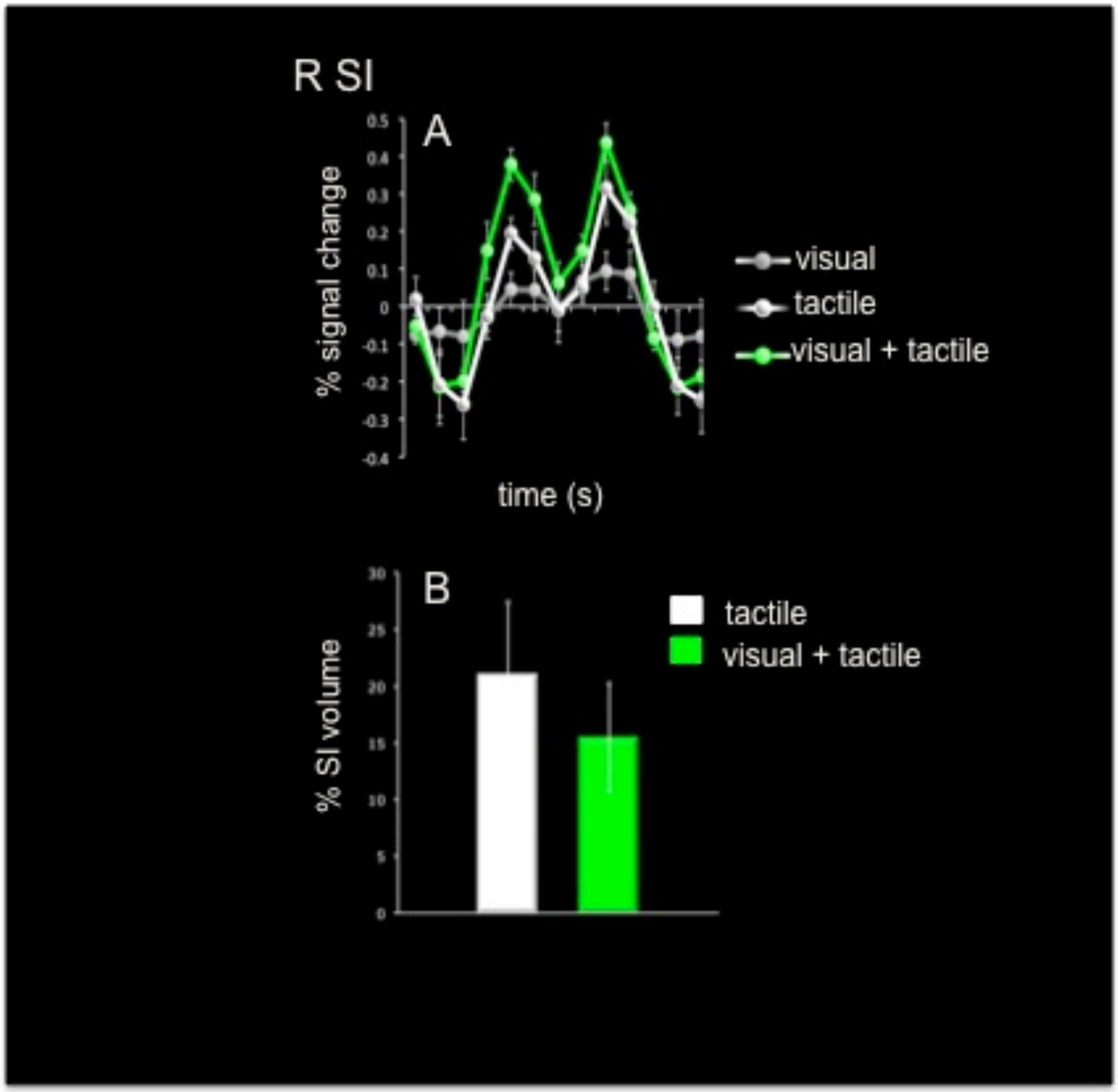


Figure 2
Region of interest (ROI) results for right somatosensory cortex (R SI). White bar/line represents the unimodal tactile task, green bar/line represents the bimodal visual + tactile task, and the grey line represents the unimodal visual task. Error bars depict SEM, asterisk indicates a significant difference ($p<0.05$).

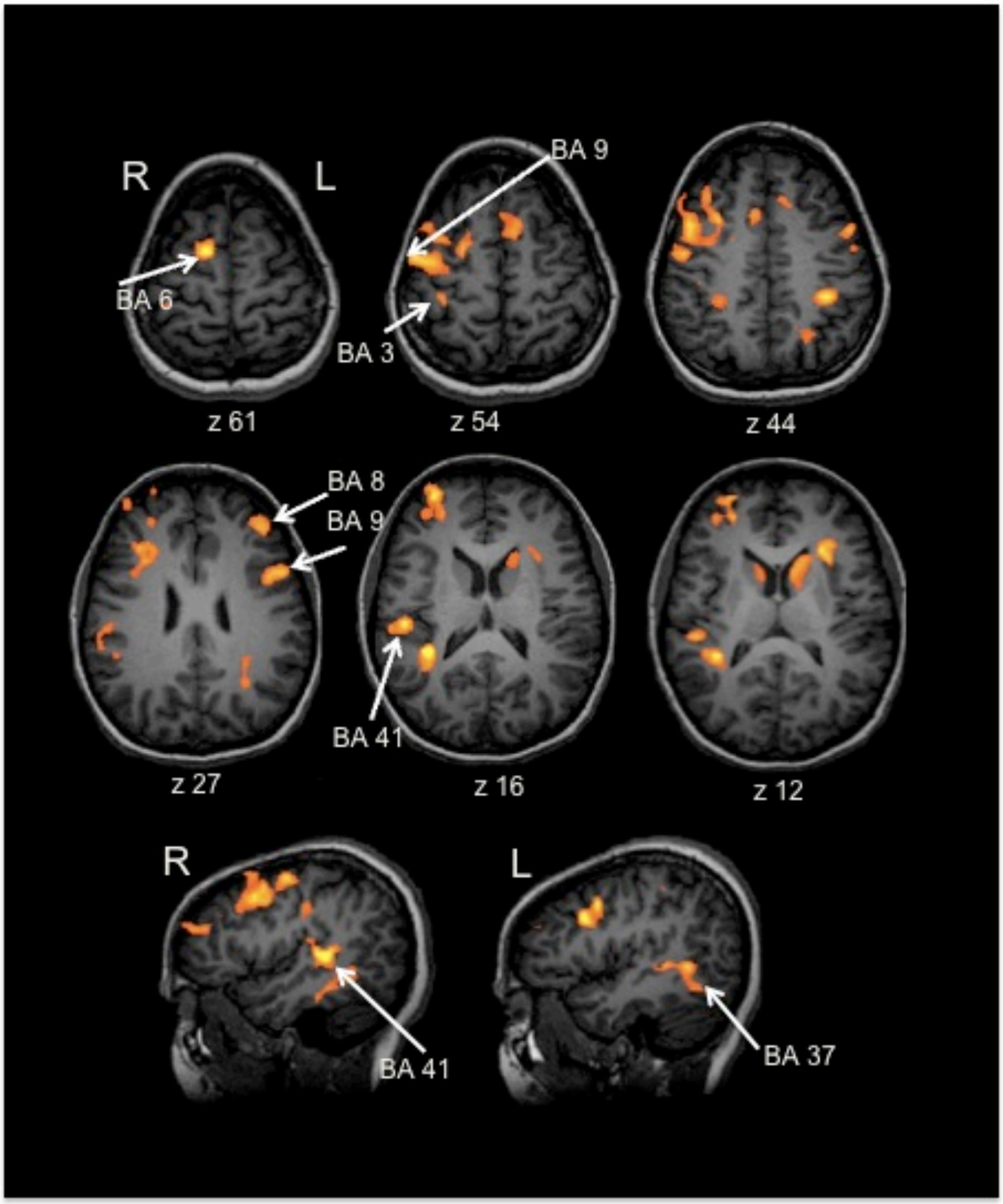


Figure 3A

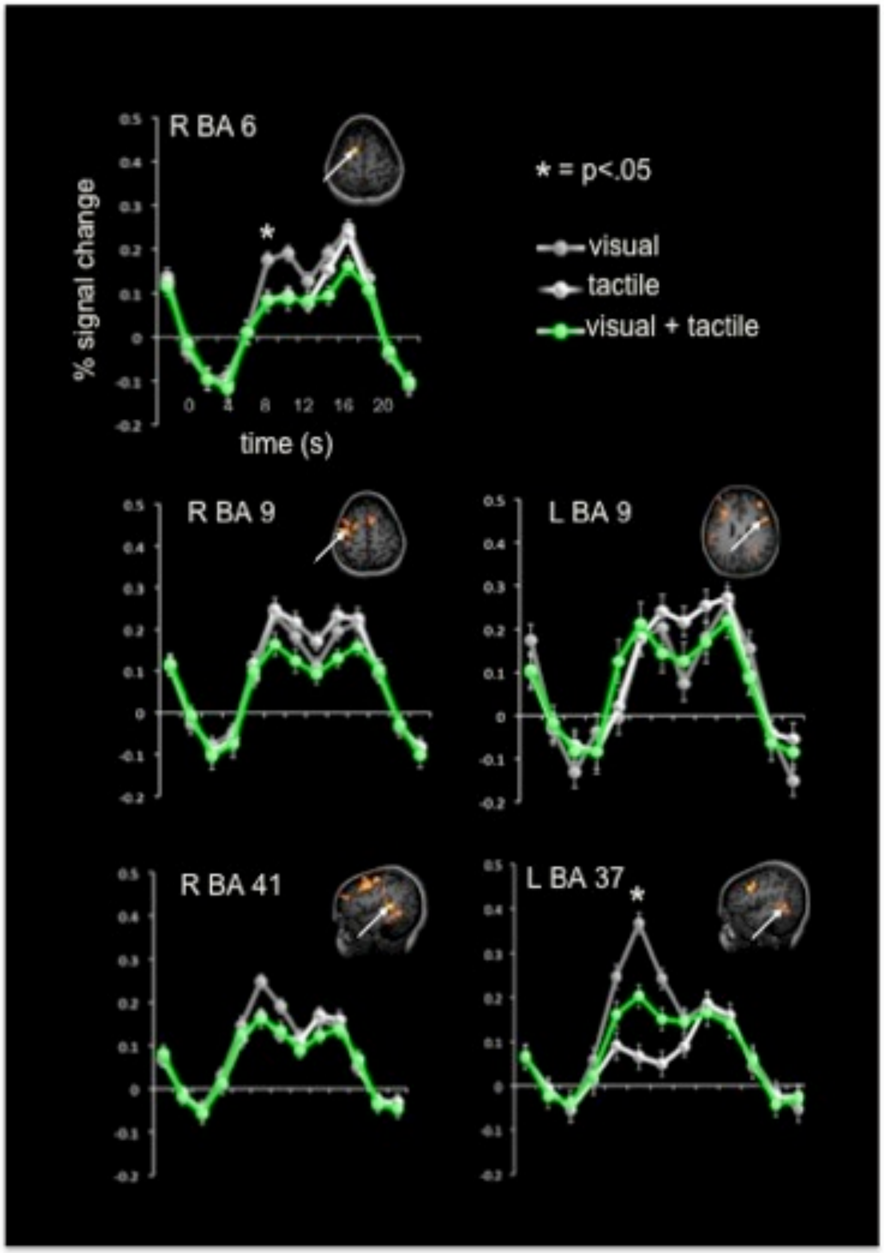


Figure 3B
Group activation maps and event-related average plots for the stimulus presentation relative to baseline. Panel A depicts areas with greater activity during the 4s stimulus "on" time compared to baseline, shown on orange colour scale, significant at $p<0.001$ with a cluster threshold of 14 voxels. Panel B shows event-related averaging plots for clusters of interest, illustrating the BOLD response of each task condition; grey lines represent the visual task, white lines show the tactile task, and green lines depict the visual + tactile task. Bars represent SEM, asterisks indicates a significant difference ($p<0.05$).

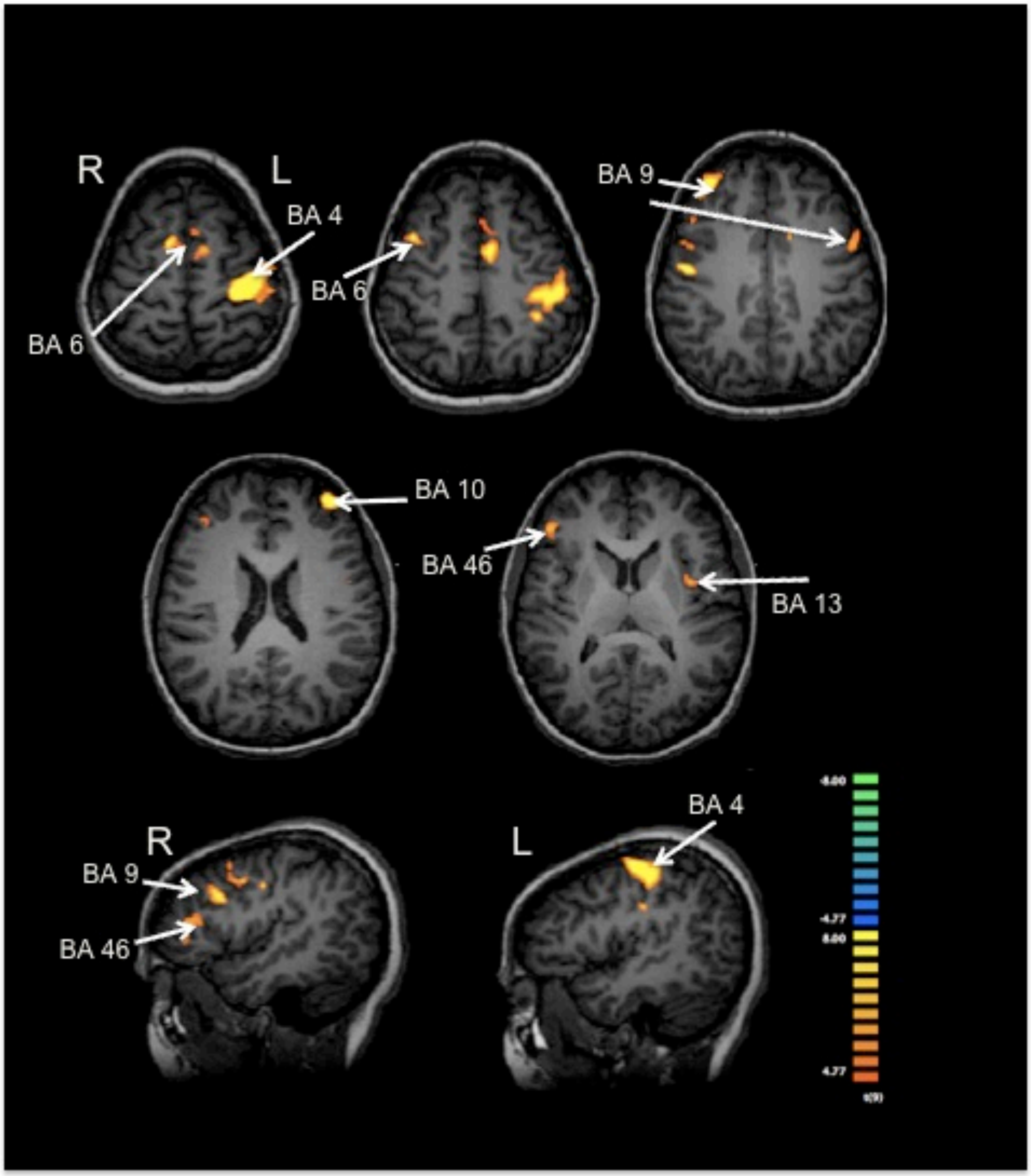


Figure 4
Group activation maps for the motor response relative to baseline. Panel A depicts areas with greater activity during the 4s stimulus “on” time compared to baseline, shown on orange colour scale, significant at p<0.001 with a cluster threshold of 14 voxels.

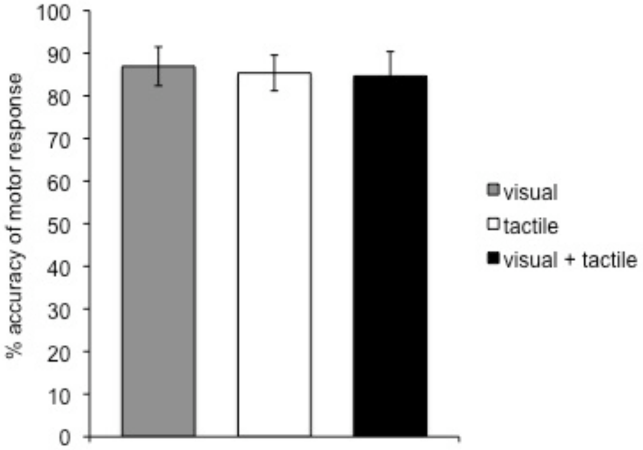


Figure 5
Behavioural results. Bars depict mean percent accuracy of all subjects in each task condition. Error bars represent standard error of the mean.

Chapter 3 – Studies 2 & 3: Crossmodal modulation of somatosensory event-related potentials is mediated by task-relevance.

3.1 Overview

Previous research has shown that somatosensory cortex is subject to modulation based on the relevancy of incoming somatosensory stimuli to behavioural goals. Further to this, recent fMRI findings provide evidence for crossmodal modulation of primary somatosensory cortex when simultaneous visual and tactile stimuli were relevant to the performance of a motor task (Dionne et al., 2010). The goals of the present study were 1) to determine the temporal characteristics of this modulation using event-related potentials (ERPs), and 2) to investigate the role of task-relevance in mediating such a modulation. Electroencephalography (EEG) was collected from healthy subjects while they received visual, vibrotactile, or both types of stimuli and performed a sensory-guided motor task. In Study 2, task-relevancy was held constant and participants responded to all stimuli. In Study 3, task-relevancy was manipulated to test the hypothesis that cross-modal effects will only be seen when both modalities are relevant. ERPs were time-locked to the onset of each stimulus and mean ERP amplitudes and latencies were extracted for the P50, P100, N140 and P230. A crossmodal enhancement was observed in the P50 component contralateral to vibrotactile stimulation and a similar enhancement was seen in the P100 and N140 components at parietal electrodes. When task relevance was manipulated, crossmodal enhancement of the P50 was observed only when both stimuli were relevant, and the same pattern was seen in the N140 at fronto-central electodes. These results provide evidence that crossmodal stimuli can modulate early somatosensory event-related potentials, and that these effects are mediated by stimulus relevance.

3.2 Introduction

Somatosensory inputs carrying information about touch travel from the periphery to the cortex where these signals can contribute to planning behavioural responses. At the cortical level, excitability of somatosensory cortex is modulated by the relevance of the stimuli to behaviour, with the goal of facilitating the extraction of relevant sensory information for further cortical processing. Functional neuroimaging studies have shown that primary somatosensory cortex (SI) is sensitive to attentional manipulations and is upregulated when tactile stimuli are made relevant to the performance of a task (Johansen-Berg et al., 2000; Nelson et al., 2004; Staines et al., 2002). Evoked potentials (EPs) to somatosensory stimuli have also yielded similar findings of task-relevant modulation, although there is a lack of consensus regarding the timing of such modulations, with reports ranging from 50-140 ms post-stimulus onset (Desmedt and Robertson, 1977; Desmedt and Tomberg, 1989; Eimer and Driver, 2000; Eimer and Forster, 2003; Michie, 1984; Michie et al., 1987; Schubert et al., 2008; Zopf et al., 2004). The cortical generators of these somatosensory EP components are of some debate, but the earlier components are thought to reflect activity within primary and secondary somatosensory cortex, while the later potentials are often associated with multiple non-modality specific generators in frontal and parietal cortex (Allison et al., 1991).

In addition to modulation by attention, somatosensory cortex may also be subject to modulation by crossmodal stimuli. Schurmann et al. (2002) reported a facilitation of EP components over midline and ipsilateral electrode sites beginning at 75 ms when visual stimuli were presented simultaneously with electrical median nerve stimulation (Schurmann et al., 2002). Effects of vision on somatosensory ERP components at 80 ms have been demonstrated by Taylor-Clarke et al., suggesting that vision may modulate excitability in SI during a tactile acuity task, and that this modulation is associated with an improvement in acuity (Taylor-Clarke et al., 2002). In an fMRI study by Meehan & Staines, subjects perfomed a continuous motor tracking task in the presence of bimodal (visual and vibrotactile) stimuli, and this task was associated with differential modulation of SI based on which modality was being tracked and was thus relevant to the task (Meehan and Staines, 2007). A recent fMRI study followed up on these findings but held task-relevance requirements constant, and the results indicated a crossmodal facilitation of the BOLD signal in SI during a sensory-guided motor task requiring the use of both visual and tactile information (Dionne et al., 2010).

With these findings in mind, the goal of the current study was two-fold: to investigate the timing of the previously observed crossmodal modulation in somatosensory cortex using event-related potentials, and to determine whether crossmodal effects are dependent on the task-relevance of the stimuli. We hypothesized that given previous findings suggesting that early somtosensory components are sensitive to both task-relevance of stimuli and crossmodal influences, then a task that requires the use of stimuli from two modalities to guide a motor response would be associated with modulation of the early EP components at electrode sites contralateral to vibrotactile stimuli. Further to this, we predicted that such a modulation would only be observed when both stimuli were relevant to the task and not when one was task irrelevant.

3.3 Methods

3.3.1 Subjects

Electroencephalography (EEG) was collected from 22 healthy participants (mean age = 26 years, 9 males). Twelve participants were recruited for Study 2 and an additional 10 participated in Study 3. One subject was excluded from analysis in Study 2 due to excessive artifacts in the EEG. Experimental procedures were approved by the University of Waterloo Office of Research Ethics. All subjects provided informed written consent.

3.3.2 Behavioural task

The behavioural task required participants to judge the amplitude of two stimuli, either visual, tactile, or both, and make a graded motor response to represent the sum of these amplitudes by squeezing a pressure-sensitive bulb with their right hand. Prior to the EEG collection participants underwent a 5-minute training session with visual feedback to learn the relationship between the amplitudes of the stimuli and the corresponding force required to apply to the bulb. During training, a horizontal target bar appeared on the visual display and subjects were instructed to squeeze the pressure-sensitive bulb with enough force to raise another visual horizontal bar to the same level as the target bar. At the same time, as subjects applied force to the bulb with their right hand the vibrotactile device vibrated against the volar surface of their left index finger with corresponding changes in amplitude, i.e. as they squeezed harder on the bulb the amplitude of the vibration increased proportionately. Subjects were instructed to pay attention to these changes in amplitude as they related to the force they were applying to the bulb, and in this way subjects became familiar with the relationship between the vibrotactile stimulus amplitude and the corresponding force applied to the bulb. To control for force-related trial-to-trial differences, stimulus amplitudes were scaled such that no single stimulus required a squeeze of more than 25% of an individual's maximum force, thus the response for adding two stimuli was never more than 50% of an individual's maximum force.

Stimuli were always presented in pairs, either unimodally (two visual or two tactile), presented sequentially or crossmodally (one visual and one tactile), presented simultaneously. In Study 2, participants were instructed to always respond to both stimuli, yielding three conditions: visual (V), tactile (T), and visual + tactile (VT). In Study 3, the identical VT condition was collected as well as two additional crossmodal conditions where participants were instructed to respond to only one of the stimuli: visual + tactile respond visual (Vt), and visual + tactile respond tactile (vT).

3.3.3 Experimental design

Stimuli were presented for 1 second followed by a 1 second delay, at which point a 500ms cue was given to signal participants to make their motor response during a 2.5 second window prior to the start of the next trial, for a total of 5 seconds per trial. Each task condition was performed in 2 blocks of 75 trials with each block lasting 5 minutes. The order of the task conditions was counter-balanced across subjects.

3.3.4 Stimuli

Visual stimuli consisted of a centrally-presented horizontal bar (6 cm wide) at varying heights representing different amplitudes. Visual stimuli were displayed on a computer monitor positioned 50 cm in front of the subject. Vibrotactile stimuli consisted of discrete vibrations delivered by a custom-made vibrotactile device applied to the volar surface of the left index finger. Vibrotactile stimulation was controlled by converting digitally generated waveforms to an analog signal (DAQCard 6024E, National Instruments, Austin, Texas) and then amplifying the signal (Bryston 2B-LP, Peterborough, Ontario) using a custom program written in LabVIEW (version 8.5, National Instruments, Austin, Texas). Varying the amplitude of the driving voltage to the vibrotactile device produced proportional changes in vibration of the device on the finger. The amplitude of each discrete vibration was constant within a trial and varied randomly between trials. The average stimulus amplitude across all 75 trials of a block did not differ between the experimental conditions. The frequency of the vibration was held constant at 25 Hz. Participants received 70 dB whitenoise (Stim2, Neuroscan, Compumedics USA, Charlotte NC) throughout the experiment to prevent auditory perception of the vibrotactile stimulus.

3.3.4 Data acquisition & recording parameters

EEG data was recorded from 32 electrode sites (32 channel Quick-Cap, Neuroscan, Compumedics USA) in accordance with the international 10-20 system for electrode placement, and referenced to the linked mastoids (impedance <5 kohms). EEG data were amplified (20 000x), filtered (DC-200 Hz) and digitized at 500 Hz (Neuroscan 4.3, Compumedics USA) before being saved for subsequent analysis. Individual traces were band-pass filtered (0.1-30 Hz) and visually inspected for artifacts (i.e. blinks, eye movements, or muscle contractions). Any contaminated epochs were eliminated before averaging.

Event-related potentials were averaged to the onset of each stimulus relative to a 100 ms pre-stimulus baseline. Somatosensory ERPs were measured from individual participant averages for each task condition. Mean ERP amplitudes and latencies were computed for each subject within specified time windows centered around the post-stimulus latencies of early somatosensory ERP components: P50 (40-70ms), P100 (80-140ms), N140 (150-200ms) and P230 (210-260ms). Figures 1 and 4 illustrate the distribution of these potentials. Amplitude and latency of the P50 component was measured from C4, CP4, and P4 electrode sites, located over right sensory-motor and parietal cortex, contralateral to the vibrotactile stimulus. The P100 is typically observed bilaterally at parietal electrode sites thus amplitude and latency of this component was measured from C3, CZ, C4, CP3, CPZ, CP4, P3, PZ, and P4. The N140 and P230 have multiple generators and broad distributions and can be recorded at frontal and parietal electrode sites; therefore for these components amplitude and latency were measured from midline electrode sites FCZ, CZ, CPZ, and PZ. All amplitudes were measured as raw voltage relative to the pre-stimulus baseline. Tables 1 and 2 list mean amplitudes for ERP components across task conditions for Experiments 2 and 3.

3.3.5 Data analysis

ERP data analysis

To test the hypothesis of Study 2 that early modality-specific EP components would be modulated by the crossmodal task, a one-way repeated measures ANOVA was carried out on the amplitude of the P50 component at electrode site CP4 (contralateral to vibrotactile stimulation) with task as a factor. In Study 3 an ANOVA with contrasts was also performed to test the hypothesis that modulation of the P50 would only be observed in the task where both stimuli were task-relevant.

For both Experiments 2 and 3, ANOVAs with task as a factor were also carried out on both the amplitude and latency of the P100 at CZ and PZ, the N140 at FCZ and PZ, and the P230 at FCZ and PZ to test for effects of task on each potential. Post-hoc tests were carried out on any main effects to test the hypothesis that the crossmodal task would be associated with greater amplitudes compared to the unimodal tasks.

Behavioural data analysis

Behavioural data was analyzed by summing the amplitudes of the two target stimuli and comparing this to the amplitude of the response. The force applied to the bulb forced air through a rubber tube in a closed system, inducing a change in pressure that was measured by a pressure sensor and converted to a voltage. There was a linear relationship between the pressure measurement and the voltage produced. The absolute percent difference between the summed target stimulus amplitude (i.e. the voltage of the 2 stimuli added together) and the actual response amplitude (in volts) was calculated and a repeated measures ANOVA was conducted to assess statistical differences across the experimental conditions.

3.4 Results

3.4.1 Study 2

P50

All subjects demonstrated a clear P50 component (mean latency 56 +/- 3 ms) in response to vibrotactile stimuli and this potential was maximal at electrode site CP4, overlying contralateral somatosensory cortex. As illustrated in Figure 1, the P50 component is only present at contralateral electrode sites and this suggests that the P50 reflects somatosensory processing of the vibrotactile stimulus. As such, there was no measurable P50 in the visual task condition. A task-related modulation of the P50 was revealed by a one-way repeated measures ANOVA ($F_{1,10} = 13.944$, $p= 0.003$). As illustrated in Figure 2A, the crossmodal task (VT) was associated with greater P50 amplitude than the tactile task.

P100

The P100 component was present in all task conditions (mean latency 112 +/- 6 ms) with a bilateral distribution at central and parietal sites and maximal amplitude at electrode site PZ. Figure 2B reveals the effect of task observed at PZ ($F_{2,20} = 11.6$, $p= 0.001$). Post-hoc tests show that the amplitude of the P100 was larger in the VT task compared to the visual task ($p=0.001$) and the tactile task ($p=0.008$)

N140

The N140 component was observed in all task conditions (mean latency at FCZ: 161 +/- 5 ms, at PZ: 178 +/- 6 ms) and although measurable at both frontal and parietal sites, significant effects of task were seen only at parietal sites: P3 ($F_{2, 20} = 5.754$, $p= 0.011$), PZ ($F_{2,20} = 3.706$, $p= 0.045$), and P4 ($F_{2, 20} = 6.367$, $p= 0.007$). Task-related effects at FCZ and PZ are illustrated in Figure 2C and E. Post-hoc tests revealed that at FCZ the VT task was associated with greater negativity than the visual task ($p=0.01$) but there was no difference in amplitude between the VT task and the tactile task ($p>0.05$). At PZ, the VT task was associated with greater negativity than the tactile task ($p=0.01$), but there was no difference between the VT task and the visual task ($p>0.05$).

P230

The P230 component was present across all 3 tasks (mean latency at FCZ: 240 +/- 6 ms, at PZ: 250 +/- 7 ms) and was broadly distributed but showed peak amplitude at electrode site PZ. Figure 2F shows the effect of task ($F_{2,20} = 6.243$, $p=0.008$), and post-hoc tests revealed that the VT task was associated with a larger P230 amplitude than the tactile task ($p=0.005$) but there was no difference between the VT task and the visual task ($p>0.05$).

Behavioural data

A one-way repeated measures ANOVA was performed on the error differences across all three task conditions and yielded no main effect ($F_{2,20}=0.070$, $p>0.05$). Thus all tasks were performed with equivalent accuracy as illustrated in Figure 3.

3.4.2 Study 3

P50

A clear P50 component was observed in all 3 task conditions in Study 3 and peak amplitude of this component was recorded at CP4, at a mean latency of 57 +/- 4 ms. As in Study 2, the P50 was only evident at electrode sites contralateral to the vibrotactile stimulus as shown in Figure 4. Figure 5A illustrates the main effect of task

($F_{2,18} = 4.709$, p=0.023) and planned contrasts revealed that the amplitude of the P50 was larger for the respond to both task (VT) compared to the respond to tactile task (vT) (p=0.006) and the respond to visual task (Vt) (p=0.02).

P100

As in Study 2, the P100 was bilaterally distributed at central and parietal sites and was present in all task conditions. No task-related effects on amplitude were observed at any electrode sites, however there was a main effect of task on latency of the P100 at C3 ($F_{2,18} = 3.97$, p=0.037), and C4 ($F_{2,18} = 5.69$, p=0.012). Table 3 lists the latencies for the P100 at C3 and C4 across tasks and shows that the P100 peaked later in the VT task compared to the respond tactile and respond visual tasks and post-hoc tests demonstrate that these differences were statistically significant (p<0.05 for both comparisons).

N140

The N140 was measurable in all task conditions at both frontal and parietal electrode sites (mean latency at FCZ: 158 +/- 4 ms, at PZ: 184 +/- 4 ms). There was a main effect of task on N140 amplitude at FCZ ($F_{2,18} = 5.377$, p=0.015). As illustrated in Figure 5C, post-hoc tests revealed a difference between the VT and respond visual tasks (p=0.01) such that the respond visual task was associated with greater N140 amplitude.

P230

Similar to Study 2, the P230 was broadly distributed across frontal and parietal electrode sites (mean latency at FCZ: 242 +/- 4 ms, at PZ: 244 +/- 5 ms). However in Study 3 no task-related effects were observed on amplitude or latency.

Behavioural data

A one-way repeated measures ANOVA was performed on the error differences across all three task conditions and yielded no main effect ($F_{2,18}$=.0,908 $p>0.05$). Figure 6 illustrates that as in Study 2, all tasks in Study 2 were performed with equivalent accuracy.

3.5 Discussion

This study set out to first probe the timing of crossmodal modulation within somatosensory cortex and subsequently to determine the role of task-relevance in mediating the modulatory effects of crossmodal stimuli. We hypothesized that a crossmodal task, requiring the use of both tactile and visual stimuli to plan and execute a motor task, would be associated with larger amplitudes in early somatosensory ERP components compared to a unimodal task. We further hypothesized that this enhancement would only be observed when both visual and tactile stimuli were relevant to the task. Both hypotheses were supported by the data as several ERP components showed task-related modulations reflecting sensitivity to both modality and relevance of the stimuli.

Early modality specific effects

In both Experiments 2 and 3, amplitude of the P50 component was modulated by the task conditions. The results of Study 2 suggest that this component is sensitive to crossmodal (visual) stimuli, as reflected by increased amplitude when visual and vibrotactile stimuli were presented simultaneously. Further to this, the results of Study 3 suggest that the somatosensory P50 component is only modulated by crossmodal stimuli when both stimuli are relevant to the behavioural task, and not when one is irrelevant. In other words, the presence of visual stimuli is not adequate to upregulate the P50; instead it is a top-down mechanism that drives this modulation.

The cortical generators of somatosensory ERP components are a matter of some debate, but the P50 typically varies in latency between 40 and 60 ms post-stimulus and is restricted to contralateral parietal electrodes (Desmedt et al., 1983). An MEG study by Zhu et al. (2007) localized the early contralateral response to tactile stimuli occurring at 45 ms to the posterior wall of the central sulcus (Zhu et al., 2007). Modulation of the P50 component is typically thought to be reflective of changes in excitability within SI, but precisely what this potential represents in terms of the processing of somatosensory stimuli is not yet known. Desmedt et al. (1989) reported on the cognitive P40, which has a similar latency and distribution to the P50 observed in the current study, and they suggested that it may represent a form of priming for the detection of infrequent targets in streams of somatosensory stimuli, but it was later shown that this potential can also be elicited by non-target stimuli and streams of identical stimuli (Desmedt and Tomberg, 1989). It has been suggested that the early latency of this potential makes it unlikely to reflect processing of the evoking stimulus but instead is more likely to reflect cognitive strategies being applied to the processing of the sensory inputs at an early stage, presumably via reciprocal thalamo-cortical networks (Brunia, 1993; Desmedt and Tomberg, 1989; Yingling and Skinner, 1976). This explanation provides a possible mechanism for task-relevant modulation of the P50 whereby relevant inputs receive enhanced early processing, mediated via thalamo-cortical sensory gating mechanisms.

In support of this idea, there are a number of studies that have shown the somatosensory P50 to be modulated by attention. Early findings using electrical stimuli reported attention effects slightly later, at 80 ms post-stimulus (Desmedt and Robertson, 1977; Michie et al., 1987), and a more recent study of transient spatial attention by Eimer & Forster reported modulation at a similar latency using vibrotactile stimuli when stimuli were applied to both hands and attention was sustained to one hand only (Eimer and Forster, 2003). Zopf et al. (2004) found an effect of transient versus sustained attention at 45-50ms post-stimulus (Zopf et al., 2004) and a recent study by Schubert et al. (2008) reported effects of spatial selective attention at a similar latency (Schubert et al., 2008). The reason for these discrepancies in latency is not yet known but is likely related to the characteristics of the stimuli (i.e. mechanical vs electrical) and the demands of the task. For example there has been some speculation that the latency of attention effects may be mediated by the difficulty of the task, such that tasks requiring greater attentional resources might be associated with earlier modulation (Schubert et al., 2008).

The crossmodal modulation of P50 observed in the current study is inline with previous ERP studies finding evidence of crossmodal effects in auditory EPs at early latencies (Foxe et al., 2002; Molholm et al., 2002; Murray et al., 2005). Reports of crossmodal modulation on the somatosensory P50 are rare, however a study by Meehan et al. reported effects on this potential during a crossmodal attention task. SEPs to median nerve stimulation were collected while subjects received simultaneous visual and vibrotactile stimuli and were instructed to track one modality and ignore the other (Meehan and Staines, 2009). The distractor stimulus was also manipulated such that it either matched the relevant stimulus or did not, but in either case subjects were instructed to ignore it and track only the relevant stimulus. In the task condition where subjects tracked the vibrotactile stimulus, the P50 increased in amplitude when the visual distractor stimulus was congruent with the tactile stimulus. This result must be interpreted cautiously as it is unknown whether subjects were aware that the stimuli were synchronous and thus difficult to know whether they adjusted their cognitive strategy for performing the task. However, one interpretation of this finding could be that the amplitude of the P50 increased when subjects could rely on both visual and tactile stimuli to perform the task, which would support our contention that the P50 is sensitive to the combination of crossmodal and behaviourally relevant stimuli.

In Study 2, amplitude of the P100 component was modulated by simultaneously presented crossmodal stimuli at bilateral parietal electrode sites. In Study 3, where all task conditions involved simultaneous bimodal stimuli, P100 amplitude did not differ between tasks. This finding is suggestive that the P100 is sensitive to the presence of bimodal stimuli, but not to the task-relevance of those stimuli. Also of interest, in Study 3 the P100 showed a latency shift at bilateral central sites such that it peaked an average of 15 ms later, at 126 (+/4) ms when both stimuli were relevant. This latency shift is in contrast to Study 2, where the mean latency of the P100 did not differ across task conditions and peaked at an average of 112 (+/6) ms. Latency shifts in ERPs are thought to reflect modulations in the speed of neural processing, such that an earlier latency would reflect a shorter time to reach maximal synchronized neural activity (Gazzaley et al. 2005). This explanation would suggest that in Study 3, the requirement to attend to both stimuli was associated with a slowing in neural processing at the P100 latency. Similarly, this shift was not observed in Study 2 because all task conditions required attention to two stimuli.

Topographic distribution of the P100, which is analogous to the P1 component often reported in ERP studies, typically starts over the contralateral posterior parietal scalp and extends towards the ipsilateral and frontal electrode sites (Desmedt and Tomberg, 1989) and this potential is thought to be generated in bilateral secondary somatosensory cortex (SII) (Gu, 2002; Mima et al., 1998). The P100 has been reported to be sensitive to effects of attention (Desmedt et al., 1983; Eimer and Forster, 2003; Josiassen et al., 1982; Kida et al., 2004b; Michie et al., 1987; Schubert et al., 2006), and if this potential is indeed generated in SII then these results align with functional imaging studies showing modulation of SII when attention is directed towards tactile stimuli (Johansen-Berg et al., 2000; Meyer et al., 1991; Nelson et al., 2004; Staines et al., 2002). While the effects of attention on the P100 appear fairly consistent, studies investigating crossmodal influences on mid-latency components fail to report any effects on this potential (Eimer and Driver, 2000; Eimer, 2001). However, these studies have employed tasks with different demands from the current study, namely oddball detection tasks requiring subjects to monitor both hands for deviant stimuli in one modality while ignoring the other, and report them with a verbal response. In contrast, in both experiments of the current study, the requirement to make a graded force response with the hand presents an entirely different task that while still requiring attention to the attributes of the stimuli, also requires judging two simultaneously presented stimuli and planning the appropriate motor response.

Interestingly, in Study 3 the amplitude of the P100 was unaffected by whether subjects attended to one or both of the crossmodal stimuli. However this result is inline with MEG evidence showing an increased SII response during active attention to somatosensory stimuli, even while ignoring stimuli of another modality (Fujiwara et al., 2002). Thus it seems possible that the increased P100 amplitude observed in the VT condition in Study 2 reflects a crossmodal modulation of somatosensory cortex and may be related to the requirement to use the stimuli to plan a motor response. In addition, the results of Study 3 suggest that this may be a generalized crossmodal enhancement that is not specific to which modality is relevant.

Longer latency effects

In Study 2, the N140 component was larger in amplitude in the crossmodal task compared to the unimodal tactile task, and this effect was only observed at parietal electrode sites. In Study 3, the manipulation of task-relevance was associated with modulation of N140 amplitude at a fronto-central electrode site. At FCZ, the tasks requiring selective attention to one stimulus showed greater N140 amplitude than the task where both stimuli were relevant to the behavioural task. With respect to the P230, in Study 2 the P230 component was maximal at electrode site PZ and was sensitive to the presentation of bimodal stimuli such that the crossmodal task was associated with larger P230 amplitude than the unimodal tactile task. No task-related effects were observed for the P230 in Study 3, although it was measurable across tasks, which is suggestive that this component may reflect task-relevance but is not sensitive to manipulations of relevance involving crossmodal stimuli.

The somatosensory N140 is evoked by tactile and electrical stimuli in association with cognitive tasks and typically occurs at latencies between 100 and 180 ms (Allison et al., 1992; Desmedt and Robertson, 1977; Josiassen et al., 1990). It overlaps temporally with the N1 component often referred to in visual and auditory ERP studies. The topography of this large negative deflection most often begins over the contralateral frontal electrodes and extends towards the midline and ipsilateral sides. The prevailing thought on the generators of the N140 is that it reflects activation of prefrontal cortex, an area that is known to play a role in retrieving and maintaining representations of stimulus relevancy in relation to behavioural goals (Allison et al., 1991; Desmedt and Tomberg, 1989; Knight et al., 1995; Pardo et al., 1991a), however the bilateral distribution of the N140 has also prompted some researchers to suggest a generator in SII (Frot and Mauguiere, 1999). There are consistent findings that attention to tactile stimuli modulates the N140 (Eimer and Driver, 2000; Eimer and Driver, 2001; Eimer and Forster, 2003; Kida et al., 2004a; Kida et al., 2004b; Michie et al., 1987) such that selective attention to a tactile stimulus is associated with increased N140 amplitude.

In terms of crossmodal effects on the N140, several studies have investigated the effects of crossmodal attention on somatosensory ERPs (Eimer and Driver, 2000; Eimer, 2001; Hotting et al., 2003; van Velzen et al., 2002). In these experiments tactile stimuli were interspersed with visual or auditory stimuli while subjects attended to a particular location and modality and ignored stimuli in the irrelevant modality. In line with previous findings, when touch was relevant the N140 component was enhanced when tactile stimuli were delivered to the attended hand. When touch was irrelevant and subjects attended to visual stimuli, no attentional modulations were observed in somatosensory ERP components. However, when subjects attended to visual stimuli and also had to monitor for and respond to rare tactile stimuli, modulations were observed in the form of enhanced negativity between 140 and 200 ms post-stimulus. These results suggest that tactile processing is unaffected by vision when the tactile information is task-irrelevant and can be ignored entirely, but that vision exerts a crossmodal influence on touch when both stimuli have the potential to be relevant. In Study 2 a similar modulation was observed at parietal electrode sites where increased N140 amplitude was observed in the VT task compared to the unimodal task, suggesting that the requirement to attend to both visual and tactile stimuli modulates this component.

The results of Study 3 show no difference in amplitude at parietal sites among the three crossmodal conditions, regardless of whether one or both stimuli were relevant to the task. In contrast, at fronto-central site FCZ, the tasks requiring selective attention to one of the crossmodal stimuli were associated with larger N140 amplitudes than the task requiring attention to both. It is possible that the different pattern of N140 results observed at frontal and parietal electrode sites is related to the multiple generators associated with this component, such that the frontal contributors are more sensitive to the selective crossmodal attention aspect of the task than the parietal areas, which based on the results of Experiments 2 and 3 may be more sensitive to the presence of crossmodal stimuli.

The topographical distribution and latency of the ERP components evoked by somatosensory stimuli provide strong evidence for the sequential involvement of postcentral, parietal, and prefrontal cortices in processing tactile stimuli. The results of the current study suggest that the relevance of tactile stimuli to behaviour and the presence of a simultaneous crossmodal stimulus exert influences on the somatosensory processing stream in different ways at different latencies, which reflects differences in the underlying neural generators that contribute to each component. This study extends previous findings of crossmodal interactions by providing evidence that crossmodal effects can be seen at very early latencies in the processing stream. In addition, these results show that early modulatory effects are mediated by the relevancy of the stimuli to behaviour, which suggests the involvement of a sensory-gating mechanism in biasing the processing of relevant stimuli over irrelevant ones in a task-relevant manner.

3.6 Conclusion

Crossmodal effects on modality-specific ERP components are mediated by the task-relevance of the stimuli. At mid-latency components the effect of task-relevance varies topographically with frontal sites being more sensitive to irrelevant stimuli.

3.7 Figures & tables

Table 1 - Study 2 ERP amplitudes (μv)

	CP4 P50	PZ P100	N140	P230	FCZ N140	P230
VT	1.88 (0.37)	2.49 (0.24)	-2.86 (0.57)	3.44 (0.32)	-3.56 (0.75)	2.14 (0.47)
T	0.65 (0.18)	1.25 (0.26)	-1.38 (0.46)	1.72 (0.36)	-2.34 (0.55)	1.63 (0.31)
V	n/a	0.96 (0.19)	-2.33 (0.42)	2.53 (0.44)	-2.49 (0.49)	2.46 (0.49)

Table 1: Mean amplitude (+/- SEM) in microvolts (μv) of ERP components recorded from electrode sites CP4, PZ, and FCZ for each task condition: visual + tactile (VT), tactile (T), and visual (V).

Table 2 - Study 3 ERP amplitudes (μv)

	CP4 P50	PZ P100	N140	P230	FCZ N140	P230
VT	1.19 (0.35)	1.44 (0.33)	-2.96 (0.29)	4.49 (0.89)	-2.1 (0.69)	3.42 (0.66)
vT	0.57 (0.28)	1.7 (0.12)	-2.49 (0.34)	3.43 (0.83)	-3.39 (0.45)	3.42 (0.53)
Vt	0.66 (0.21)	1.45 (0.23)	-3.06 (0.2)	2.68 (0.61)	-3.75 (0.48)	3.34 (0.66)

Table 2: Mean amplitude (+/- SEM) in microvolts (μv) of ERP components recorded from electrode sites CP4, PZ, and FCZ for each task condition: visual + tactile (VT), respond tactile (vT), and respond visual (Vt).

Table 3 – Study 3 ERP latencies (ms)

	C3 P100	C4 P100
VT	126 (4)	124 (5)
vT	116 (5)	110 (4)
Vt	117 (3)	113 (5)

Table 3: Mean latency (+/- SEM) in milliseconds (ms) of ERP components recorded from electrode sites C3 and C4 for each task condition: visual + tactile (VT), respond tactile (vT), and respond visual (Vt).

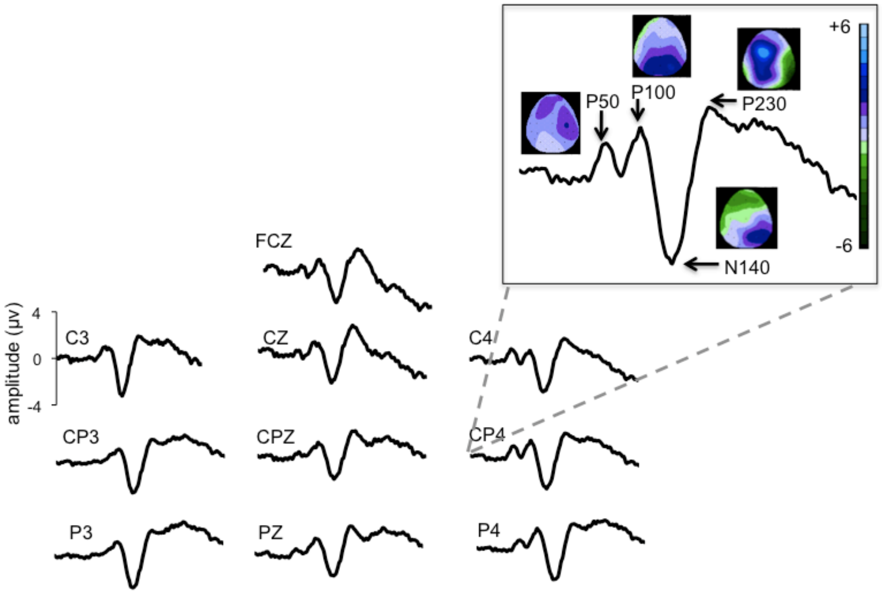


Figure 1
Grand average waveforms in Study 2 (N=11) for the visual + tactile (VT) task condition at central and parietal electrode sites. ERP components of interest are labeled on the trace for electrode site CP4, shown in the inset, indicating the latency and topographical distribution of each component. Electrode sites on the right are contralateral to vibrotactile stimulation.

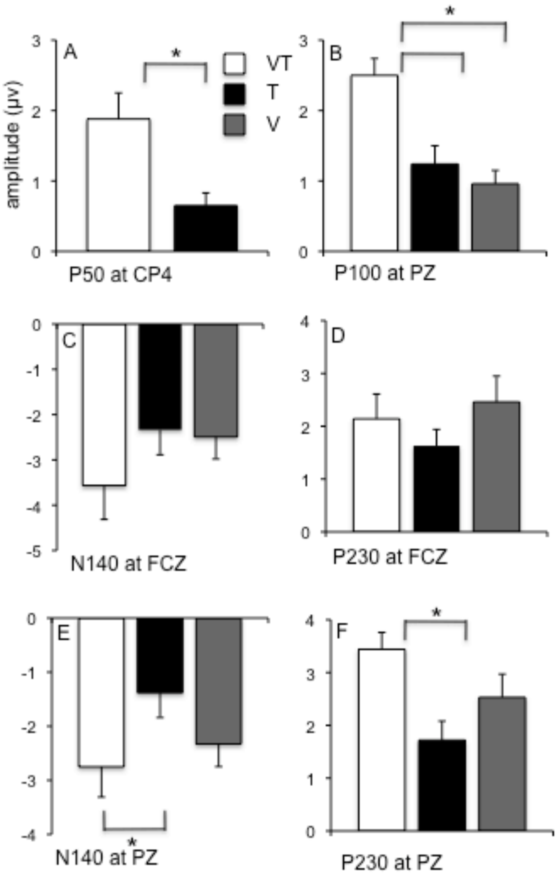


Figure 2
Group means for Study 2 (n=11). White bars represent group data for the visual + tactile task condition (VT), black bars represent group data for the tactile task condition (T), and grey bars represent group data for the visual task condition (V). Error bars show SEM, * denotes significance $p<0.05$. (A) shows the mean P50 amplitude measured at CP4, (B) depicts the mean P100 amplitude at PZ, (C) and (E) show mean 140 amplitudes measured at FCZ and PZ respectively, and (D) and (F) show the mean P230 amplitudes at FCZ and PZ respectively.

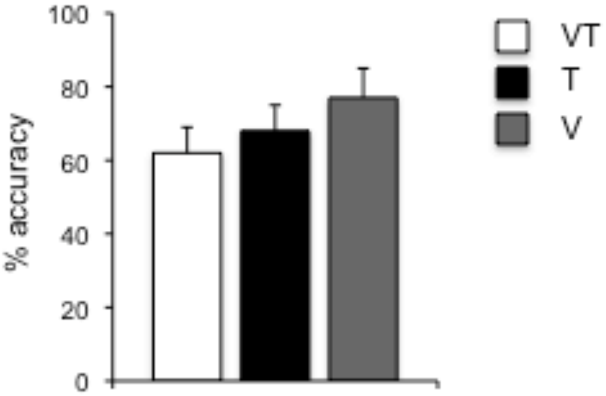


Figure 3
Group means for Experiment 1 (n=11). Percent accuracy is shown on the y-axis. White bars represent group data for the visual + tactile task condition (VT), black bars represent group data for the tactile task condition (T), and grey bars represent group data for the visual task condition (V). Error bars show SEM

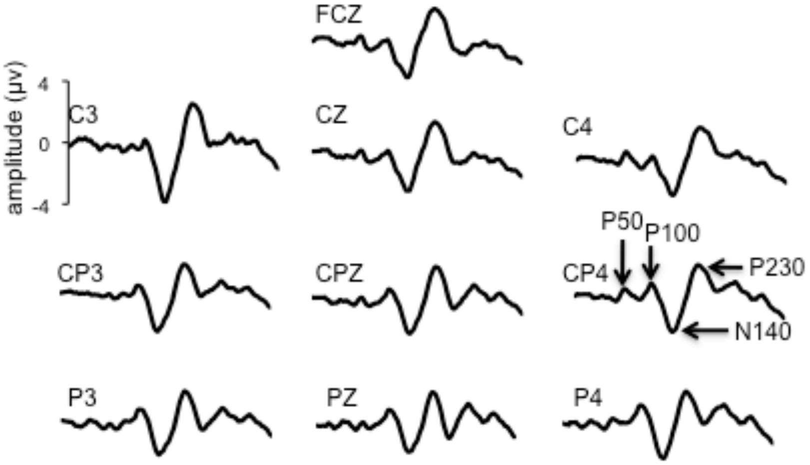


Figure 4
Grand average waveforms in Study 3 (n=10) for the visual + tactile (VT) task condition at central and parietal electrode sites. Latencies of ERP components of interest are labeled on the CP4 trace. Electrode sites on the right are contralateral to vibrotactile stimulation.

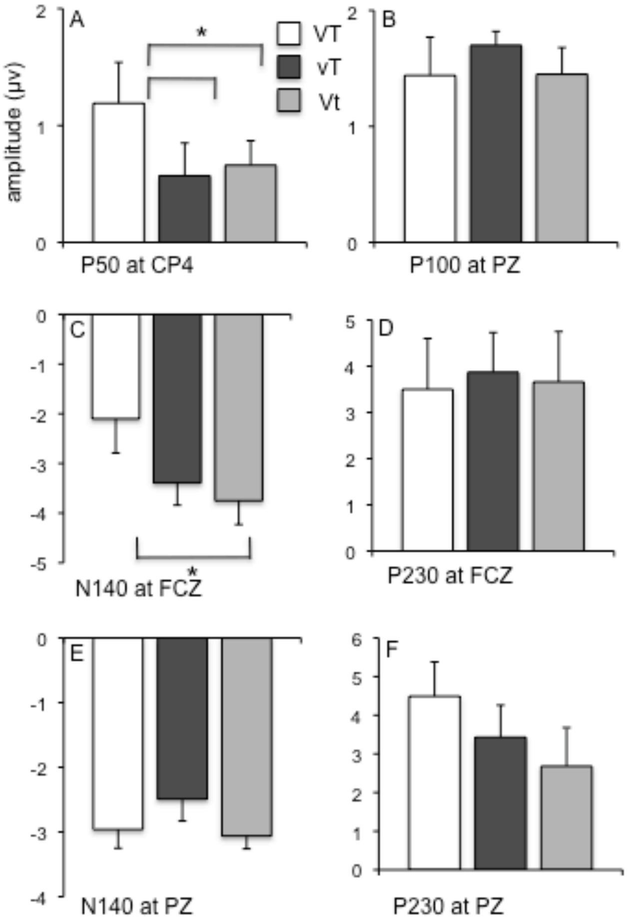


Figure 5
Group means for Study 3 (n=10). White bars represent group data for the visual + tactile task condition (VT), dark grey bars represent group data for the respond tactile task condition (vT), and light grey bars represent group data for the respond visual task condition (Vt). Error bars show SEM, * denotes significance $p<0.05$. (A) shows the mean P50 amplitude measured at CP4, (B) depicts the mean P100 amplitude at PZ, (C) and (E) show mean 140 amplitudes measured at FCZ and PZ respectively, and (D) and (F) show the mean P230 amplitudes at FCZ and PZ respectively.

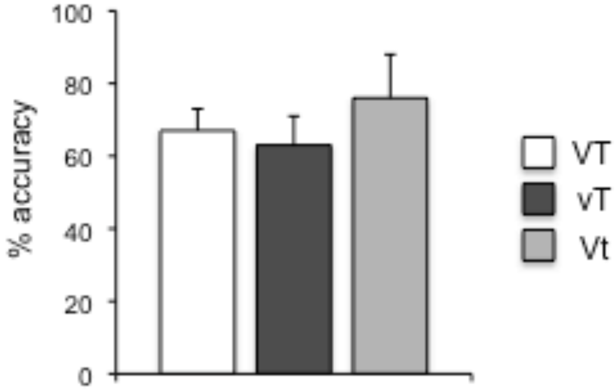


Figure 6
Group means for Study 3 (n=10). Percent accuracy is shown on the y-axis. White bars represent group data for the visual + tactile task condition (VT), dark grey bars represent group data for the respond tactile task condition (vT), and light grey bars represent group data for the respond visual task condition (Vt). Error bars show SEM.

Chapter 4 – Study 4: Task-relevance, crossmodal effects, and response requirements modulate somatosensory event-related potentials.

4.1 Overview

The first three studies of this thesis have reliably shown that the somatosensory P50 is sensitive to the presence of a visual stimulus when it occurs simultaneously with a tactile stimulus, and only when both are relevant to performing a motor task. However previous studies of crossmodal effects on somatosensory ERPs do not consistently show effects on the P50 (Taylor-Clarke et al., 2002, Eimer and van Velzen, 2005, Schurmann et al., 2006). There has been some speculation that task difficulty or the amount of attention required to perform a task is associated with modulation at earlier latencies (Schubert et al 2009), and with this in mind Study 4 set out to determine if task requirements, specifically the degree to which the motor response relies on extracting features of the stimulus, mediates P50 modulation by crossmodal stimuli. It was hypothesized that crossmodal enhancement of task-relevant stimuli is dependent on the specific task demands and will be greater in a graded motor task compared to detection and discrimination tasks. Streams of crossmodal (visual and tactile) and unimodal (tactile) stimuli were presented and participants were instructed to pay attention to one type of stimuli and perform one of three tasks: detect, judge, or grade. ERPs were time-locked to the onset of each stimulus and mean ERP amplitudes and latencies were extracted for the P50, P100, and N140. Crossmodal effects were observed on the P50, replicating previous studies. Further to this, effects of task and interaction of task and modality were also significant, and the graded motor task was associated with crossmodal modulation but the other tasks were not. This finding provides support for the hypothesis that crossmodal effects on the P50 are dependent on the requirements of the motor task. Effects of task were also seen at the P100, but crossmodal effects were not, and in this case the graded task was associated with smaller amplitudes. For the N140, different effects were seen at parietal and frontal sites. At parietal site PZ the detection task was associated with greater negativity regardless of modality. At frontal site FCZ the graded task was associated with greatest amplitude in both unimodal and crossmodal conditions.. These results suggest that a) crossmodal modulation of sensory-specific ERP components is dependent on specific task requirements and b) frontal and parietal contributions to the N140 are both sensitive to task requirements but these effects go in opposite directions, with the parietal component being most responsive to the detection task and the frontal component more sensitive to the graded task.

4.2 Introduction

Excitability of somatosensory cortex is modulated by the relevance of stimuli to behaviour, with the goal of facilitating the extraction of relevant sensory information for further cortical processing. The modulation of movement-related gating provides evidence that SI is sensitive to the relevance of somatosensory stimuli to behaviour. Movement-related gating is seen when SEP components to passive somatosensory stimuli are attenuated during movement (Cheron and Borenstein, 1991; Jones et al., 1989). Interestingly, this gating effect is lifted, at least partially, when the stimuli are made relevant to the performance of a task (Staines et al., 1997; Staines et al., 2000). In a non-gating context, recent ERP findings (Dionne et al, 2010, submitted) provide evidence that task-relevance of stimuli facilitates crossmodal modulation of early somatosensory-specific ERP components, namely the P50. These results are novel as crossmodal effects on the somatosensory P50 have not been previously reported, and even attentional modulation of this potential is not consistently observed (Desmedt and Robertson, 1977; Eimer and Forster, 2003; Michie et al., 1987; Schubert et al., 2008; Zopf et al., 2004). Part of the difficulty in reconciling the inconsistent reports of P50 modulation can be attributed to a lack of clarity in what it represents. Although the P50 is typically thought to reflect SI excitability, early reports on SEPs suggested that the latency of this potential makes it unlikely to reflect processing of the evoking stimulus, but instead is more likely to represent the application of cognitive strategies to stimulus processing (Desmedt and Tomberg, 1989). If this is the case, then modulation of the P50 could be highly dependent on elements of the task that contribute to the strategy used by the subject, which could account for the lack of consensus on modulation of this potential across different tasks and paradigms. With this in mind, the objective of the current study was to investigate the role of task requirements in mediating the previously observed crossmodal modulation of P50. It was predicted that P50 modulation would be dependent on task demands, specifically modulation will scale with the degree of stimulus feature extraction required to execute the motor response. To manipulate this relationship between stimulus and response three tasks were chosen to represent a gradient of reliance on the attributes of the stimulus to inform the motor response: a detection task, a discrimination task, and a graded motor task. It was hypothesized that the P50 would only be sensitive to crossmodal modulation in the graded motor task. Based on previous findings that the N140 at frontal electrode sites is sensitive to the task-relevance of stimuli, it was also predicted that the frontal N140 would scale with the increased demand to extract sensory information and incorporate it into a motor response.

4.3 Methods

4.3.1 Subjects

Electroencephalography (EEG) was collected from 10 healthy participants (mean age = 24, 3 males). Experimental procedures were approved by the University of Waterloo Office of Research Ethics. All subjects provided informed written consent.

4.3.2 Behavioural task

Three versions of the behavioural task were performed, although the stimuli were identical throughout and consisted of a stream of pseudorandomly intermixed unimodal (tactile paired with tactile, T) stimuli and crossmodal (tactile paired with visual, VT) stimuli. In the “detect” task participants were instructed to press a button with their right index finger when they detected the target stimulus (detect T or detect VT). In the “judge” task, participants were required to discriminate between the two target stimuli (judge T or judge VT) and press pre-assigned buttons to indicate which one they perceived as larger in amplitude. The “grade” task required participants to judge the amplitude of the target stimuli and make a graded motor response to represent the sum of these amplitudes by squeezing a pressure-sensitive bulb with their right hand (grade T or grade VT).

Prior to the EEG collection participants underwent a 5-minute training session with visual feedback to learn the relationship between the amplitudes of the stimuli and the corresponding force required to apply to the bulb. During training, a horizontal target bar appeared on the visual display and subjects were instructed to squeeze the pressure-sensitive bulb with enough force to raise another visual horizontal bar to the same level as the target bar. At the same time, as subjects applied force to the bulb with their right hand the vibrotactile device vibrated against the volar surface of their left index finger with corresponding changes in amplitude, i.e. as they squeezed harder on the bulb the amplitude of the vibration increased proportionately. Subjects were instructed to pay attention to these changes in amplitude as they related to the force they were applying to the bulb, and in this way subjects became familiar with the relationship between the vibrotactile stimulus amplitude and the corresponding force applied to the bulb. To control for force-related trial-to-trial differences, stimulus amplitudes were scaled such that no single stimulus required a squeeze of more than 25% of an individual's maximum force, thus the response for adding two stimuli was never more than 50% of an individual's maximum force.

4.3.3 Experimental design

Paired tactile stimuli were presented for 500 ms each, separated by a 300 ms inter-stimulus interval. Paired visual and tactile stimuli were presented for 1 second simultaneously. A trial consisted of one set of paired stimuli followed by 2.5 s for the participant to make a response prior to the onset of the next pair of stimuli. Each task condition was performed in 2 blocks of 70 trials (35 T, 35 VT in each block). The order of the six task conditions was counter-balanced across subjects.

4.3.4 Stimuli

Visual stimuli consisted of a centrally-presented horizontal bar (6 cm wide) at varying heights representing different amplitudes. Visual stimuli were displayed on a computer monitor positioned 50 cm in front of the subject. Vibrotactile stimuli consisted of discrete vibrations delivered by a custom-made vibrotactile device applied to the volar surface of the left index finger. Vibrotactile stimulation was controlled by converting digitally generated waveforms to an analog signal (DAQCard 6024E, National Instruments, Austin, Texas) and then amplifying the signal (Bryston 2B-LP, Peterborough, Ontario) using a custom program written in LabVIEW (version 8.5, National Instruments, Austin, Texas). Varying the amplitude of the driving voltage to the vibrotactile device produced proportional changes in vibration of the device on the finger. The amplitude of each discrete vibration was constant within a trial and varied randomly between trials. The average stimulus amplitude across all 75 trials of a block did not differ between the experimental conditions. The frequency of the vibration was held constant at 25 Hz. Participants received 70 dB whitenoise (Stim2, Neuroscan, Compumedics USA, Charlotte NC) throughout the experiment to prevent auditory perception of the vibrotactile stimulus.

4.3.5 Data acquisition & recording parameters

EEG data was recorded from 32 electrode sites (32 channel Quick-Cap, Neuroscan, Compumedics USA) in accordance with the international 10-20 system for electrode placement, and referenced to the linked mastoids (impedance <5 kohms). EEG data were amplified (20 000x), filtered (DC-200 Hz) and digitized at 500 Hz (Neuroscan 4.3, Compumedics USA) before being saved for subsequent analysis.

Individual traces were band-pass filtered (0.1 - 30 Hz) and visually inspected for artifacts (i.e. blinks, eye movements, or muscle contractions). Any contaminated epochs were eliminated before averaging.

Event-related potentials were averaged to the onset of each stimulus relative to a 100 ms pre-stimulus baseline. Somatosensory ERPs were measured from individual participant averages for each task condition. Mean ERP amplitudes and latencies were computed for each subject within specified time windows centered around the post-stimulus latencies of early somatosensory ERP components: P50 (40-70ms), P100 (80-140ms), and N140 (150-200ms). Figures 1 and 4 illustrate the distribution of these potentials. Amplitude and latency of the P50 component was measured from electrode site CP4 located over right sensory-motor cortex, contralateral to the vibrotactile stimulus. The P100 is typically observed bilaterally at parietal electrode sites thus amplitude and latency of this component was measured from P3, PZ, and P4. The N140 has multiple generators and broad distributions and can be recorded at frontal and parietal electrode sites; therefore for this component amplitude and latency were measured from midline electrode sites FCZ, and PZ. All amplitudes were measured as raw voltage relative to the pre-stimulus baseline. Table 1 lists ERP amplitudes for each potential across electrode sites.

4.3.6 Data analysis

ERP data analysis

To test the hypothesis that crossmodal effects will be mediated by task demands, a two-way repeated measures ANOVA was carried out on the amplitude of the P50 component with task (3 levels: detect, judge, grade) and modality (2 levels: unimodal, crossmodal) as within subject factors. Pre-planned contrasts were used to test whether crossmodal modulation occurs only in the graded task as hypothesized. Two-way ANOVAs were also carried out on both the amplitude and latency of the P100 at PZ, and the N140 at FCZ and PZ to test for main effects and interactions on each potential. Grand average traces illustrating the electrode sites and ERP components of interest are shown in Figure 1.

Behavioural data analysis

Behavioural data were analyzed for each task. For the detection task, the number of hits, misses, and false alarms were counted and for the discrimination task the number of correct and incorrect responses were counted and percent accuracy was calculated for both tasks. For the graded task, behavioural data was analyzed by summing the amplitudes of the two target stimuli and comparing this to the amplitude of the response. The force applied to the bulb forced air through a rubber tube in a closed system, inducing a change in pressure that was measured by a pressure sensor and converted to a voltage. There was a linear relationship between the pressure measurement and the voltage produced. The absolute percent difference between the summed target stimulus amplitude (i.e. the voltage of the 2 stimuli added together) and the actual response amplitude (in volts) was calculated. Paired t-tests were conducted to assess statistical differences between unimodal and crossmodal stimuli for each task.

4.4 Results

P50

All subjects demonstrated a clear P50 component (mean latency 56 +/- SE 7 ms) in response to vibrotactile stimuli and this potential was maximal at electrode site CP4, overlying contralateral somatosensory cortex. Main effects of modality ($F_{1,9} = 5.7$, $p=0.04$) and task ($F_{2,18} = 14.1$, $p=0.001$) were observed, as well as a significant interaction of modality x task ($F_{2,18} = 4.3$, $p=0.03$). The VT condition was associated with greater P50 amplitude than the T condition for the graded task ($p=0.01$), and there was no difference between these conditions for the detect or judge tasks ($p>0.05$ for both). These results are illustrated in Figure 2.

P100

The P100 component was present in all task conditions (mean latency 120 +/- SE 7 ms) with a bilateral distribution at central and parietal sites and maximal amplitude at electrode site PZ. Figure 3 reveals the effect of task observed at PZ ($F_{2,18} = 6.1$, $p= 0.009$), collapsed across T and VT tasks as modality was not a significant factor and no interaction was observed. Post-hoc tests show that the amplitude of the P100 was larger in the detect task compared to the grade task ($p=0.02$).

N140

The N140 component was observed in all task conditions (mean latency at FCZ: 164 +/- SE 6 ms, at PZ: 170 +/- SE 8 ms). A main effect of task was observed at PZ ($F_{2,18} = 5.7$, $p=0.01$) and is illustrated in Figure 4A, collapsed across modality as the effect of modality and the interaction was significant. Post-hoc tests revealed that the detect task was associated with greater negativity than the judge ($p=0.02$) and grade (p=0.04) tasks. At FCZ, main effects of task ($F_{2,18}$ = 12.1, p=0.001) and modality ($F_{1,9}$ = 7.1, p=0.026) were significant, but no interaction was observed. As illustrated in Figure 4B and revealed by post-hoc tests, for the T condition the grade task was associated with greater negativity than the detect task (p=0.01). This was also true of the VT condition (p=0.02), as well as a significant difference between the grade task and the judge task (p=0.04).

Behavioural data

Paired t-tests were carried out on the behavioural data for each task to test whether the unimodal task differed from the crossmodal task. No significant differences were found for any of the tasks (p<0.05) and this is illustrated in Figure 5.

4.5 Discussion

This study set out to probe the role of task requirements in mediating crossmodal modulation of P50. The greater purpose was to provide insight into what the somatosensory P50 may represent by testing the hypothesis that it would be sensitive to changes in task set despite identical stimulus parameters.

It was predicted that P50 modulation would be sensitive to task demands, specifically that crossmodal modulation would only be observed in the grade task, when the relationship between stimulus attributes and motor response was greatest. Further to this, it was hypothesized that the N140 component, particularly at frontal site FCZ, would scale with the requirement to extract sensory information and incorporate it into a motor response. Both hypotheses were supported by the data, and some unexpected results were seen for the P100 component and the parietal N140; neither potential was sensitive to crossmodal effects and for both components increased amplitude was associated with the detection task compared to the graded task.

Early modality specific effects

In the present study, crossmodal modulation of the P50 was replicated as in previous studies when the behavioural task required a graded motor response linked to the amplitude of the stimuli. Yet this modulation was not observed when the task requirements were changed despite the stimuli being identical. This finding provides fairly compelling evidence that crossmodal effects on the P50 are mediated by the demands of the task. The detection, discrimination, and graded tasks represent varying requirements to extract sensory information in order to make the appropriate motor response, with the detection task being the least demanding and the graded task the most demanding. In support of this argument, the behavioural data show that the detection task was performed with near perfect accuracy, whereas the graded was associated with less accurate performance, which would suggest it was the most difficult to perform. However, there were no differences in the accuracy of each task between the VT and T conditions, so although the crossmodal stimuli are associated with increased P50 amplitude in the most demanding task in a way that unimodal tactile stimuli are not, this difference is not associated with a behavioural benefit in terms of performance accuracy.

Considering all these findings together, some interesting possibilities arise about what the somatosensory P50 might represent. The lack of crossmodal effects in the detection and discrimination tasks argues strongly against the idea of a global crossmodal facilitation in response to visual and tactile stimuli. The finding that crossmodal effects only emerge under specific task requirements suggests that modulation of this potential is likely to reflect cognitive strategies being applied to the processing of the sensory inputs at an early stage, as was suggested by Desmedt and Tomberg (1989) in their discussion of what they termed the cognitive P40, which showed a similar topographical distribution to the P50 recorded in this experiment. A recent study by Schubert et al (2009) provides support for this idea and suggests that early sensory-specific modulations are associated with more demanding tasks. Such enhancements are presumably mediated via reciprocal thalamo-cortical networks that act to bias processing towards selected inputs (Brunia, 1993; Yingling and Skinner, 1976).

An entirely different pattern of results was observed for the P100 component, which did not demonstrate sensitivity to crossmodal effects but did show an effect of task. The detection task was associated with larger P100 amplitude than the graded task, regardless of whether the stimuli were crossmodal or unimodal. The P100 is bilaterally distributed over parietal electode sites and is thought to be generated in bilateral secondary somatosensory cortex (SII) (Gu, 2002; Mima et al., 1998). Several studies report sensitivity of this potential to effects of attention (Desmedt et al., 1983; Eimer and Forster, 2003; Josiassen et al., 1982; Kida et al., 2004b; Michie et al., 1987; Schubert et al., 2006), and functional imaging studies show modulation of SII when attention is directed towards tactile stimuli (Johansen-Berg et al., 2000; Meyer et al., 1991; Nelson et al., 2004; Staines et al., 2002). While the effects of attention on the P100 appear fairly consistent, studies investigating crossmodal influences on mid-latency components are mixed. Studies employing an oddball detection task that required subjects to monitor both hands for deviant stimuli in one modality while ignoring the other and reporting detections with a verbal response also failed to find crossmodal effects on this potential (Eimer and Driver, 2000; Eimer, 2001). Dionne et al. (submitted), reported that the P100 was sensitive to the presence of crossmodal stimuli but not to the task-relevance of those stimuli during the performance of a graded motor task, yet that same effect was not observed in the current study. However there are differences in the design of these two experiments that may account for this discrepancy. In the current study the stimuli received by participants were intermixed pairs of either tactile (T) or visual and tactile (VT) stimuli, and they were required to attend to either the T or VT events, essentially a crossmodal oddball task with varying motor requirements. In the previous experiment, pairs of crossmodal or unimodal stimuli were presented in different blocks while participants performed the same task. Thus it seems that the requirement to selectively attend to crossmodal stimuli intermixed with unimodal stimuli does not modulate the P100, but sustaining attention to crossmodal stimuli enhances this component compared to sustaining attention to unimodal stimuli.

Longer latency effects

The N140 component was sensitive to task requirements at both the parietal and frontal sites, but while the N140 was more sensitive to crossmodal stimuli than unimodal stimuli at the frontal site, at the parietal site it was not. Also of interest, the two sites showed different patterns of task-related N140 modulation. At the parietal site, greater negativity was associated with the detection task than the discrimination and graded tasks, whereas at the frontal site the graded task was associated with largest negativity.

The somatosensory N140 is evoked by tactile and electrical stimuli in association with cognitive tasks and typically occurs at latencies between 100 and 180 ms (Allison et al., 1992; Desmedt and Robertson, 1977; Josiassen et al., 1990). The topography of this large negative deflection most often begins over the contralateral frontal electrodes and extends towards the midline and ipsilateral sides. The prevailing thought on the generators of the N140 is that it reflects activation of prefrontal cortex, an area that is known to play a role in retrieving and maintaining representations of stimulus relevancy in relation to behavioural goals (Allison et al., 1991; Desmedt and Tomberg, 1989; Knight et al., 1995; Pardo et al., 1991a), however the bilateral distribution of the N140 at parietal sites has also prompted some researchers to suggest a generator in SII (Frot and Mauguiere, 1999), which as mentioned previously has been implicated in attention to tactile stimuli. Similar to the current study, the results of Dionne et al. (submitted) also showed different patterns of N140 modulation at frontal and parietal sites and these results provide further support that this component might be associated with multiple generators such that the frontal and parietal generators are sensitive to different factors.

Given the results of these two studies, it seems that the parietal component of the N140 shows specificity for task demands but not crossmodal stimuli, and the frontal component is sensitive to both crossmodal stimuli in addition to task requirements. The finding that different task demands produce different patterns of modulation at frontal and parietal sites likely speaks to the functions associated with the underlying cortical areas. While both frontal and parietal regions are part of a fronto-parietal network attention network, the nodes in this network subserve different aspects of attending to and responding to stimuli. Areas of the parietal cortex, particularly the temporoparietal junction are known to play a role in stimulus-driven shifts of attention, regardless of stimulus modality (Corbetta and Shulman, 2002; Downar et al., 2001; Kincade et al., 2005), thus parietal contributions to the N140 may be most responsive to the detection task that relies more on this form of stimulus-driven attention. In contrast, at frontal sites the N140 is most responsive to the graded task, which requires greater extraction of stimulus features to execute an accurate motor response. This finding fits with a role for prefrontal cortex in transforming sensory information into behaviour via gating mechanisms that bias activity in sensory-specific cortex in response to behavioural demands (Gazzaley et al., 2005; Gazzaley et al., 2007).

4.6 Conclusion

Crossmodal effects on somatosensory P50 component depends on the requirements of the behavioural task, suggesting this component may reflect the application of cognitive strategies to sensory processing. Task demands also modulate mid-latency components, with frontal and parietal sites showing sensitivity to different task requirements.

4.7 Figures & tables

Table 1 – ERP amplitudes (μv +/- SEM) by task and electrode site

	Detect				**Judge**				**Grade**			
	CP4	**PZ**		**FCZ**	**CP4**	**PZ**		**FCZ**	**CP4**	**PZ**		**FCZ**
	P50	P100	N140	N140	P50	P100	N140	N140	P50	P100	N140	N140
VT	0.38 (0.06)	1.72 (0.32)	-2.38 (0.46)	-1.74 (0.3)	1.07 (0.21)	1.65 (0.31)	-2.0 (0.3)	-2.2 (0.24)	1.68 (0.29)	0.94 (0.16)	-2.0 (0.39)	-3.1 (0.21)
T	0.43 (0.07)	1.54 (0.33)	-2.2 (0.25)	-1.5 (0.12)	0.74 (0.13)	0.86 (0.19)	-1.4 (0.25)	-1.6 (0.27)	0.85 (0.17)	0.85 (0.13)	-1.2 (0.1)	-2.1 (0.28)

Table 1: Mean amplitude (+/- SEM) in microvolts (μv) of ERP components recorded from electrode sites CP4, PZ, and FCZ for each task and stimulus condition: crossmodal, visual + tactile (VT) and unimodal, tactile (T).

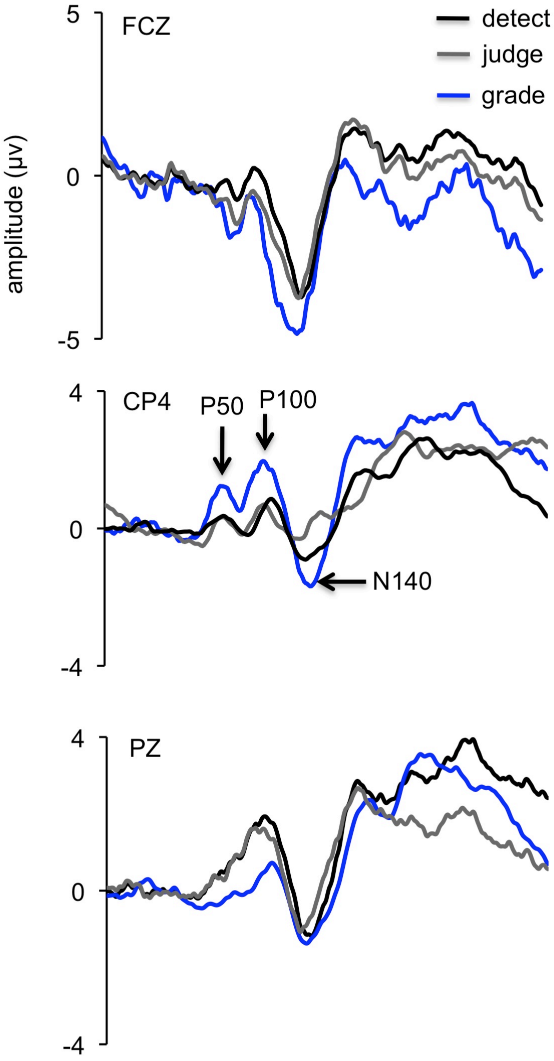


Figure 1
Grand average waveforms (n=10) for the visual + tactile (VT) task condition at FCZ (top), CP4 (middle) and PZ (bottom) electrode sites. Black traces show the detect task, grey traces depict the judge task, and blue traces illustrate the graded task.

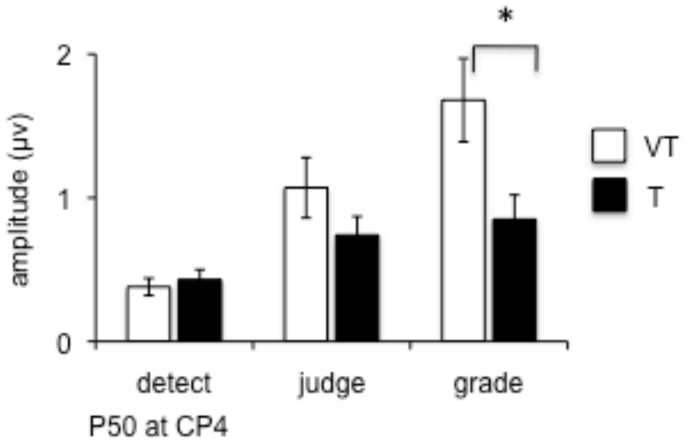


Figure 2
Group means (n=10) for P50 amplitude measured at CP4. White bars represent group data for the crossmodal visual + tactile task condition (VT), black bars represent group data for the unimodal tactile condition (T). Error bars show SEM, * denotes significance $p<0.05$.

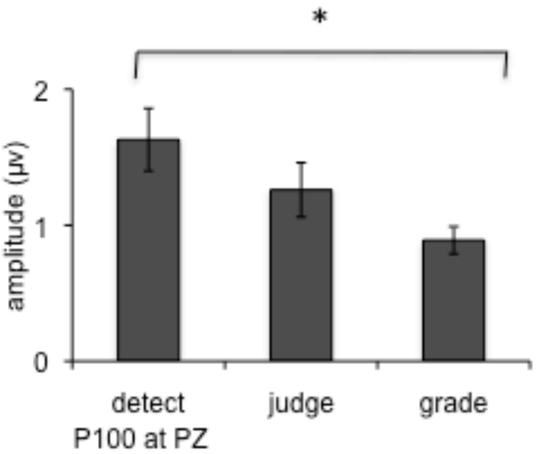
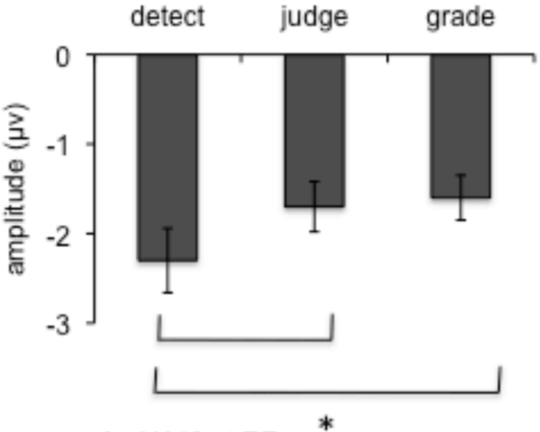
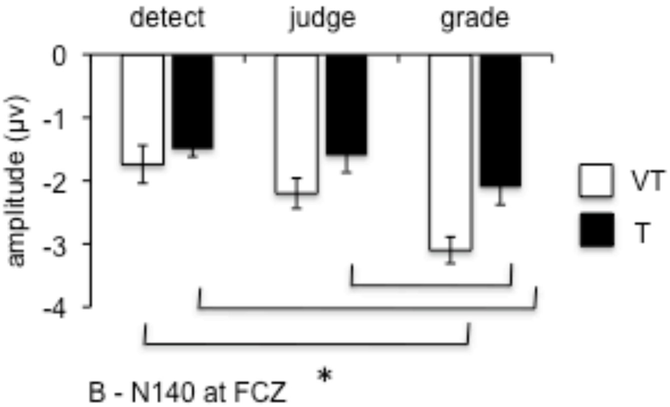


Figure 3
Group means (n=10) for P100 amplitude measured at PZ. Bars represent group data for the three task conditions collapsed across modality. Error bars show SEM, * denotes significance $p<0.05$.



A - N140 at PZ



B - N140 at FCZ

Figure 4
Group means (n=10) for N140 amplitude measured at PZ (A) and FCZ (B). White bars represent group data for the crossmodal visual + tactile task condition (VT), black bars represent group data for the unimodal tactile condition (T). Error bars show SEM, * denotes significance $p<0.05$.

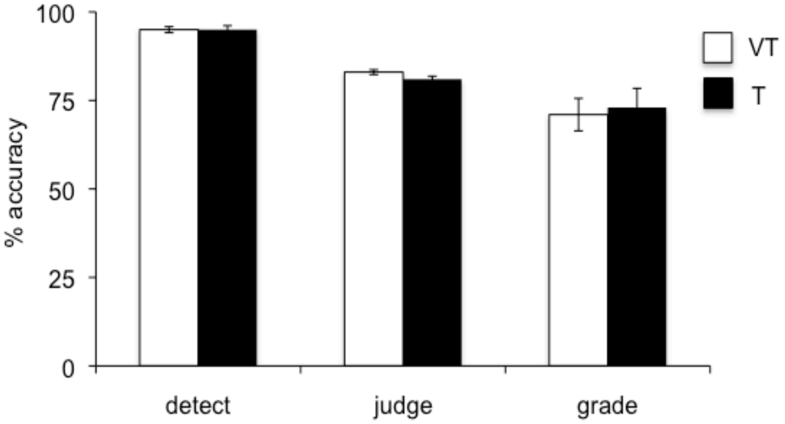


Figure 5
Group means (n=10) for behavioural performance. White bars represent group data for the crossmodal visual + tactile task condition (VT), black bars represent group data for the unimodal tactile condition (T). Error bars show SEM.

Chapter 5

5.1 General Discussion

The objective of this thesis was to probe how somatosensory cortex is modulated by task-relevant, crossmodal stimuli. The main findings of this thesis suggest that somatosensory cortex is subject to top-down modulation based on a set of stimulus- and response-driven expectancies. This finding is significant in that it contributes to our understanding of how cognitive factors like attention and response planning can exert an influence on early cortical processing within sensory-specific cortex.

The first study set out to determine the effects of simultaneous visual and tactile stimuli on somatosensory cortex, in the context of a behavioural task requiring attention to both modalities to inform the motor response. Given that somatosensory cortex is sensitive to the task-relevance of stimuli and recent reports of crossmodal sensitivity in primary sensory cortex, it was hypothesized that relying on both visual and tactile stimuli to perform a sensory-guided motor task would be associated with increased SI excitability, compared to tactile stimuli alone. Secondary to this, it was also hypothesized that activity in a frontoparietal network would be upregulated in the crossmodal task which would implicate this network in driving SI modulation. Study 1 tested these hypotheses using functional magnetic resonance imaging (fMRI) to determine whether activity in SI is modulated by the requirement to use both visual and vibrotactile information to guide a motor response, and if so to identify regions that may contribute to or drive this modulation. The hypothesis that SI activity would be modulated in the crossmodal visual + tactile task relative to the unimodal visual and tactile tasks was supported by the results of the ROI analysis, which revealed an increase in peak percent BOLD signal change in the visual + tactile condition compared to the tactile-only and visual-only conditions. Results of the whole-brain analysis revealed a common fronto-parietal network that was active across both the crossmodal and unimodal task conditions, suggesting that these regions are sensitive to the attentional and motor planning aspects that were common to all tasks rather than the unimodal or crossmodal nature of the stimuli. This study provides evidence for crossmodal interactions within sensory-specific cortex, and is the first to demonstrate an upregulation of somatosensory cortex with simultaneous visual and tactile stimulation using fMRI.

The goal of Study 2 was to determine the temporal characteristics of crossmodal modulation in SI using ERPs. It was hypothesized that the crossmodal task, requiring the use of both tactile and visual stimuli to plan and execute a motor task, would be associated with larger amplitudes in early somatosensory ERP components compared to a unimodal task, echoing the fMRI findings of study 1 but with more precise temporal resolution to determine how early in the processing stream such a modulation might occur. Study 3 aimed to determine if crossmodal effects in somatosensory cortex are contingent upon the task-relevance of the stimuli, based on the assumption that if such modulation is a product of top-down processes, it will only occur when both modalities are relevant and attended. Conversely, if crossmodal modulation of SI is mediated by bottom-up mechanisms, the relevance of the stimuli to behaviour should not influence crossmodal effects in SI. Thus Study 3 set out to test the hypothesis that crossmodal enhancement in SI will only be observed when both visual and tactile stimuli are task-relevant. The hypotheses of both studies were supported by the data; a crossmodal enhancement was observed in the somatosensory P50 component, indicative of increased excitability in SI and when task relevance was manipulated this modulation was observed only when both visual and tactile stimuli were relevant. These results provide evidence that crossmodal stimuli can modulate early somatosensory event-related potentials, and that these effects are mediated by stimulus relevance.

An interesting pattern of results emerged at mid-latency components, reflecting activity outside of primary somatosensory cortex. In Study 2, the N140 was modulated by crossmodal stimuli at a parietal electrode site, whereas in Study 3 the N140 was not modulated at PZ but was at FCZ, where the tasks requiring selective attention to one of the crossmodal stimuli were associated with larger N140 amplitudes than the task requiring attention to both. The results of these two studies indicate that the relevance of stimuli to behaviour and the presence of a simultaneous crossmodal stimulus both exert influences on somatosensory processing. Further to this, frontal and parietal regions contributing to the N140 are differentially modulated by modality and relevance. This finding is suggestive that a fronto-parietal network may indeed be involved in modulating excitability in SI by providing evidence that frontal and parietal regions show sensitivity, albeit in different ways, to the same manipulations that modulate SI.

The first two studies of this thesis provided evidence that measures of somatosensory cortical excitability are sensitive to crossmodal stimuli, in the context of a sensory-guided motor task. The third study revealed that this modulation is contingent on the relevancy of the stimuli to the motor task, such that modality-specific ERP components are enhanced when both visual and tactile stimuli are relevant to the task, but not when one is irrelevant. The final study set out to determine whether the specific task requirements, specifically the degree to which the motor response relies on sensory information, influence somatosensory ERP components. The greater purpose was to provide insight into what the somatosensory P50 may represent by testing the hypothesis that it would be sensitive to changes in task set despite identical stimulus parameters. It was predicted that P50 modulation would be sensitive to task demands, specifically that crossmodal modulation would only be observed in the graded task, when the relationship between stimulus attributes and motor response was greatest. Replicating previous studies, crossmodal effects were observed on the P50, but novel to this study, only in the graded motor task. This finding supported the hypothesis that crossmodal effects on the P50 are dependent on the requirements of the motor task.

Some unexpected results were observed for the P100 component and the parietal N140; neither potential was sensitive to crossmodal stimuli compared to unimodal stimuli, and for both components increased amplitude was associated with the detection task compared to the graded task. At frontal site FCZ, the graded task was associated with greatest N140 amplitude in both unimodal and crossmodal conditions. These results suggest that frontal and parietal contributions to the N140 are both sensitive to task requirements but these effects go in opposite directions, with the parietal component being most responsive to the detection task and the frontal component more sensitive to the graded task.

The lack of crossmodal effects in the detection and discrimination tasks in Study 4 argues against the idea of a global crossmodal facilitation in response to visual and tactile stimuli. The finding that crossmodal effects only emerge under specific task requirements suggests that this potential is likely to reflect cognitive strategies being applied to the processing of the sensory inputs at an early stage, as was suggested by Desmedt and Tomberg (1989) in their discussion of what they termed the cognitive P40, which showed similar distribution to the P50 recorded in this experiment. A recent study by Schubert et al (2009) provides support for this idea and suggests that early sensory-specific modulations are associated with more demanding tasks. Such enhancements are presumably mediated via reciprocal thalamo-cortical networks that act to bias processing towards selected inputs (Brunia, 1993; Yingling and Skinner, 1976), and the prefrontal cortex has been implicated as an important node in this sensory gating and enhancement network.

With this in mind, the N140 effects recorded from frontal sites that are reported in this thesis may in fact be indicative of the role of PFC in mediating sensory-specific modulations, as the prevailing thought is that the N140 has at least one generator in prefrontal cortex (Allison et al., 1991; Desmedt and Tomberg, 1989). The results of studies 3 and 4 show that the parietal component of the N140 shows specificity for task demands but not crossmodal stimuli, and the frontal component is sensitive to crossmodal stimuli and the presence of a distractor, in addition to specific task requirements. The finding that different task demands produce different patterns of modulation at frontal and parietal sites likely speaks to the functions associated with the underlying cortical areas. While both frontal and parietal regions are part of a fronto-parietal attention network, the nodes in this network subserve different aspects of attending to sensory events. Areas of the posterior parietal cortex are known to play a role in stimulus-driven shifts of attention, regardless of stimulus modality (Corbetta and Shulman, 2002; Downar et al., 2001; Kincade et al., 2005), thus parietal contributions to the N140 may be most responsive to the detection task that relies more on this form of stimulus-driven attention. In contrast, at frontal sites the N140 is most responsive to the graded task, which requires greater extraction of stimulus features to execute an accurate motor response. This finding fits with a role for prefrontal cortex in transforming sensory information into behaviour via gating mechanisms that bias activity in sensory-specific cortex in response to behavioural demands (Gazzaley et al., 2005; Gazzaley et al., 2007).

Considering the findings of these four studies together, some interesting possibilities arise about what the early modulation of somatosensory cortex might represent. Before considering these possibilities, it is important to note that the experimental techniques used in this thesis, while complementary to each other, capture different measures of cortical excitability. fMRI measures the blood oxygen level dependent (BOLD) response, which reflects changes in the relative proportion of oxygenated and deoxygenated hemoglobin in blood vessels of the brain. These changes in blood flow are coupled to changes in the metabolic activity of neurons since active neurons require more oxygen, which in turn is a reflection of neuronal activity because neuronal firing relies on oxygen-dependent cellular mechanisms. A study by Logothetis et al (2001) attempted to discern what type of neural activity is best reflected by the BOLD response and found that BOLD activation reflects the activity related to the inputs and local processing of neurons in a given area, which is energetically expensive and thus likely to contribute heavily to hemodynamic changes. In contrast, EEG measures cortical activity by recording electrical activity at the surface of the scalp, and this signal reflects the summated excitatory postsynaptic potential (EPSP) activity of synaptic potentials in the dendrites of cortical pyramidal neurons (Gloor, 1985). Thus, while these two techniques are quite different in the way in which they record changes in cortical excitability, both capture similar underlying cortical processes (Logothetis et al., 2001).

To return to the SI modulation observed with both fMRI and ERP, there are several possibilities about what this modulation might represent. It is possible the observed changes in excitability reflect increased attention being directed to the stimulus, or it could be related to the amount of planning required to make the response, in which case the modulation may reflect the degree of coupling between the stimulus and the response. These explanations are in fact not mutually exclusive and it is entirely possible that the observed modulations of SI reflect both of these processes. The next logical question is what drives this modulation? The two most likely routes of modulation are via bottom-up cortico-cortical connections between visual and somatosensory areas or via top-down influences of higher-order cortical areas on somatosensory cortex, and each of these options will be considered along with the potential neuroanatomical pathways and neurophysiological mechanisms that may underlie these modulatory influences.

One possible route of SI modulation is via connections between primary visual cortex, visual association cortex, and somatosensory cortex. There is anatomical evidence for such connections in monkeys (Cappe and Barone, 2005) and it has been suggested that such pathways could mediate cross-modality effects in a feedforward fashion (Foxe and Schroeder, 2005). However, given that the initial response in visual cortex typically occurs within 45-60ms after stimulus onset (Foxe and Simpson, 2002), which is the same time window the somatosensory P50 occurs in, it is unlikely that projections from the visual cortex influence SI directly at this latency. However, this does not preclude the possibility that visual inputs could influence somatosensory excitability indirectly via connections with the posterior parietal cortex (PPC). In nonhuman primates, area 7a (the caudal portion of the posterior parietal lobe) is reciprocally interconnected with multiple visual-processing related areas, including the upper bank of the superior temporal sulcus (STS), visual motion processing area MT, and portion of V2 (Cavada and Goldman-Rakic, 1989). Area 7b, the rostral part of the posterior parietal lobe shares connections with SI, regions of secondary somatosensory cortex, and area 5. Given the convergence of visual inputs on regions of the PPC, and the connections of PPC to SI, an alternative explanation of the SI modulation observed in this thesis could lie in a role for parietal regions in mediating these effects. A recent TMS study provides some support for this idea, as TMS to the PPC eliminated the behavioural advantage normally conferred by congruent visual and tactile stimuli in a discrimination task, which suggests that this region is critical for integrating information about visual and tactile stimuli (Pasalar et al., 2010). Thus while the PPC is a candidate for mediating the crossmodal modulation of SI, the strongest piece of evidence arguing in favour of prefrontal mediated mechanisms is that SI modulation by crossmodal visual stimuli only occurs when both stimuli are task-relevant. Although the parietal N140 is by no means a direct measurement of PPC activity, it is a measure of excitability over parietal cortex and in Study 3 it was not sensitive to the manipulation of task-relevance, which would suggest that the population of cells in parietal cortex that contributes to that potential does not drive the task-relevant modulation observed in SI.

On the other hand, several features of the modulation observed in this thesis argue strongly in favour of top-down mechanisms driving the facilitation of SI. The strongest evidence comes from the observation of excitability changes when the physical stimuli were identical and the task requirements were varied, both by changing which stimulus was relevant and by introducing different sensorimotor tasks. This finding suggests that a cognitive or attentional set related to the task plays a role in driving the upregulation of SI. Regions of the prefrontal cortex, particularly the DLPFC, have been implicated in assessing the behavioural goals of the task and determining the attentional set required to achieve these goals, This set of expectations about the stimuli and the required response could then drive an increase in SI excitability.

In general, it is thought that the prefrontal cortex is involved in both the selection of relevant stimuli and the suppression of irrelevant inputs. The mechanisms involved in these processes are not entirely understood, but the underlying circuits that carry out these functions have been the focus of much research. The ability to select task-relevant stimuli is likely mediated by connections between the prefrontal cortex and sensory cortices that process incoming sensory information, memory-related regions that store information gained from experience, and limbic structures that provide motivational context (Barbas and Zikopoulos, 2007). Evidence for the networks of anatomical connections between these regions and prefrontal cortex comes from tracer studies carried out in nonhuman primates (Barbas et al., 1999, Goldman-Rakic 1988, Fuster 1990), so although the precise neurophysiological mechanisms underlying enhancement of relevant inputs are unclear, because the pathways that link cortical or subcortical structures in primates are excitatory glutamatergic pathways (White and Keller, 1989), the existence of these connections provides the substrates for excitatory prefrontal pathways. The mechanisms underlying inhibitory processes carried out by the prefrontal cortex are also the topic of some debate, although two proposed mechanisms for suppression and excitation suggest that prefrontal pathways can actively suppress irrelevant stimuli by synapsing with inhibitory neurons in other cortical regions, which then inhibit neighbouring neurons, or prefrontal projections may target inhibitory systems which would produce disinhibition and trigger diverse outcomes that could include excitation or suppression (Barbas and Zikopoulos, 2007).

In terms of providing possible explanations for the modulation of SI observed in this thesis, there are two likely routes for this to occur: either directly via connections between prefrontal cortex and SI, or indirectly via a thalamo-cortical loop. Evidence for direct connections between DLPFC (BA 9) and somatosensory cortex come from anatomical tracer studies mentioned above (Barbas et al. 1999), and also from a lesion study reporting effects of DLPFC damage on SEP components reflecting SI processing but not the afferent volley from thalamic inputs (Yamaguchi and Knight, 1990). However, there is evidence that prefrontal cortex may exert an influence on SI excitability via the inhibitory circuits of the thalamic reticular nucleus (TRN). The TRN has reciprocal connections with the thalamic nuclei and receives projections from the cortex, permitting it to act as a filter between cortical influences and the transmission of signals into the cortex. This filtering process is carried out by mechanisms whereby reticular neurons innervate and inhibit thalamic relay neurons, or disinhibit them by innervating thalamic inhibitory neurons (Jones, 2002). The topography of the axonal projections from the prefrontal cortex to the TRN overlaps with projections from sensory association areas, which suggests that these axons may be in a position to influence signals passing from sensory-related thalamic nuclei to the cortex (Zikopoulos and Barbas, 2006), thus allowing for the selection of some signals and suppression of others at an early stage of processing. Recent investigations of the influence of prefrontal pathways on TRN suggest that the role of these projections might be most critical in fine-tuning the transmission of relevant signals and eliminating distractors in complex situations involving multimodal stimuli and cognitively-demanding tasks (Zikopoulos and Barbas, 2010).

The modulation of SI reported in the studies in this thesis cannot be definitively attributed to either direct or indirect influences from prefrontal cortex, however in light of the top-down factors observed to influence SI excitability in the four studies of the thesis, decades of research that implicates prefrontal regions in modulating sensory processing, and the existence of anatomical and physiological mechanisms to subserve these effects, it seems very likely that these regions play a role in mediating the SI modulation observed in these four studies. From a big picture perspective, these early modulations in somatosensory cortex may have consequences for how sensory-guided motor responses are carried out. Somatosensory information projects from SI to secondary somatosensory regions and posterior parietal cortex where it undergoes higher-order processing and can be used to direct attention and inform motor responses. These processes are carried out via connections between the posterior parietal cortex and prefrontal cortex, frontal premotor regions, and motor cortex. In this way, changes in SI excitability can have an effect on the planning and execution of motor behaviour.

5.2 Conclusions

Somatosensory cortex is sensitive to the presence of simultaneous, crossmodal (visual and vibrotactile) stimuli when both stimuli are relevant to the performance of a tightly coupled sensory-motor task. This modulation of sensory cortex is associated with activity in a fronto-parietal network, which has been previously implicated in the top-down control of attention. The findings of this thesis show that frontal and parietal nodes in this network are differentially modulated by crossmodal demands, stimulus relevance, and motor task requirements. Taken together, these findings contribute to the mechanistic understanding of how somatosensory cortex is modulated and are suggestive that modulation of excitability in SI is governed by top-down mechanisms that act to enhance the processing of relevant stimuli based on task demands, and that a fronto-parietal network relies on perceptual and motor sets to bias the processing of incoming sensory information. These attentional sets are representations used to select task-relevant stimuli and responses based on knowledge about upcoming sensory events and behavioural goals (Corbetta and

Shulman, 2002). The most likely routes for this effect involve a prefrontal-thalamic-cortical loop and direct cortico-cortical connections between PFC and SI that allow the prefrontal cortex to exert an influence on somatosensory cortex. Although the precise mechanisms underlying this enhancement are not clear, these findings do contribute to our understanding of how exogenous factors like stimulus modality interact with endogenous factors like task-relevance by revealing the consequences of this interaction on somatosensory cortex.

5.3 Limitations

This thesis suffers from a number of methodological limitations that are inherent in using indirect measures to infer changes in neural activity. As mentioned in the General Discussion, fMRI measures the blood oxygen level dependent (BOLD) response, which reflects changes in the relative proportion of oxygenated and deoxygenated hemoglobin in blood vessels of the brain. From these changes in blood flow we infer changes in neural activity, because active neurons require more oxygen and despite efforts to understand the neural activity underlying the BOLD signal, the bottom-line is that it is still a correlative measure that does not permit any conclusions about the cause and effect relationship between neural activity and the task it is associated with. A different but not unrelated set of limitations arises from EEG as a measure of cortical activity, which measures electrical activity at the surface of the scalp and reflects the summated synaptic activity occurring in the underlying cortex. While this measure has the advantage of very precise temporal resolution, it suffers from the problem of current spread whereby the EEG signal is attenuated and distorted by tissue and bone between the cortex and the electrodes, which makes it difficult to localize the generators of components of the EEG waveform, particularly those with broad topographical distributions. The limitations of both of these techniques constrain the interpretation of the results of this thesis to inferences about the underlying neurophysiology and anatomy rather than direct cause and effect relationships between the observed neurophysiological effects and the cortical and subcortical regions that subserve them.

Another limitation common to studies that attempt to link physiology to behaviour is the artificial nature of behavioural tasks used in a laboratory setting, and the tasks employed in this thesis are no exception. The behavioural tasks in this thesis were designed to manipulate attention and stimulus modality, and although these factors undoubtedly influence everyday behaviour, the way in which they were compartmentalized for the purposes of experimental design most certainly does not reflect the fluidity of real-world tasks. However this sacrifice in ecological validity is a necessary evil in efforts to understand the relationships between behaviour, cognitive processes, and the underlying neurophysiology.

5.4 Future Directions

The logical next question stemming from the results of this thesis relates to what might be the functional consequences of the observed SI modulation. In none of the studies of this thesis did SI modulation coincide with improvements in behaviour, which suggests that in young, healthy participants these changes in somatosensory cortex do not impact motor performance. But this is not to say that the same results would be seen in patients with neurological impairments affecting their ability to attend to relevant stimuli and incorporate it into a motor response, such as those with prefrontal lesions. As mentioned in the introduction of this thesis, understanding the role of sensory information in motor behaviour has implications for recovery of motor function in clinical populations, and determining the optimal conditions for increasing excitability in somatosensory cortex is an important preliminary step towards informing rehabilitation strategies. Thus one future direction could be to test whether modulations in sensory-specific cortex are indicative of performance deficits in patients presenting with sensory-gating deficits. Another possible extension of this work would be to test the hypothesized contributions of nodes in the fronto-parietal network by applying a theta-burst transcranial magnetic stimulation (TMS) protocol to regions in this network and measuring the behavioural and physiological consequences of disrupting function in these areas. By systematically disrupting function in hypothesized critical nodes in the fronto-parietal network and measuring SI excitability and behavioural performance it might be possible to disentangle the relative contributions of frontal and parietal regions to SI modulation.

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