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Topographic analysis of pain components in the somatosensory evoked potential

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TOPOGRAPHIC ANALYSIS OF PAIN COMPONENTS IN THE SOMATOSENSORY EVOKED POTENTIAL

by

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DISSERTATION

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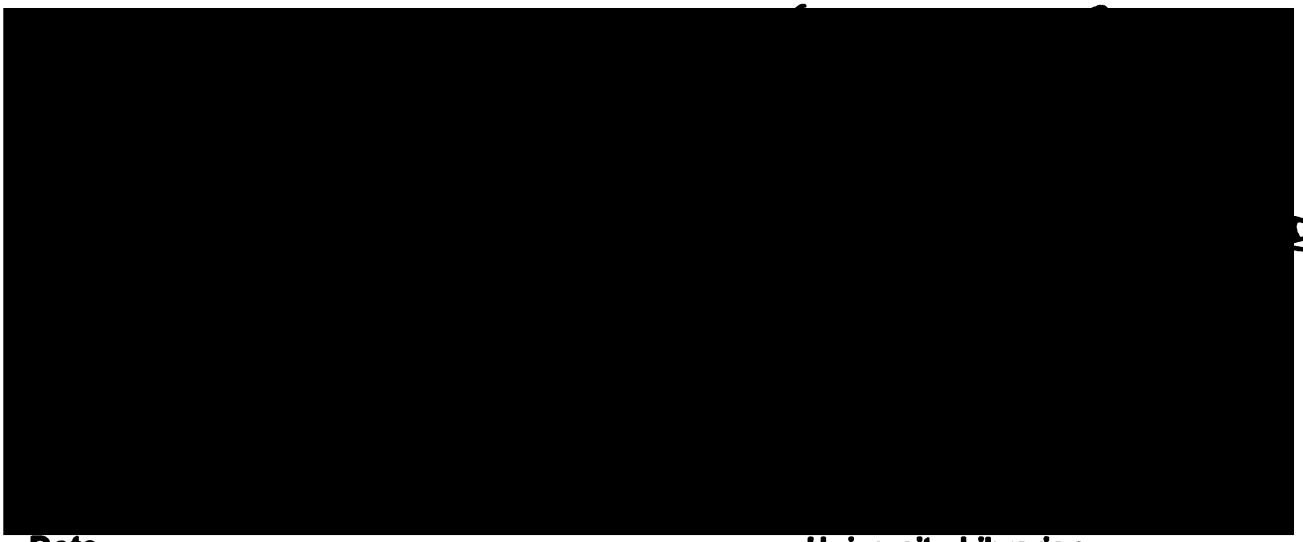

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DEDICATION

I would like to dedicate this dissertation to my father, Newton Becker, my mother, Sally Wade, and my wife, Ann Becker. Each of them, in their own way, made this dissertation possible.

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PREFACE

I would like to thank the many people who have helped me and taught me during my years in graduate school at UCSF. I appreciate the time and effort spent by the members of my dissertation committee, Chuck Yingling, George Fein and Pete Ralston, by the members of my qualifying exam committee, David Galin, Chuck Yingling, George Fein, Ernest Hilgard and Larry Jamner, by the director of the Health Psychology Program, Nancy Adler, and by the many other fine teachers whose courses I have taken here. I especially want to thank Chuck Yingling and George Fein who honored me with their confidence and help, and who gave me the freedom to pursue a research area that diverged somewhat from their ongoing projects.

The text of Chapter Two of this dissertation is a reprint of the material as it appears in *Electroencephalography and clinical Neurophysiology, Volume 88, pages 290-301, 1993.* The article is reprinted with permission of Elsevier Scientific Publishers Ireland, Ltd. The coauthors listed in this publication, Dr. Yingling and Dr. Fein, directed and supervised the research which forms the basis for the dissertation.

ABSTRACT

Topographic Analysis of Pain Components in the Somatosensory Evoked Potential

David E. Becker

This dissertation examines the validity of the Pain SEP (the somatosensory evoked potential in response to painful stimuli) as a measure of central nervous system processing of pain. Chapter One provides a background on research relating the cerebral cortex to pain processing. Chapter Two reprints my 1993 publication, "Identification of pain, intensity and P300 components in the pain evoked potential" *(Electroenceph. clin. Neurophysiol. 88:* 290-301, 1993). This article shows that three different components related to 1) pain, 2) non-painful intensity and 3) cognitive processing of task relevant stimuli (P300) can be identified in the Pain SEP by using difference waves. Pain was the difference between somatosensory evoked potentials (SEPs) in response to painful stimuli vs. strong but non-painful stimuli; Intensity was the difference between SEPs to strong non-painful vs. mild non-painful stimuli; P300 was the difference between SEPs to the same stimuli under Target instructions vs. Non-target instructions. Painful stimuli were produced using intracutaneous electrical stimulation of a fingertip and two levels of non-painful stimuli were produced by superficial electrical stimulation of a neighboring fingertip. The analysis utilized only two recording electrodes, Cz and Pz, and used the components' latencies and amplitudes to differentiate them from each other.

New analyses in Chapter Three extends the work on the three components by topographically mapping their scalp distribution using 30 electrodes. The positive peaks in the three types of difference waves differed in latency: Intensity was earliest, then Pain, then P300. An analysis of topographic similarity using Desmedt and Chalklin's Z Estimator and Lehmann's Global Dissimilarity scores showed that the positive peak of the Pain difference wave (Pain component) had a topography that was significantly different from the P300 component (Pain was broad and symmetrical around the vertex whereas P300 was broad with a more posterior distribution around Pz). The Pain and Intensity positive components were both broad and usually maximal at Cz, however there was a non-significant trend for these two components to differ in topography. Our results illustrate how the SEP to painful stimuli is a weighted combination of multiple overlapping components.

Key words: Pain; Pain evoked potential; Somatosensory evoked potential; P300; Intensity; Topographical mapping

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INTRODUCTION

This dissertation examines the validity of the Pain SEP (the somatosensory evoked potential in response to painful stimuli) as a measure of central nervous system processing of pain. Chapter One provides a background on research relating the cerebral cortex to pain processing. An overview is provided of animal studies, clinical studies, and recent functional imaging studies as well as a more in depth review of work using Pain SEPs.

Chapter Two reprints my 1993 publication, "Identification of pain, intensity and P300 components in the pain evoked potential." This article presents my dissertation research showing that three different components can be identified in the Pain SEP by using difference waves. The analysis utilizes only two electrodes, Cz and Pz, and uses the components' latencies and amplitudes to differentiate them from each other.

Chapter Three extends the work on the three components by topographically mapping their scalp distribution using an additional 28 electrodes from the same recording sessions that were reported on in Chapter Two. A statistical analysis is carried out to differentiate the three components based on scalp topography alone.

Chapter Four concludes the dissertation with a summary of the experimental results and an overall discussion on how these results relate to other work.

CHAPTER 1

PAIN AND THE CEREBRAL CORTEX BACKGROUND AND SIGNIFICANCE

For most of this century, the research agenda on the relationship between the cerebral cortex and pain seems to have been set by two influential research groups, Head and Holmes (1918) and Penfield and Boldrey (1937) . Head and Holmes suggested that "pure cortical lesions cause no increase or decrease of sensibility to measured painful stimuli" and Penfield and Boldrey observed that electrical stimulation of the cortex rarely evoked painful sensations (Gingold et al. 1991). In the following years, so few studies were conducted that, in a 1982 review of the nociceptive system, only one of 59 pages was devoted to cortical mechanisms (Yaksh and Hammond 1982). It has only been in the last 10-15 years that a concerted research program has set out to discover the role that the cortex plays in pain processing.

Animal studies

A number of recent animal studies have used extracellular and intracellular recordings to identify cortical neurons that respond to noxious stimuli. Although no specific cortical "pain center" has been discovered, neurons responding to noxious stimulation have been identified in regions of the cortex that also process non-noxious somatosensory information, namely primary somatosensory cortex (SI) (e.g., Andersson and Rydenhag 1985; Matsumoto et al. 1987; Kenshalo et al. 1988; Chudler et al. 1990; Kozlov 1991; Guilbaud et al. 1992; Vin-Christian et al. 1992; Guilbaud et al. 1993; Kalliomäki et al. 1993), and secondary somatosensory

cortex (SII) and bordering area 7b (e.g., Chudler et al. 1986; Dong et al. 1989), as well as in other cortical areas (medial prefrontal cortex, (Condés-Lara et al. 1989); ventrolateral orbital cortex, (Backonja and Miletic 1991; Snow et al. 1992); cingulate cortex, (Sikes and Vogt 1992)). These studies have identified cortical neurons with a varied assortment of properties, some of which are more complex than the categorization as "wide dynamic range" (WDR) or "high threshold" (HT) used for spinal cord and thalamic neurons.

Primary somatosensory cortex

The primary somatosensory cortex has been studied more extensively than any other cortical area. For example, Kenshalo & Isensee (1983) recorded from 68 cortical cells in 10 macaque monkeys and classified 37 as WDR and 31 as HT neurons. Most of the nociceptive neurons were somatotopically organized, like the mechanoreceptors in the same region of SI. Most neurons had restricted contralateral receptive fields with the WDR neurons having somewhat smaller receptive fields than the HT neurons. In the hand region of SI, most nociceptive neurons were found in area 1, in the foot region of SI, they were found on the area 1-3b border. The HT neurons were found mainly in the anterior half of the region where the nociceptive neurons were identified; the WDR neurons were distributed evenly across the whole region. This was consistent with the finding that HT neurons tended to be aggregated while the WDR neurons were intermingled with neurons responding to non-noxious stimulation of the same receptive field as the WDR neurons (Kenshalo and Perkins 1984). This pattern, along with the finding that there were no nociceptive cells in cortical layer VI, led the authors to conclude that there were no "pain columns" in SI.

Interestingly, there were 12 neurons (included in the group of 37 classified as WDR) with a different pattern of responding. These cells responded to *low* threshold stimulation in a small restricted contralateral receptive field, but also responded to *high* threshold stimulation to the rest of the body--certainly not the usual WDR pattern. The authors suggest that these cells are unlikely to code for the sensory-discriminative aspects of pain and might be involved with a post-stimulus arousal response.

In studies by Lamour et al. (Lamour et al. 1982, 1983a, 1983b), nociceptive SI cortical neurons in anesthetized rats were identified. About one third of all neurons responded to nociception. These cells were intermingled with non-nociceptive neurons and were not arranged in columns. They identified 35 WDR neurons with small receptive fields that were located mainly in layer V (with a few in layer VI) of the cortex. They also identified 56 HT neurons, mainly in layers Vb and VI, that had large receptive fields covering most of the body.

Two types of SI neurons have been identified in cat and monkey in response to electrical tooth pulp stimulation (Kenshalo and Willis 1991). Type 1 have restricted receptive fields, respond at a short latency (about 10 msec) after the stimulus, and are located mainly in layer IV. Type 2 have large receptive fields, respond more variably, usually requiring temporal summation of a number of stimuli before activation, are not organized in a topographic fashion and are located in superficial layers of cortex in area 3b and possibly area 3a.

A recent study investigated C fiber stimulation in rats using CO_2 laser stimulation (Kalliomäki et al. 1993). They found neurons that had crude graded responses to different intensity stimuli and had widespread receptive fields that had a crude topographic organization.

In summary, many different types of SI neurons have been identified that respond to stimuli in the noxious range. These range from WDR neurons that closely follow the intensity of the stimulus, through neurons that crudely follow the intensity, to cells that only respond at the highest levels. In addition, cells have been identified that respond easily to low threshold, non-noxious stimuli in a specific region, but also respond to noxious stimuli over most of the rest of the body. In their review, Kenshalo and Willis (1991) suggest that SI underlies the sensory-discriminative aspect of pain. In support of this view, they discuss the ability of WDR neurons to represent changes in intensity and they cite evidence that complete bilateral ablation of areas 4, 3a, 3b, 1 and 2 in monkeys slowed their ability to discriminate changes in noxious thermal stimuli. While this evidence indicates that SI is likely to be involved with the sensory-discriminative aspect of pain, the fact that the monkeys were still able to make the discriminations at all implies that other brain regions also provide a discriminative capability. In addition, the presence of HT neurons (that do not code for small changes in intensity) may imply that SI participates in more than just the sensory-discriminative aspects of pain.

Secondary somatosensory cortex

Neurons have also been identified in the SII region of primates that respond to noxious levels of stimulation. Robinson and Burton (1980) found only 3% noxious responding cells in SII proper, but found clusters of both WDR and HT neurons in the neighboring area 7b. Both kinds of neurons had large receptive fields. Dong et al. (1989) found only HT neurons on the border of SII and 7b (located in the lateral sulcus on the upper bank of the frontoparietal operculum) in

layers IV-VI. These neurons were not topographically organized.

SII, unlike SI, receives its major thalamic input from the ventroposterior inferior nucleus which is known to receive spinothalamic tract terminations, not VPL. Area 7b receives input primarily from the medial and oral divisions of the pulvinar and the lateral posterior nucleus. There are also reciprocal cortical connections between SI, SII, and 7b. SII has access to the limbic system via projections to the insular cortex and area 7b has access to the limbic system via projections to area 5 and SII (Dong et al. 1989; Friedman et al. 1993). Since area 7b is an area with multimodal input from both the somatosensory system and the visual system, the authors speculate that learned behavior, such as the avoidance of pain-producing objects, may depend on the nociceptive SII-7b neurons (Dong et al. 1989).

Other cortical regions

The ventrolateral orbital cortex of the cat, a prefrontal lobe region possibly corresponding to the inferomedial orbital cortex in man, has recently been investigated (Snow et al. 1992). Forty four of 60 neurons studied responded to noxious stimulation. These were HT neurons that only responded to prolonged pinching, heating, or twisting. Neurons were relatively unresponsive to non-noxious stimulation. Sometimes the noxious stimulation increased the activity from baseline levels and sometimes it *decreased* it from baseline. These cells had very large receptive fields often covering all four limbs, and showed no evidence of somatotopic organization. This region of cortex receives input from the thalamic nucleus submedius (Sm) which contains neurons that respond to noxious stimuli applied over wide areas of the body. The authors suggest that the ventrolateral

orbital cortex may be involved with the affective-motivational aspect of pain.

The last cortical area presented here is area 24 of the cingulate cortex, studied in rabbits by Sikes and Vogt (1992). Most of these neurons did not respond to non-noxious stimuli, except for a "tap" to the skin, which elicited a response in 11 of 14 neurons (79%). Noxious transcutaneous stimuli activated 150 of 542 neurons (27%); noxious mechanical stimuli activated 93 of 221 neurons (42%); and noxious heat activated 9 of 47 neurons (19%). All neurons had broad receptive fields with 30% having a contralateral preference for activation, 24% having an ipsilateral preference and 46% having no preference. Most nociceptive responding neurons were located in layers III, II and V, and showed a somewhat graded response to different levels of noxious intensity. The authors note that the response properties of these cingulate neurons, including their responsiveness to "tapping," are similar to the properties of thalamic neurons in the parafascicular, centrolateral and submedial nuclei, all of which project to area 24. Sikes and Vogt ruled out a number of cortico-cortical inputs as the source of the nociceptive responding by making surgical lesions to remove the multisynaptic input from somatosensory, insula, parietal, and posterior cingulate cortices. However they did not rule out input from areas 25 and 11 (which is the ventrolateral orbital cortex in the rat) which was shown above to respond to noxious stimuli.

In summary, the analysis of cortical responses to noxious stimuli is still in the early stages. A number of structures have been identified as candidates for involvement in pain processing, but their exact roles and functional properties are not yet clear. An additional problem, that is rarely discussed, is that the results from this line of work are severely limited by the use of general anesthesia in most of the animal studies, which is used for ethical and practical reasons, and which

must surely interfere with pain processing in higher centers. Recent work by Kochs, Treede, Esch & Bromm (1990) has shown that halothane, a general anesthetic, dramatically suppresses somatosensory evoked responses to painful stimuli in humans, indicating altered cortical processing of pain. The general anesthesia may greatly limit the number of cells that respond and could conceivably also change their response properties.

Clinical studies

Clinical evidence for the role of the cerebral cortex in pain processing has been reviewed by Kenshalo and Willis (1991) and by Sweet (1982). Most injuries affecting pain sensation point to the involvement of SI and SII. Many clinical investigations have found that lesions to SI decreased pain sensitivity and in some cases led to a permanent and highly localized contralateral analgesia. There are also reports of several patients who developed hypalgesia or analgesia as a results of lesions in the SII region in the Rolandic opercular region. Surgical lesions to SI have been attempted for pain relief, but it is no longer an "attractive option" because the patient's pain usually returns after several months.

Surgical lesions have also been made in the prefrontal cortex (prefrontal lobotomy) in an attempt to relieve pain. This intervention often results in the patient being able to sense pain but without being concerned about it. This suggests that the affective-motivational system has been disrupted. The severe side effects have discouraged the use of this procedure. Sweet (1982) suggests the use of cingulotomy or subcaudate tractotomy as alternatives to prefrontal lobotomy, and comments that they do not produce the same severe psychological effects.

The possible role of the cortex in pain *inhibition* is suggested by clinical lesions of SI or SII that produce a central pain syndrome similar to the "thalamic syndrome." The thalamic syndrome results from a lesion to the ventral posterolateral nucleus of the thalamus and involves spontaneous pain with spasms of severe pain and exaggerated responses to noxious stimuli. Sometimes the spasms of severe pain can be triggered by light stroking of the skin, loud noises, bright lights, or other mild irritants (Fields 1987). Kenshalo and Willis (1991) speculate that there may be a separate "pain *inhibitory* control mechanism" located in the postcentral gyrus, posterior to the pain *sensation* mechanism near the central gyrus. This could explain why cortical lesions sometimes produce analgesia, sometimes produce central pain, and sometimes have no clear effect.

Two recent papers have pointed to the insula as an area with a key role. Berthier et al. (1988) found that six patients with lesions all involving the insular cortex displayed asymbolia for pain, a clinical syndrome involving a lack of withdrawal from, and inadequate emotional responses to, painful stimuli and other threatening stimuli. These patients did not display primary sensory deficits and their disorder was interpreted as a result of an interruption of connections between sensory cortices and the limbic system. The posterior insula has been shown to be reciprocally connected with the limbic system (basomedial and lateral amygdaloid nuclei) and various sensory cortices (SI, SII, areas 5 and 7b, as well as auditory and visual cortical areas) (Berthier et al. 1988). The authors speculate that the sensory-limbic disconnection may interfere with the limbic elaboration of sensory information, or alternatively, may interfere with the later cortical elaboration of a limbic signal that may be necessary for the appropriate cognitive and behavioral reactions to pain.

Greenspan and Winfield (1992) documented a case where a patient had lateralized sensory differences (a higher mechanical pain and heat pain threshold, greater cold pain tolerance, and poorer ability to discriminate roughness on one side) that was eliminated after neurosurgery. The authors attributed the deficit to tumor pressure on the retroinsula and the neighboring parietal operculum, and its elimination to the removal of the tumor.

Functional imaging studies

Another approach that is just beginning, but that promises to make an important contribution, is to study cortical activation in response to painful stimuli in awake, unanesthetized humans using functional imaging methods. Three published studies and four as yet unpublished studies have been completed in the last three years.

In a study published in *Science*, Talbot et al. (1991) from the University of Montreal, used PET-MRI technology to study human cortical responses to noxious thermal stimuli. They found three areas that responded more to painful heat probes than to warm, non-painful probes: anterior cingulate gyrus, SII and SI, all significantly activated only on the contralateral side. As the anterior cingulate activation was somewhat unexpected, an analysis on six subjects verified that the anterior cingulate was not also activated by the warm probes (as compared to a no probe control). In this study the authors did not report an analysis of thalamic activity as they did not have a complete data set for subcortical levels (Duncan et al. 1992). The results of this and other functional imaging studies are summarized in Table 1.

At the October, 1992 American Pain Society meeting, the Montreal group

presented the results from a second PET-MRI study (Coghill et al. 1992). In this study, each subject was scanned during painful heat probes, neutral probes, and vibration probes. When compared with the neutral probes, both the painful and vibration probes produced increases in SI, SII and areas adjacent to SII "such as the retroinsular cortex." The painful probes, but not the vibration probes, produced activation significantly greater than neutral probes at contralateral anterior cingulate gyrus (area 24), supplementary motor areas, and contralateral thalamus. However, when painful and vibration probes were directly compared, only one region was significantly more active in response to pain: the anterior portion of the contralateral insular cortex.

Jones et al. (1991; 1992) performed a similar experiment using PET (but not MRI) to study responses to a heat probe in six subjects. Jones et al.'s heat probes differed from the Montreal experiments in that Jones et al.'s probe was used on only one site on the back of the hand, whereas Talbot et al.'s probe was moved to different positions on the forearm (Jones et al. 1992). Jones et al. also used a milder temperature probe (46.4 °C vs. Montreal's 48-49°C). When comparing responses to painful heat with responses to non-painful heat, they found regional blood flow increases in the contralateral cingulate cortex, contralateral thalamus and contralateral lentiform nucleus. There were also non-significant trends for activation in the ipsilateral lentiform nucleus and prefrontal cortex (areas 45 and 46), but not in SI or SII of either hemisphere. In a control analysis, no significant areas of difference between *non-painful* warm and *non-painful* heat probes were found.

Apkarian et al. (1992) studied regional cerebral blood flow (rCBF) using SPECT with three subjects in response to finger immersion for three minutes in a

hot water bath rated as moderately painful compared to immersion in a tepid water bath. They found a *decrease* in rCBF in contralateral SI to this pain stimulus in contrast to an *increase* in rCBF when the subject received a vibratory stimulus or manipulated something in his hand. The authors suggest that the decrease in rCBF is due to the "sustained" or "persistent" nature of the painful stimulus in their experiment.

At the November, 1993 American Pain Society meeting Ken Casey presented results from three PET rCBF studies (Casey 1993). Using nine subjects, and comparing movable probes of 40°C (warm) and 50°C (painful) he found significant rCBF increases on the contralateral side in thalamus, insular cortex, SII, anterior cingulate cortex and SI. On the ipsilateral side, there were increases in thalamus, SII, and some anterior cingulate. On the midline, there were increases in the vermis of the cerebellum and the dorsal midbrain in the region of the periaqueductal gray. In a second study, the forearm was cooled to 21-24°C and non-painful probes of 32°C and 42°C were compared. Consistent, with the results of Talbot et al. and Jones et al. (Jones et al. 1991; Talbot et al. 1991), no significant differences were found between two *non-painful* probes.

In a third study, the pain stimulus was the cold pressor test (immersion of the hand in 5-6°C water), with immersion in room temperature water as the control condition. The cold pressor produces a deep and aching pain and contrasts with the cutaneous pain of the heat probes (Dowling 1983; Rainville et al. 1992; Casey 1993). Significant pain vs. control activation was found contralaterally at SI, anterior cingulate, superior parietal lobule, primary motor cortex, and bilaterally at insula (or possibly the lentiform nucleus), and SII, and at the vermis of the cerebellum. The anterior cingulate was more activated by the cold pressor than

the heat probes. There was no significant thalamic activation.

Finally, at the same 1993 conference, Mike Iadarola of the NIH presented PET results using painful capsaicin injections in 13 subjects (Iadarola 1993). Compared to a resting state, the acute pain response to the capsaicin produces greater activation in several slices of the anterior cingulate, SI, midline thalamus, lentiform nucleus bilaterally, insula bilaterally, the periaqueductal gray and the cerebellar vermis. After the acute pain from the capsaicin injection subsides, the area remains sensitized so that even light touch will produce pain (allodynia). Scans were made of light touch at the beginning of the experiment and of the same light touch during the phase of allodynia. The main differences were in anterior cingulate, SI and some of the insula.

TABLE 1. SUMMARY OF FUNCTIONAL IMAGING STUDIES OF PAIN RESPONSE

Region of statistically significant increase	Talbot 1991 moving heat probe vs. warm probe	Coghill 1992* moving heat probe vs. neutral probe	Coghill 1992* moving heat probe vs. vibratng probe	Jones 1991 statnry heat pain vs. non-painful heat	Casey 1993* moving heat probe vs. warm probe	Casey 1993* cold pressor vs. room temp. water	Iadarola 1993* acute capsaicn respnse vs. prestim. resting	Iadarola 1993* all'dynia brushng respnse vs. prestim. brushng	Apkar'n 1992 hot water vs. room temp. water SPECT
Contralateral									
SI	✓	✓			✓	✓	✓	✓	decrease
SII	✓	✓			✓	✓			
Cingulate	✓	✓		✓	✓	✓	✓	✓	
Insula			✓		✓	✓	✓	✓	
Thalamus	—	✓		✓	✓				
Lentiform nucleus				✓			✓		
Supl. motor area		✓							
Sup. parietal lobule						✓			
Prim. motor cortex						✓			
Ipsilateral									
SII					✓	✓			
Cingulate					✓				
Insula						?	✓		
Thalamus					✓				
Lentiform nucleus						?	✓		
Midline									
Cerebellar vermis					✓	✓	✓		
Dorsal midbrain					✓		✓		
Thalamus (near)							✓		

*Unpublished study

Inspection of Table 1 reveals some consistency, but also a great deal of inconsistency in the regions showing an increased pain response. SI and SII, the

most studied regions in the animal experiments, show results that vary widely. SI shows increases in six comparisons, a *decrease* in one comparison and no significant change in two comparisons. SII shows four out of nine increases. It may be that the somatosensory cortical response is dependent on the specific type of pain stimulus and is not *necessarily* involved in the essential elements of painfulness.

The cingulate cortex, usually the anterior cingulate, showed significant increases in all but one of the PET comparisons and may very well be a key structure in pain processing. However, one note of caution, at a seminar on functional imaging at the recent AAAS conference in San Francisco in February 1994, Kenneth Kwong mentioned that his functional MRI lab is finding that the cingulate cortex is active in almost all of their studies dealing with a wide variety of functions, including motor function, language, and olfaction. He said it has become a "landmark"; if they don't see it activated, they doublecheck their methodology!

Jones et al. (1991) suggested that the activation they observed in the lentiform nucleus might be related to an "alerting or priming mechanism for the motor system," even though there was no detectable movement by the subjects. This same logic may apply to other activated regions that are part of the motor system: primary motor cortex, supplementary motor area, and cerebellum. Inherent in the affective-*motivational* aspect of pain is a tendency or urge to withdraw from the pain. Perhaps there is a "hard-wired" connection to the motor system that is an intrinsic part of a response to pain.

The insula was activated in five of the nine PET comparisons, but importantly, was the only region activated more by painful heat probes than non-painful vibration probes (Coghill et al. 1992). In addition, the two clinical studies

cited above, and the insula's position linking the sensory cortex with the limbic system, point to the important role for this area of cortex. It is not clear to me how well these PET studies are able to separate activity in the insula from activity in the nearby areas of SII, retroinsular cortex, and area 7b (located on the inner bank of the frontoparietal operculum and overlaying the insula) and from the lentiform nucleus (located just medial to the insula), especially if MRI is not used to assess individual differences in anatomy. As presented above, area 7b has been shown to contain noxious responding neurons and also has multimodal links to different sensory cortices and to the limbic system.

While it must almost certainly be the case that the full expression of the pain system requires a network of many different structures, the insula, and/or the nearly adjacent area 7b, may be the prime candidates for *essential* structures underlying painfulness.

It is also interesting to note the inconsistent activation of ipsilateral structures. Few comparisons showed ipsilateral increases, and only ipsilateral SII showed significant increases in more than one comparison. Until the Coghill, Casey and Iadarola studies are published it is not possible to tell if the different studies are using different criteria for activation or are using different alpha levels for their tests of statistical significance.

Somatosensory evoked potential studies

Somatosensory evoked potentials (SEPs) to painful stimuli provide another avenue of research into cortical processing of pain. SEPs, like all event-related potentials (ERPs), are measures of the electrical field produced by the brain that is recorded from one or more locations on the scalp. The brain's electrical field goes through a reliable series of changes in response to a specific stimulus. The field is

mainly due to activity in the cerebral cortex consisting of synchronized EPSPs and IPSPs (excitatory and inhibitory postsynaptic potentials) in groups of pyramidal cells (Rockstroh et al., 1989). Unlike most other neurons, these cells have a morphology that produces an open (vs. closed) field potential. The field is produced as a result of the parallel arrangement of the cells' elongated apical dendrites.

This analysis indicates that ERPs in general, and SEPs in particular, are indicators of the activity of a very specific subset of total brain activity, i.e., the activity of cortical tissue containing pyramidal cells. Much CNS activity is completely invisible to ERP recording. However, the ability to assess activity in this very important subgroup of cells in human cerebral cortex is invaluable for the study of higher order brain function. ERPs can be recorded non-invasively from awake humans performing various cognitive tasks and can be correlated with subjective reports made by humans. They can provide extremely fine-grained analyses of the time course of cortical responses, with resolution below the msec level. Furthermore, recent advances in topographic mapping of evoked potentials coupled with large arrays of recording electrodes, can contribute to the localization of the cortical activity in the brain.

Given these advantages, SEP methodology might have the power to identify and characterize some aspects of the physiology and anatomy of cortical processing of painful stimuli. This research can be done non-invasively with awake human volunteers and, unlike animal research, without analgesics or anesthetics. In addition, SEP recording is inexpensive and the necessary equipment is widely available, in contrast to the inaccessibility and expense of PET and other functional imaging technologies.

SEPs as measures of pain processing or pain experience

Somatosensory evoked potentials to painful stimuli also relate to a body of research with goals quite different from the physiological and anatomical research goals mentioned above. Literally hundreds of studies have demonstrated that a large number of psychological influences bear upon the experience of pain. These include attention & distraction, imagery, coping self-statements, hypnosis, operant conditioning, social modeling, biofeedback, expectancy and placebo effects, perceived controllability, cognitive dissonance, reinterpretation of the stimulus, and relaxation. Since past research has shown that there are no valid and reliable autonomic or behavioral measures of pain, most of the psychology of pain and analgesia studies have utilized *self-report measures* of experienced pain as their dependent measure.

Self-report measures are problematic in that they are subject to response biases, the demand characteristics of the situation, and falsification. In addition, they are considered "reactive" measures in that they interfere with the very effect they are supposed to measure. For example, it is not possible to adequately study the effects of distraction on pain using self-report measures because the act of making a pain rating necessarily requires the subject to refocus his attention on the pain experience, and breaks the distraction.

If an SEP measure is specifically related to pain processing or pain experience, it could be used as a dependent measure in studies of the psychology of pain and analgesia, as well as in studies of the pharmacology of pain and analgesia, and perhaps even as a physiological correlate of pain in the clinic. So when Chatrian, Canfield, Knauss & Lettich (1975) reported the discovery of "an objective correlate of acute experimental pain," a large body of research examining

the relationship of the SEP to experimental pain followed (for reviews, see Bromm 1984; Stowell 1984; Bromm 1985; Chapman 1986; Bromm 1989; Bromm and Treede 1991; Chen 1993; Handwerker and Kobal 1993).

A number of studies have found high correlations between SEP measures and subjects' self-report of pain sensation (Stowell 1977; Carmon et al. 1978; Harkins and Chapman 1978; Chen et al. 1979; Bromm and Scharein 1982a; Fernandes de Lima et al. 1982; Umino et al. 1988), although results have not been unanimous (Brennum and Jensen 1992). The two most comprehensive studies examining the relationship of SEP measures to self-report of sensation and to stimulus intensity (Chen et al. 1979; Bromm and Scharein 1982a) both used partial correlation analyses to show that some SEP measures (those in the latency range of 170-340 msec after the stimulus) were more closely related to the subjective report than they were to the intensity of the physical stimulus used to produce the painful sensation.

These results have been largely responsible for the view that the SEP to painful stimuli may be an objective correlate of painful sensation. This view has been supported by findings that the SEP, like the subject's self-report of pain sensation, is sensitive to the effect of analgesic drugs and their antagonists. More than 60 studies have been conducted with both opioid and non-opioid drugs. Although there were important methodological problems with many of these studies (Handwerker and Kobal 1993), most found that SEPs were affected by the analgesic drugs. In addition, of the few studies that examined psychological analgesic processes: placebo analgesia (Cruccu et al. 1983), changes in attention (Leandri et al. 1985), and hypnosis (Arendt-Nielsen et al. 1990; Zachariae et al. 1991; Meier et al. 1993), all but one (Meier et al. 1993) found significant effects on

SEP amplitude.

SEPs generated by different types of pain stimuli

Another argument used in support of the SEP as a measure of pain processing is that a number of different types of painful stimuli (e.g. electrical stimulation of the skin and teeth, mechanical stimulation of the skin and laser stimulation of the skin) all produce a morphologically similar SEP at the vertex (electrode "Cz") (Bromm, 1985). Recently, SEPs have also been recorded in response to focused ultrasonic stimulation of the articular nociceptors in finger joints (which produces a "throbbing, penetrating, dull, aching" pain) (Wright and Davies 1989; Wright et al. 1993), and to painful concentrations of CO_2 or nicotine gasses delivered to a nostril with a rapid rise time as part of a constantly flowing air stream (Kobal et al. 1990; Hummel et al. 1992). While the waveforms produced by all of these stimuli have some crude similarity, i.e., the waveform contains a series of positive and negative peaks with very roughly the same latencies, it may be more indicative of somatosensory processing in general than of pain processing.

A number of recent studies (for review see Bromm and Treede 1991) have utilized CO_2 -laser or Argon-laser stimuli to evoke SEPs. The short heat pulses produced by the laser selectively activate peripheral A delta and C fibers and produce two pain sensations: a pinprick followed by a burn. There is also a small range of non-painful sensations produced at low stimulus intensities which also appear to be triggered via A delta fibers (Pertovaara et al. 1988). The typical laser evoked waveform is characterized by an N240 and P370 (a negative peak at 240 msec and a positive peak at 370 msec) which presumably corresponds to the N150-P250 evoked by electrical stimuli (Treede et al. 1988). Laser evoked SEPs have

been shown to be capable of assessing altered cutaneous sensitivity of temperature and pain in neurological patients, including those with syringomyelia, encephalomyelitis disseminata, myelitis, Brown-Sequard syndrome, and Wallenberg syndrome, in contrast to short latency electrical SEPs which are triggered via different fiber populations.

"Ultralate" laser evoked SEP peaks (N1050, P1250) have been linked to transmission via C fibers. These peaks usually appear only when the A fibers are blocked with a pressure block, or in cases where a polyneuropathy has predominantly affected large fibers and so has mimicked an A fiber block (Bromm and Treede 1991). It is not clear why the ultralate peaks are not visible without a pressure block. Bromm and Treede suggest that the C fiber peaks are attenuated because the A fibers have already "announced" the stimulus. Furthermore, if the same neural generators are involved for the two sets of peaks, the second response may be in the refractory period of the first.

The validity of the pain SEP

Dozens of studies have been carried out using the SEP as a measure of pain processing. Yet the validity of the SEP as a measure of pain is compromised by two important issues. First, as a number of authors have pointed out (e.g. Harkins and Chapman 1978; Fernandes de Lima et al. 1982; Bromm 1985; Miltner et al. 1989) all of the obvious positive and negative waveform peaks of the SEP to painful stimuli are also present in the SEPs to lower intensity, *non-painful* stimuli, thus indicating that none of the SEP waveform peaks has a one-to-one relationship with painful sensation. This calls into question what aspects of the SEP are related to pain sensation. Most studies have either measured peak amplitudes or have measured the spectral power in the low frequency range which is functionally

equivalent to measuring the peak amplitudes of the later, broader peaks. It is conceivable that the SEP is a measure of subjective *intensity* and not of subjective *pain*. Since previous studies had not analyzed the effect of increased intensity among stimuli that were below the pain threshold, they were not able to determine whether the SEP measures that correlate with subjective *pain* intensity would also correlate with subjective *non-pain* intensity for lower intensity stimuli.

The second issue deals with the relationship of the pain component to other so-called "endogenous" components of SEPs, i.e., those components that are not primarily tied to the physical characteristics of the stimuli, but rather result from cognitive processes involving the meaning of the particular stimulus to the subject, the state of the subject, and/or the information-processing demands of the subject's task (for reviews see Rösler et al. 1986; Hillyard and Picton 1987). In particular, the group of endogenous components known as P300 components occur during the same latency range as the pain-evoked late positive waveform and are prominent at the same scalp sites as the pain-evoked late positive waveform. P300 waveforms are large positive waveforms that peak approximately 300 msec after the stimulus. They are typically seen in evoked potentials to infrequent stimuli that have been designated as "targets" by requiring the subject to respond to those stimuli by performing a motor movement or a cognitive operation (such as counting the stimuli). The same physical stimuli, if presented frequently and not designated as targets, do not elicit a P300 response.

To review, previous work has indicated that under certain conditions, different measures of the SEP to painful stimuli do correlate with subjective pain ratings. However, despite the large number of studies that have employed the pain evoked potential, it is not yet clear whether the SEP measures are actually

measures of CNS pain processing. One possibility is that the correlation with subjective pain is due to a P300 in the SEP that results from a *secondary reaction* to pain (such as "orienting," "surprise," or "recognition" of an important stimulus) that is larger for higher levels of pain. Another possibility is that the SEP measures are measures of CNS activity underlying subjective intensity across both the pre-pain and pain ranges of intensities, and are thus not measures of pain processing, per se.

A clear identification and characterization of an SEP component that is specifically and unambiguously related to CNS processing of pain would be a major advance. This component would have great value as an objective and non-invasive measure of pain processing and could be used with more validity in studies of the efficacy of various analgesic interventions than are current SEP methods which seemingly confound a number of different processes.

Research goals of this dissertation

The goal of my dissertation research, stated generally, is to examine the validity of the Pain SEP. More specifically, the goal is to determine which aspects, if any, of the Pain SEP are specifically related to pain processing, and which aspects, if any, are related to the two issues discussed above. A second goal is to characterize the latencies and topographies of these three effects.

Chapter Two of this dissertation reprints the already published article, *Identification of pain, intensity and P300 components in the pain evoked potential* (Becker et al. 1993). It outlines the strategy for separating these three effects using a subtraction, or "difference wave," method to produce a "pain component," "intensity component," and "P300 component." Three hypotheses are tested:

1. The Pain component occurs at a later latency than the Intensity component.

2. The Pain component occurs at an earlier latency than the P300 component.
3. The Pain component and P300 component have different topographies as measured at two electrodes (Cz and Pz), with the P300 component having a more posterior distribution than the Pain component.

Chapter Three reports analyses on additional data from the same recording sessions that were reported on in Chapter Two. These analyses focused on the overall scalp topography as measured with 30 electrodes. The same three components that were identified in Chapter Two were mapped, and a statistical analysis was conducted that compared the topographies of the different components using the results from all 30 electrodes simultaneously. Four hypotheses were tested:

1. The Pain component occurs at a later latency than the Intensity component (using 30 electrodes).
2. The Pain component occurs at an earlier latency than the P300 component (using 30 electrodes).
3. The Pain component's topography is different from that of the P300 component.
4. The Pain component's topography is different from that of the Intensity component.

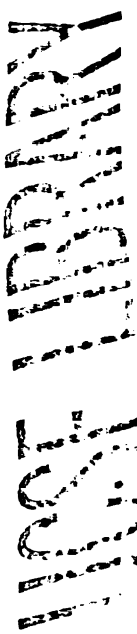
Chapter Three also presents the topographic maps of the peaks of the raw SEP waveforms (i.e., not of the difference waves) for comparison with the few studies that have previously examined the topography of these peaks, and makes some rudimentary observations about the anatomy of the neural generators that

must give rise to the observed topographies.

The dissertation concludes with a short summary and overall discussion in Chapter Four.

CHAPTER 2

IDENTIFICATION OF PAIN, INTENSITY AND P300 COMPONENTS IN THE PAIN EVOKED POTENTIAL



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Identification of pain, intensity and P300 components in the pain evoked potential *

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Summary This study examined the relationships among 3 components of the somatosensory evoked potential (SEP) to painful stimuli. Painful stimuli were produced using intracutaneous electrical stimulation of a fingertip and two levels of non-painful stimuli were produced by superficial electrical stimulation of a neighboring fingertip. SEPs were recorded from Cz-A1 and Pz-A1, and difference waves were computed for 3 components: (1) a pain component (the difference between SEPs to painful vs. strong but non-painful stimuli); (2) an intensity component that is not related to pain (the difference between SEPs to strong non-painful vs. mild non-painful stimuli); and (3) a P300 component (the difference between SEPs to the same stimuli under Target instructions vs. Standard instructions).

The positive peaks in the 3 types of difference waves differed in both latency and topography, although with latency and topography overlap. The intensity component had an earlier positive peak than the pain component, and the pain component had an earlier positive peak than the P300 component. The pain and intensity components were larger at Cz than Pz, whereas the P300 component was larger at Pz than Cz. Under certain conditions, the pain evoked SEP consists of a weighted combination of the 3 components, complicating interpretation of the positive peaks in the recorded wave forms.

Key words: Pain evoked potential; Somatosensory evoked potential; P300 component; Pain measurement

Since Chatrian et al.'s (1975) purported discovery of "an objective correlate of acute experimental pain," the relationship of the somatosensory evoked potential (SEP) to experimental pain (the "pain SEP") has received considerable attention (for reviews, see Chapman et al. 1979; Bromm 1984, 1985, 1989; Stowell 1984; Chapman 1986). High correlations between SEP measures and subjects' self-report of pain sensation have been consistently reported (Stowell 1977; Carmon et al. 1978; Harkins and Chapman 1978; Chen et al. 1979; Bromm and Scharein 1982a; Fernandes de Lima et al. 1982; Umino et al. 1988), with two studies finding higher correlations of SEP measures (in the 170–340 msec latency range) with subjective report than with the intensity of the pain producing stimulus (Chen et al. 1979; Bromm and Scharein 1982a). The view that the pain SEP may be an objective correlate of painful sensation is supported by findings that different painful stimuli (e.g., electrical stimulation of the skin or teeth, mechanical stimulation of the skin, or laser stimulation of the skin) produce morphologically similar SEPs at Cz (Bromm 1985) and by findings that changes in the pain SEP produced by analgesic drugs and their antagonists parallel the effects of the drugs on pain sensation (e.g., Chapman et al. 1979; Bromm et al. 1983).

However, all of the obvious wave forms or components of the pain SEP are also present in SEPs to lower intensity, *non-painful* stimuli (Harkins and Chapman 1978; Fernandes de Lima et al. 1982; Bromm 1985; Miltner et al. 1989). Although the pain SEP consists of larger amplitude wave forms, it is conceivable that all or part of the larger wave forms result from some aspect of the subject's reaction to the relatively higher *intensity* of the painful stimuli, and not to their *painful* quality, per se. Since previous pain studies had not analyzed the effect of increased intensity among stimuli that were below the pain threshold, they could not determine whether the pain SEP measures would also correlate with subjective intensity for lower intensity (non-painful) stimuli.

In addition, the interpretation of the pain SEP is complicated by its relationship to the endogenous components of the SEP (for reviews see Rösler et al. 1986;

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Hillyard and Picton 1987). For example, in the SEP to weak, *non-painful* target stimuli, the P300 component, which reflects processing of stimulus meaning (Desmedt and Robertson 1977; Desmedt et al. 1987) largely overlaps, in both latency and topography, the wave forms elicited in response to *painful* stimuli that are *not* explicitly designated as targets. To date, no studies have specifically examined the relationship between the pain SEP and P300 components. It is conceivable that the late positive component of the pain SEP may reflect some aspect of the subject's reaction to the stimulus, such as the "orienting," "surprise," or "recognition" response to an important (in this case, painful) stimulus, and not the neural processing of pain, per se.

We hypothesized that the 3 processes discussed above, loosely stated as: (1) reaction to intensity, (2) reaction to pain, and (3) target recognition, are separable and give rise to distinct neural activity with differing effects on the SEP. We designed a protocol where these 3 SEP processes could be measured and differentiated from each other by comparing their latencies and topographies using difference waves. Specifically, we hypothesized that target recognition processing would occur later than pain processing and have a more posterior ERP topography, and that pain processing and intensity processing would occur at different latencies.

Methods

Subjects

Fourteen right-handed males, aged 19–36 years, were recruited as paid volunteers from a local college. All indicated that they were in good health, had no neurological problems and were not taking medication that affected their alertness.

Stimuli

Stimuli consisted of single unipolar electrical pulses of 1 msec duration delivered to the centers of the palmar surfaces of the distal phalanges (fingertips) of the middle or index fingers of the left hand. Fingertips were prepared by vigorously rubbing with an alcohol swab. For half of the subjects, the index finger served as fingertip no. 1 and the middle finger served as fingertip no. 2. The other half of the subjects had the opposite configuration.

Fingertip no. 1 was covered with a piece of plastic Tegaderm (TM) adhesive bandage with a 7 mm diameter hole in order to limit the spread of current. A Grass gold cup electrode filled with Grass EC2 electrode cream was used as the positive stimulating electrode. It was taped to the intact skin within the 7 mm hole.

Fingertip no. 2 was prepared for stimulation following a modified version of the procedure suggested for "intracutaneous pain stimuli" by Bromm and Meier (1984). An approximately 1.5 mm diameter shallow cavity in the center of the fingertip was created by gently abrading the skin with a rotating Dremel engraving cutter burr (model no. 106; steam-autoclave sterilized before each use) using a high-speed moto-tool. Care was taken to avoid damage to the underlying dermis. In the rare case of bleeding, the procedure was interrupted and repeated on a neighboring skin area. The positive stimulating electrode for fingertip no. 2 was a custom-made blunt stainless steel pin, 1.2 mm in diameter by 1 mm in length, embedded in a plastic cover. A tiny dab of ECI Electro-gel was placed in the skin cavity and the electrode was then taped into place in the cavity. Impedance of this electrode was kept below 5 kΩ (in contrast to impedances of 50–100 kΩ for fingertip no. 1). Impedance was checked before each recording period and additional electrode jelly added, if necessary, to maintain 5 kΩ impedance.

The negative stimulating electrode used for both fingertips was a Grass gold cup electrode filled with Grass EC2 electrode cream and taped to the palmar surface of the middle phalanx of finger no. 1. Electrode cream was rubbed into the entire palmar surface of this phalanx before applying the electrode, and the entire phalanx was covered with tape. The mean impedance of this electrode was 30 kΩ.

These two methods yielded very different subjective sensations (see Bromm and Meier 1984). Stimuli delivered to fingertip no. 1 produced sensations that at low levels were perceived as "pulsing," or "dull." As the current was increased, these sensations could become subjectively quite strong, *without being uncomfortable or painful*. As current levels were increased further, the sensation became an increasingly unpleasant paresthesia that could become very uncomfortable. However, even at high levels described as "very uncomfortable," many subjects did not describe the sensation as "painful," perhaps because it lacked the "sharp" quality often associated with "pain." Prior to the introduction of the intracutaneous stimulation method, many studies used the above method for their "painful" electrical stimulation (e.g., Stowell 1977; Bromm and Scharein 1982a,b).

In contrast, the intracutaneous stimulation method (fingertip no. 2) produced a clearly "painful" sensation. At currents just above sensory threshold, a slight tingling sensation was reported. With increasing currents, subjects soon reported painful sensation, without reporting the dull pulsing sensations elicited on fingertip no. 1. The subjective intensity of the pain increased with increasing currents, becoming extreme at high currents. This stimulus has been most often described as "stabbing," "sharp" and "hot."

Three levels of stimuli were individually determined for each subject (see Procedure). Two levels of *non-painful* (and not uncomfortable) stimuli were delivered to fingertip no. 1. Using this method of skin preparation allowed us to deliver two levels of stimuli that were both non-painful and yet were clearly different in intensity. One level of *painful* stimuli was delivered to fingertip no. 2. This method allowed us to deliver stimuli that were quite painful without a strong paresthesia.

Stimulating hardware

All aspects of the experiment, including stimulus generation, EEG sampling, averaging, generation of difference waves and identification of peak latencies and amplitudes, were controlled by ERPSYSTEM software (Neurobehavioral Laboratory Software) running on an IBM compatible 80386 microcomputer. The stimulus signal from the computer's DAC was put through a Constant Current Isolation Unit (CCIU) (Frederick Haer and Co., Model No. 74-65-1) which also amplified the current but left the computer generated wave shape intact. The output of the CCIU, from 2 to 90 V batteries wired in series, was then put through a custom-made, isolated switching box that directed the current to one of the fingers under computer control.

Procedure

Each subject was read an overview of the experiment and completed consent forms approved by the Committee on Human Research before the recording and stimulating electrodes were attached.

Sensory threshold, pain threshold and pain tolerance levels were assessed using an ascending method of limits (Gescheider 1985). Subjects were informed that the intensity of stimuli to be used later in the experiment would be much lower than the high levels used in the pain tolerance assessment. As the two fingertips were prepared in different ways, they had very different threshold and tolerance levels. Series of stimuli were first delivered to fingertip no. 1 and then to fingertip no. 2, and the procedure was then repeated a second time. Only ratings from the second series were used since, after having experienced the full range of intensities, subjects were less apprehensive and much more confident in their judgments. This procedure provided reference points for the stimulus levels chosen by the subjects for the recording portion of the experiment and also served to familiarize the subject with the range of possible intensities he would experience.

For fingertip no. 1, subjects were given a 0–9 rating scale with the following points anchored: 0 = undetectable; 1 = just detectable; 2 = mild pulse; 3 = clear pulse; 5 = strong pulse; 6 = begins to be uncomfortable; 7 = clearly uncomfortable; 8 = very uncomfortable. Stimuli were first increased in 0.1 mA units until detection (i.e., sensory threshold) occurred. Stimuli were then increased in 0.5 mA increments. The lowest intensity rated, a 6, was the discomfort threshold, and the "highest level that you are willing to experience" was considered the pain tolerance level. Stimuli were discontinued at 10 mA (or at the compliance limit of the stimulator, if lower), even if the tolerance level had not been reached. No subject reached their tolerance level for fingertip no. 1, with the average rating of the highest stimulus (range 4–9) being 6.4 ("beginning to be uncomfortable").

For fingertip no. 2, subjects were given a *different* 0–9 rating scale that better fitted the sensations for this finger, with the following points anchored: 0 = undetectable; 1 = just detectable; 3 = faintly painful; 4 = mildly painful; 5 = moderately painful; 6 = rather painful; 7 = very painful; 8 = extremely painful. These descriptors were based on the psychometric work done by Gracely and Dubner (1987). Stimuli started below sensory threshold and were increased in units of 0.1 mA. The lowest intensity with a rating of 3 was considered the pain threshold. After the pain threshold was reached, subsequent stimuli were increased in 0.5 mA units. The "highest level that you are willing to experience" was considered the pain tolerance level. As with fingertip no. 1, we discontinued stimuli at a level of 10 mA (or the compliance limit, if lower). Only 2 of the 14 subjects had reached their tolerance level at that point, with the average rating of the highest stimulus (range 7–9) being 8.7 (above "extremely painful").

Determination of stimulus intensity levels used during the recording periods

Subjects were asked to choose 3 stimulus levels for use during subsequent recordings. Two, corresponding to ratings of 2 (mild pulse) and 5 (strong pulse), were used for fingertip no. 1. Since a rating of 6 indicated "begins to be uncomfortable," it was repeatedly emphasized that level 5 should be as strong as possible, but *"without being uncomfortable or painful."*

The third stimulus level, for fingertip no. 2, corresponded to a 6 rating: "rather painful" (above "moderately painful" and below "very painful.") Subjects were informed of the frequency of painful stimuli during subsequent recording periods and were asked to keep two things in mind in choosing the painful stimulus level: First, since the main purpose of the experiment was to analyze physiological responses to painful stimuli, it was necessary for them to choose stimuli that were clearly and definitely painful and not just mildly uncomfortable or strange. Second, we would not be able to change the levels of the stimuli during the session without starting over. Therefore, they should

not choose a level that was so high that they would not be willing to finish the experiment.

To determine the "mild pulse" to fingertip no. 1, a stimulus corresponding to a 2 during the thresholding procedure was presented to the subject, who was given the opportunity to raise or lower that level so as to produce the best "mild pulse" in light of all of their experience with the stimuli. Levels for the other two stimuli were chosen in the same way. As a result of experiencing the range of stimuli in the threshold and tolerance assessment, subjects reported no problem in choosing stimulus intensities in this way. Furthermore, after having experienced the very high intensity stimuli in the tolerance assessment, subjects did not seem particularly anxious about the relatively lower stimulus levels used in the recording sessions.

Mean stimulus levels chosen by the subjects (based on 13 subjects with accurate calibrations) were 1.79 mA for the "2 – mild pulse" and 6.32 mA for the "5 – strong pulse" for fingertip no. 1, and 3.41 mA for the "6 – rather painful" stimulus to fingertip no. 2. These levels for fingertip no. 1 corresponded to a mean of 14% and 77% of the distance from the sensory threshold to the discomfort threshold (based on 9 subjects; 5 subjects did not reach their discomfort level for fingertip no. 1 before we stopped the threshold assessment procedure at 10 mA). The level for fingertip no. 2 corresponded to a mean of 3.7 times each subject's individual pain threshold (based on all 14 subjects; range was 1.7–6.3).

Recording periods

During each recording period 1 of the 3 stimuli was designated as the target by instructions on a computer screen. The subject's task was to lift his right index finger immediately after the target, with no response required for the other 2 stimuli. The stimulus designated as the target was changed every 5–6 min. See Table I for a description of the stimuli in each recording period.

Evoked potential recording

Evoked potentials were recorded from 31 scalp sites using the ECI Electro-Cap electrode system. Only re-

TABLE I

Recording periods. Between blocks, subjects took short breaks of 1–2 min. Between periods B and C and periods C and D, the electrodes were disconnected so that subjects could walk around the building to refresh themselves.

Period A – practice
2 blocks of 50 stimuli each; ISI = 5–8 sec randomly.

Stimulus probability

First block		Second block	
Mild non-painful Standard	60%	Mild non-painful Standard	60%
Strong non-painful Target	20%	Strong non-painful Rare non-target	20%
Painful Rare non-target	20%	Painful Target	20%

Period B
Alternating blocks of 50 stimuli each; ISI = 5–8 sec randomly.

Stimulus probability

Half of blocks		Half of blocks	
Mild non-painful Standard	60%	Mild non-painful Standard	60%
Strong non-painful Target	20%	Strong non-painful Rare non-target	20%
Painful Rare non-target	20%	Painful Target	20%

The first 3 mild shocks of each block were "throw-away" stimuli that were not included in the averages. The type of block used as the first block was counterbalanced among subjects. Period B continued until a minimum of 20 artifact-free trials were collected for each type of stimulus.

Period C
Multiple blocks of 50 stimuli each; ISI = 5 sec fixed.

Stimulus probability

Blocks 1 and 4		Blocks 2 and 3	
Mild non-painful Target	10%	Mild non-painful Target	10%
Painful Standard	90%	Strong non-painful Standard	90%

Blocks 1 and 2 began with 12 "throw-away" Standard shocks and blocks 3 and 4 began with 5 "throw-away" Standard shocks. Period C continued until a minimum of 40 artifact-free trials were collected for the Painful Standard and the Strong non-painful Standard stimuli.

Period D
Exactly the same as period B.
Trials from periods B and D were combined so as to produce a minimum of 40 artifact-free trials for each type of stimulus.

TABLE II

Generation of difference waves. For each difference wave, the second SEP was subtracted from the first.

Dif. wave no.	1st SEP	Recorded during periods	2nd SEP	Recorded during periods
P300 component (Target – Standard)				
1	Painful Target	B and D	Painful Standard	C
2	Strong non-painful Target	B and D	Strong non-painful Standard	C
Pain component (Painful – Strong non-painful)				
3	Painful Target	B and D	Strong non-painful Target	B and D
4	Painful Standard	C	Strong non-painful Standard	C
5	Painful Rare non-target	B and D	Strong non-painful Rare non-target	B and D
Intensity component (Strong non-painful – Mild non-painful)				
6	Strong non-painful Standard	C	Mild non-painful Standard	B and D

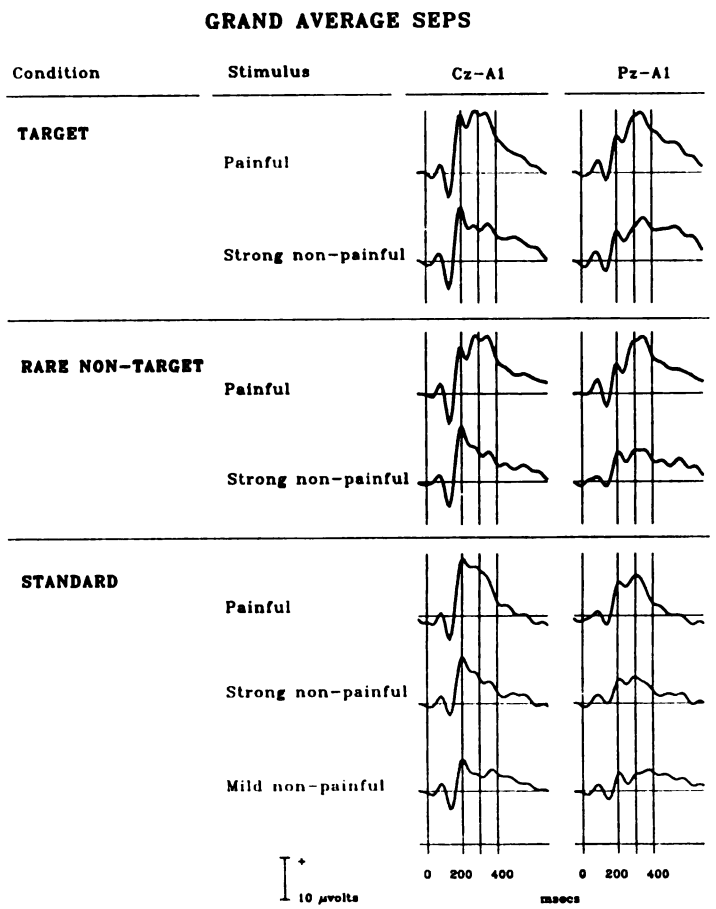

Fig. 1. Grand average SEPs at Cz-A1 and Pz-A1. Shown are SEPs to Painful stimuli and to Strong but not-painful and not uncomfortable stimuli. These two types of stimuli each served as Targets, Rare non-targets and Standards at different times during the session. Also shown is a SEP to Mild non-painful stimuli serving as Standards. All records shown in figures 1–4 are digitally bandpass filtered at 0.5–15 Hz.

sults from Cz and Pz, each referenced to the left earlobe (A1), will be presented here. Vertical and horizontal EOGs were recorded between gold cup electrodes placed above and below the left eye, and at the left and right outer canthi, respectively. Electrode impedances were kept below 1 kΩ at Cz, Pz, and A1 in order to minimize a possible contribution from a skin potential response. Subjects were grounded with a broad grounding plate attached to the left forearm.

Signals were amplified by a Grass Model 12 Neurodata Acquisition System (half amplitude at 0.1 and 100 Hz). Signals were sampled at 200 Hz from 50 msec before each stimulus to 600 msec after each stimulus. From 600 to 1800 msec signals were sampled at 100 Hz. Only data from the first 700 msec after the stimulus will be presented here. Trials contaminated by significant horizontal or vertical EOG artifact (i.e., signal excursions greater than 90 μV, peak-to-peak), with EEG artifact in any channel (signal excursion greater than 170 μV, peak-to-peak), or with incorrect or missing responses were excluded from analysis.

Generation of difference waves and identification of peaks

Data for each subject were processed separately. First, average SEPs were computed over all non-rejected trials for each type of stimulus. Six difference waves were then created by subtracting the SEP for one condition from the SEP for another condition.

Two difference waves represented the difference between the SEPs to the Target condition vs. the Standard condition for physically identical stimuli (a target recognition, or P300, component). Three difference waves represented the difference between the SEPs to the Painful vs. the Strong non-painful stimuli (a pain component), when both stimuli served the same

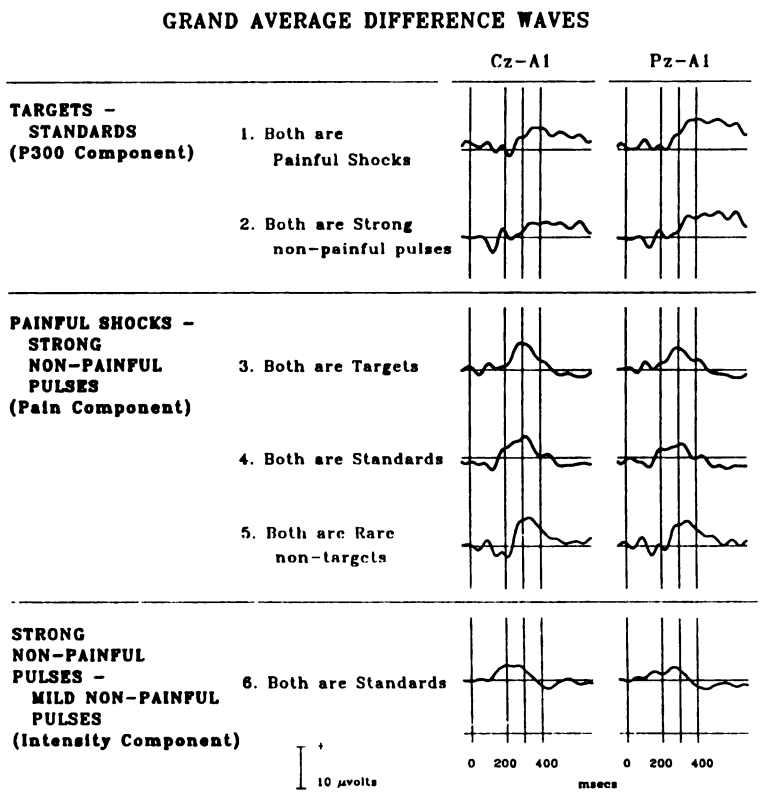

Fig. 2. Grand average difference waves at Cz-A1 and Pz-A1. Difference waves 1 and 2 are differences between Target and Standard conditions using physically identical stimuli. Difference waves 3, 4 and 5 are differences between the Painful and Strong non-painful stimuli with both stimuli serving as either Targets, Standards or Rare non-targets. Difference wave 6 is the difference between Strong non-painful and Mild non-painful stimuli with both stimuli serving as Standards. Note that waves 1 and 2 peak later than waves 3–5 and 6 and have larger amplitudes at Pz, in contrast to waves 3–5 and 6 which have larger amplitudes at Cz. Also note that waves 3–5 peak later than wave 6.

role. These 3 difference waves were generated under the 3 different task instructions: as target stimuli, standard stimuli, or rare non-target stimuli. Finally, one difference wave represented the difference between the SEPs to the Strong non-painful stimuli vs. the Mild non-painful stimuli (an intensity component), when both stimuli served the same role as standard stimuli (see Table II).

The single largest positive peak occurring in the window 120–660 msec after the stimulus was identified in each difference wave (scored with the wave form digitally filtered using a half amplitude bandpass of 0.5–15 Hz). The amplitude (relative to the average amplitude of the 50 msec prestimulus baseline) and latency of the peak was scored by computer and verified by individual inspection.

The peaks in the difference waves were examined using PC/SAS General Linear Model Procedure for analysis of variance with repeated measures. We treated both electrode (Cz and Pz) and the 6 difference waves

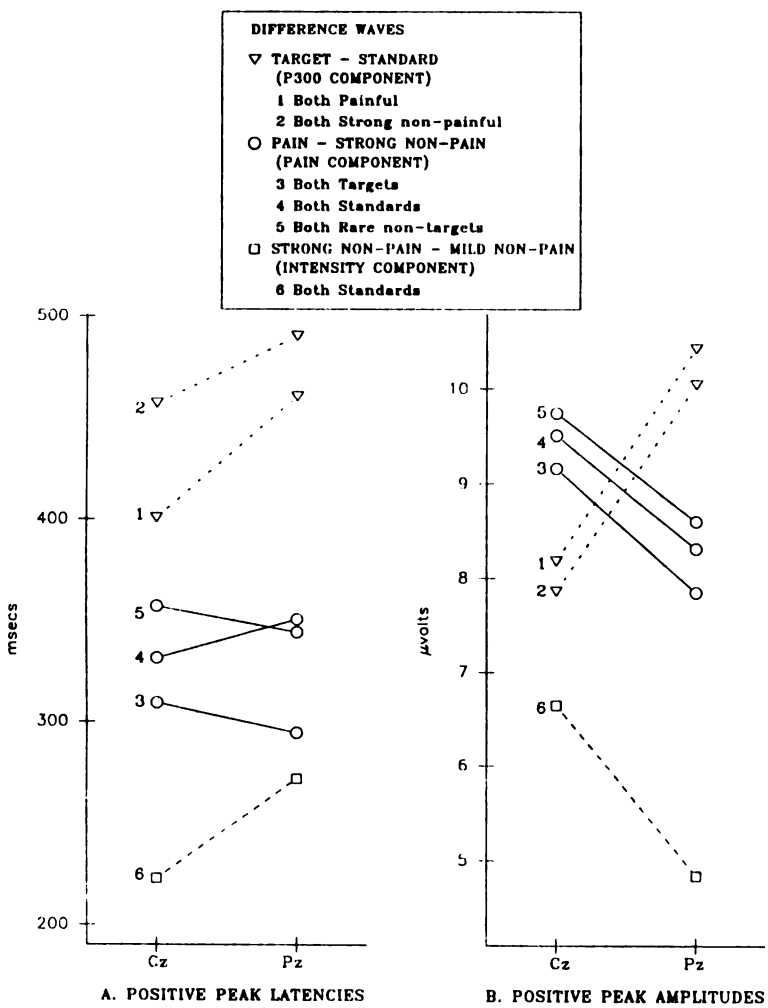

Fig. 3. Latencies and amplitudes of the positive peaks of the 6 difference waves.

as repeated measures. Separate analyses were performed on peak latency and peak amplitude.

Results

Peak latencies

Figs. 1 and 2 show the grand averages for the SEPs and difference waves from Cz-A1 and Pz-A1. Peak latencies for the 6 difference waves and 2 electrode sites are shown in Fig. 3A. The difference waves corresponding to the target vs. standard distinction (P300 component) had positive peaks with longer latencies than the difference waves corresponding to the pain vs. non-pain distinction (pain component). Mean latencies were 452 msec and 331 msec respectively, with a mean difference of 121 ± S.E. 25 msec. (The planned contrast comparing latency of difference waves 1 and 2 vs. difference waves 3, 4, and 5 was significant (F (1, 13) = 23.65, P = 0.0003).) Similarly, the difference waves corresponding to the pain component had positive peaks with longer latencies than the difference waves corresponding to the strong non-pain vs. mild non-pain distinction (intensity component). Mean latencies were 331 msec and 247 msec respectively, with a mean difference of 84 ± S.E. 26 msec. (The planned contrast of difference waves 3, 4, and 5 with difference wave 6 was significant (F (1, 13) = 10.25, P = 0.007).) There were no significant effects for the interaction of either contrast with electrodes (Pz vs. Cz).

Peak amplitudes

Peak amplitudes for the 6 difference waves and 2 electrode sites are shown in Fig. 3B. Both difference waves corresponding to the P300 component (difference waves 1–2) had positive peaks with larger amplitudes at Pz (mean 10.2 μV) than at Cz (mean 8.0 μV), whereas all 3 difference waves corresponding to the pain component (difference waves 3–5) and the difference wave corresponding to the intensity component (difference wave 6) had positive peaks with larger amplitudes at Cz than at Pz (means of 9.5 μV vs. 8.3 μV for the pain component and 6.7 μV vs. 4.8 μV for the intensity component). This resulted in a significant difference wave x electrode interaction when comparing difference waves 1 and 2 vs. 3, 4, and 5 (F (1, 13) = 52.53, P = 0.0001) or when comparing difference waves 1 and 2 vs. 6 (F (1, 13) = 70.91, P = 0.0001).

Discussion

The SEP to painful stimuli can consist of at least 3 overlapping components related to pain, (non-painful) intensity and target detection. Assessment of the specifically pain-related activity in the SEP requires that these 3 components be taken into account. In this study, we have demonstrated a paradigm for isolating these different components.

Identification of 3 different components

Our results indicate that 3 different positive wave form components can be identified in the 200–550 msec latency window of the midline SEP to painful stimuli: the earliest component is a positive wave form that peaks at about 223 msec and is larger at Cz than at Pz. This component reflects the neural response difference between mild and strong (but non-painful) stimuli, i.e., a (non-pain) intensity component. The next component is also a positive wave form that is larger at Cz than Pz, but peaks later, at about 333 msec. It reflects the neural response difference between strong non-painful stimuli and painful stimuli, i.e., a pain component. The third component is a positive wave form that peaks at about 475 msec and is larger at Pz than at Cz. It reflects the neural response difference between physically identical stimuli serving as low probability targets vs. high probability standards, i.e., a P300 component. The 3 components are shown in Fig. 2. They overlap in latency and topography such that the recorded wave forms reflect composite activity of the 3 components (see Fig. 1).

Our findings regarding these different components are consistent with past reports of the characteristics of the pain-related SEP and of the somatosensory P300. For example, pain-related positive components maximal at the vertex have been reported in the latency range of 260–360 msec (Buchsbaum 1984; Bromm 1985, 1989), whereas the somatosensory P300 has maximal amplitude at parietal locations and latencies of approximately 400 msec (Desmedt and Robertson 1977).

Overlap of the components

Fig. 2 shows that all 3 components have broad latency and topography, with significant overlap among them. Conditions that produce both pain and P300 components give rise to a positive peak that, at many electrodes, combines the positive amplitudes of these two components. This is especially true at Cz, where the pain SEP is usually recorded, and this must be taken into account in interpreting SEPs to painful stimuli.

This temporal overlap of the pain and P300 components may contribute to the somewhat different wave forms of the grand average SEPs to the painful stimuli resulting from different instructions (see Fig. 1). When the painful stimuli serve as Targets or as Rare non-targets, the grand averages include a very long-lasting positivity that at longer latencies is greater at Pz than at Cz. However, when the painful stimulus occurs as a standard stimulus and would therefore not be expected to produce a large P300, the positivity returns to base-

line at a much earlier latency and remains greater at Cz than at Pz.

The long lasting positivity at Pz in the Painful Target and Painful Rare non-target SEPs may result from a P300 component in these SEPs similar to the long lasting positivity at Pz in the Strong non-painful Target SEP. The SEP to the Painful Standard stimuli, like the SEP to the Strong non-painful Standard stimuli, does not show this prolonged positivity.

These data suggest that, whenever painful stimuli are presented unpredictably and/or designated as targets by requiring some response by the subject (e.g., a finger lift or perhaps a report of a subjective pain rating), they may give rise to a non-pain-specific P300 component which adds to the pain-related positivity in the SEP.

Part of the problem of "unwanted" P300 components may be eliminated by using difference waves, as was done in the present study. By subtracting SEPs to Non-painful Targets from SEPs to Painful Targets, the difference waves primarily correspond to the difference in painfulness. However, because of the "innate" target value of the painful stimuli, it is impossible to exactly match the target value of the painful and non-painful stimuli. Another approach is to present the painful stimuli in a predictable series with a predictable ISI, as was done for our Painful Standard SEP. Contrary to the concern of Bromm (1984), this did not appear to bring about a low arousal level in our subjects who had to attend to the stimuli in order to identify the mild non-painful stimuli that served as low probability targets. While collecting SEPs to Painful Standards may eliminate most of the unwanted P300, in order to eliminate other "unwanted" non-pain components, it is still necessary to create a difference wave by subtracting a SEP to non-painful Standards.

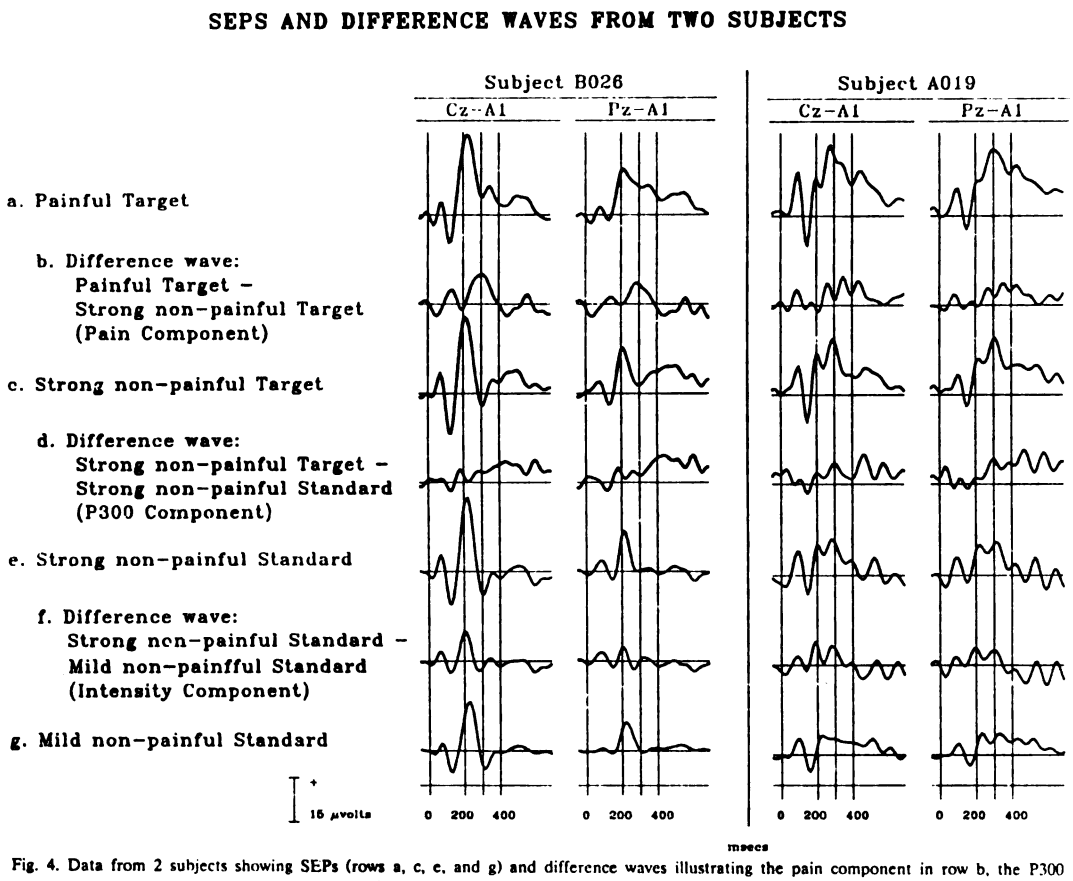

Fig. 4. Data from 2 subjects showing SEPs (rows a, c, e, and g) and difference waves illustrating the pain component in row b, the P300 component in row d, and the non-pain intensity component in row f.

Relationship of pain component difference wave to SEP peaks

Miltner et al. (1989) pointed out that the pain SEPs from individual subjects often show two late positive peaks (at means of 215 msec and 332 msec) and that, due to latency variability, the grand averages across subjects result in a single peak at about 260 msec. They suggest quantifying the two peaks separately. We also found that the SEPs from many, but not all, subjects had two positive peaks. However, *neither one of them necessarily corresponded to the peak in the pain component difference waves.*

As Fig. 4, subject B026, shows the clear positive peak in the pain component difference wave at 300 msec (row b) is at a latency corresponding to a trough in the SEPs (rows a and c). The same pattern is present for subject A019 in Fig. 4. This circumstance also argues for the use of difference waves in future research, rather than the measurement of peaks in the raw SEPs.

Importance of pain stimulus levels

We think it is critically important that painful stimuli be clearly and definitely painful. Our subjects chose levels that, on the average, were 3.7 times their pain threshold (range 1.7–6.3). This contrasts with other studies using the intracutaneous pain stimulus that, for example, utilized fixed levels of 2 times and 3 times the pain threshold (Bromm and Meier 1984) or of 1.2 times and 1.4 times the pain threshold (Miltner et al. 1989). This last study used stimuli that our subjects would have rated as only "faintly" or "mildly" painful. We had no problems with our comparatively intense painful stimuli. Subjects reported no problems tolerating the stimuli and did not produce excessive EOG or EMG artifact. In order to clearly elicit a pain component, future studies should ensure that the painful stimuli be well above the pain threshold.

Directions for future research

Our paradigm involves several possible confounds. First, the pain component difference waves reflect not only the difference between painful and non-painful stimuli, but also the difference between the intracutaneous vs. superficial methods of stimulation. In contrast, our (non-pain) intensity component difference waves reflect only an intensity difference, not a method difference. Given our goal of collecting each type of stimulus as a target and a standard in a single session, we were not able to eliminate this confound by collecting SEPs to different intensities of intracutaneous stimulation (the session was already 5–6 h long).

We believe that this difference in stimulation method, per se, is unlikely to be responsible for the difference between the pain and intensity components identified in this study. Examination of Fig. 1 shows that the relatively early components of the SEP (P90, N130) do not appear to differ in latency for the two methods, as one might expect if the difference in the SEPs was primarily due to the physical characteristics of the stimuli. The pain component has a relatively late peak (averaging 331 msec) indicating that it is most likely an index of neural processing many steps removed from the physical characteristics of the stimulus. This interpretation may be confirmed in future studies by delivering more than one level of painful stimulus.

A second possible confound involves the relationship of the pain component with a hypothetical (non-pain) intensity component that might be present only at very high intensities. While we have shown that the pain component can be reliably discriminated (based on latency) from an intensity component that differentiates low and moderately intense stimuli, it is conceivable that at higher intensities, different neural processes (other than pain processes) become involved. Our pain component could conceivably be a measure of these higher intensity processes. Arguing against this possibility are findings by Chen et al. (1979) that SEP peak latencies are stable over 5 different stimulus intensities. Again, including more stimulus levels in future designs may help clarify this issue.

A third possible confound concerns the effect of different stimulus sequences in different conditions. In order to minimize the number of painful stimuli presented to our subjects in an already long session, we used a design that was not completely balanced with respect to the exact probabilities, ISIs and type of ISIs (random vs. fixed) used for the SEPs that were combined in the difference waves. This concern does not apply to the pain component difference waves which were the focus of this experiment since these factors were always exactly matched for those SEPs. It also does not apply to the P300 difference waves since these factors were intentionally manipulated in order to generate large P300s in the target condition and small or absent P300s in the standard condition. Within certain parameters, lower probability, longer ISIs, and random ISIs have been shown to increase P300 amplitude or delay its habituation (e.g., Schandry and Hoefling 1979; Donchin et al. 1986; Johnson 1988; Miltner et al. 1991; Polich et al. 1991).

In the present study, these concerns are only relevant to the intensity component difference wave. This wave was computed by subtracting Mild non-painful standards (0.6 probability, random ISI of 5–8 sec, average 6.5 sec) from Strong non-painful standards (0.9 probability, fixed ISI of 5 sec). However, these probability and ISI differences should either *reduce* the relative size of the Strong standard's positive wave form at about 260 msec or should have no effect (e.g., Laurian and Gaillard 1976; Mallardi 1979; Miltner et al. 1991) and would thus bias our results *against* find-

ing an effect of intensity. Therefore the *larger* positivity in the Strong vs. Mild standard is most likely due to the difference in intensity rather than probability or ISI. Our results are consistent with other findings of somatosensory intensity differences (Jacobson et al. 1985; Miltner et al. 1987).

Conclusion

In this study, we have shown that the SEP in response to painful intracutaneous stimuli does indeed contain a component that is specifically related to the painfulness of the stimuli. This pain component can be differentiated from two other components that may also be present in the SEP to painful stimuli and that may even correlate with the painfulness of the stimuli without being specifically related to painfulness: a non-pain intensity component and a target recognition (P300) component. Since our results show that these 3 components overlap in both latency and topography, we have shown that simple peak measures of the SEP confound activity related to all 3 components and are thus poor measures of the specifically pain-related activity in the SEP. We have demonstrated a paradigm for isolating the various components that holds promise for the further study of different aspects of the CNS response to painful stimuli.

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References

Bromm, B. Pain-related components in the cerebral potential: experimental and multivariate statistical approaches. In: B. Bromm (Ed.), Pain Measurement in Man: Neurophysiological Correlates of Pain. Elsevier, Amsterdam, 1984: 257–290.

Bromm, B. Evoked cerebral potential and pain. In: H.L. Fields et al. (Eds.), Advances in Pain Research and Therapy, Vol. 9. Raven Press, New York, 1985: 305–329.

Bromm, B. Laboratory animal and human volunteer in the assessment of analgesic efficacy. In: R.C. Chapman and H. Loeser (Eds.), Issues in Pain Measurement. Raven Press, New York, 1989: 117–143.

Bromm, B. and Meier, W. The intracutaneous stimulus: a new pain model for algesimetric studies. Meth. Find. Exp. Clin. Pharmacol., 1984, 6: 405–410.

Bromm, B. and Scharein, E. Principal component analysis of pain-related cerebral potentials to mechanical and electrical stimulation in man. Electroenceph. clin. Neurophysiol., 1982a, 53: 94–103.

Bromm, B. and Scharein, E. Response plasticity of pain evoked reactions in man. Physiol. Behav., 1982b, 28: 109–116.

Bromm, B., Meier, W. and Scharein, E. Antagonism between tilidine and naloxone on cerebral potentials and pain ratings in man. Eur. J. Pharmacol., 1983, 87: 431–439.

Buchsbaum, M.S. Quantification of analgesic effects by evoked potentials. In: B. Bromm (Ed.), Pain Measurement in Man. Neurophysiological Correlates of Pain. Elsevier, Amsterdam, 1984: 291–300.

Carmon, A., Dotan, Y. and Sarne, Y. Correlation of subjective pain experience with cerebral evoked responses to noxious thermal stimulations. Exp. Brain Res., 1978, 33: 445–453.

Chapman, C.R. Evoked potentials as correlates of pain and pain relief in man. Agents Actions, 1986, 19 (Suppl.): 51–73.

Chapman, C.R., Chen, A.C.N. and Harkins, S.W. Brain evoked potentials as correlates of laboratory pain: a review and perspective. In: J.J. Bonica et al. (Eds.), Advances in Pain Research and Therapy, Vol. 3. Raven Press, New York, 1979: 791–803.

Chatrian, G.E., Canfield, R.C., Knauss, T.A. and Lettich, E. Cerebral responses to electrical tooth pulp stimulation in man. Neurology, 1975, 25: 745–757.

Chen, A.C.N., Chapman, C.R. and Harkins, S.W. Brain evoked potentials are functional correlates of induced pain in man. Pain, 1979, 6: 365–374.

Desmedt, J.E. and Robertson, D. Differential enhancement of early and late components of the cerebral somatosensory evoked potentials during forced-paced cognitive tasks in man. J. Physiol. (Lond.), 1977, 271: 761–782.

Desmedt, J.E., Tomberg, C., Zhu, Y. and Nguyen, T.H. Bit-mapped scalp field topographies of early and late cognitive components to somatosensory (finger) target stimuli. In: R. Johnson, J.W. Rohrbaugh and R. Parasuraman (Eds.), Current Trends in Event-Related Potential Research (EEG Suppl. 40). Elsevier, Amsterdam, 1987: 170–177.

Donchin, E., Karis, D., Bashore, T.R., Coles, M.G.H. and Gratton, G. Cognitive psychophysiology and human information processing. In: M.G.H. Coles, E. Donchin and S.W. Porges (Eds.), Psychophysiology: Systems, Processes, and Applications. Guilford Press, New York, 1986: 244–267.

Fernandes de Lima, V.M., Chatrian, G.E., Lettich, E., Canfield, R.C., Miller, R.C. and Soso, M.J. Electrical stimulation of tooth pulp in humans. I. Relationships among physical stimulus intensities, psychological magnitude estimates and cerebral evoked potentials. Pain, 1982, 14: 207–232.

Gescheider, G.A. Psychophysics: Method, Theory and Application (2nd edn.). Lawrence Erlbaum, Hillsdale, NJ, 1985.

Gracely, R.H. and Dubner, R. Reliability and validity of verbal descriptor scales of painfulness. Pain, 1987, 29: 175–185.

Harkins, S.W. and Chapman, C.R. Cerebral evoked potentials to noxious dental stimulation: relationship to subjective pain report. Psychophysiology, 1978, 15: 248–252.

Hillyard, S.A. and Picton, T.W. Electrophysiology of cognition. In: F. Plum (Ed.), Handbook of Physiology: Section 1. The Nervous System. Vol. 5. Higher Functions of the Brain. American Physiological Society, Bethesda, MD, 1987: 519–584.

Jacobson, R.C., Chapman, C.R. and Gerlach, R. Stimulus intensity and inter-stimulus interval effects on pain-related cerebral potentials. Electroenceph. clin. Neurophysiol., 1985, 62: 352–363.

Johnson, Jr., R. The amplitude of the P300 component of the event-related potential: review and synthesis. In: P.K. Ackles, J.P. Jennings and M.G.H. Coles (Eds.), Advances in Psychophysiology: a Research Annual, Vol. 3. JAI Press, Greenwich, CT, 1988: 69–138.

Laurian, S. and Gaillard, J.-M. Habituation of visually evoked responses in man: a study of its time course. Neuropsychobiology, 1976, 2: 297–306.

Mallardi, V. The interstimulus interval effect on the amplitude of the evoked acoustic response and habituation phenomenon. Acta Neurol. (Napoli), 1979, 34: 188–203.

Miltner, W., Larbig, W. and Braun, C. Habituation of subjective ratings and event related potentials to painful intracutaneous electrical stimulation of the skin. J. Psychophysiol., 1987, 1: 221–228.

Miltner, W., Johnson, R., Braun, C. and Larbig, W. Somatosensory event-related potentials to painful and non-painful stimuli: effects of attention. Pain, 1989, 38: 303–312.

Miltner, W., Johnson, Jr., R. and Braun, C. Auditory and somatosen-

sory event-related potentials. II. Effects of inter-stimulus interval. J. Psychophysiol., 1991, 5: 27–42.

Polich, J., Brock, T. and Geisler, M.W. P300 from auditory and somatosensory stimuli: probability and inter-stimulus interval. Int. J. Psychophysiol., 1991, 11: 219–223.

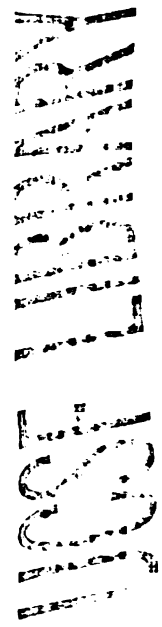
Rösler, F., Sutton, S., Johnson, R., Mulder, G., Fabiani, M., Gorsel, E.P. and Roth, W.T. Endogenous ERP components and cognitive constructs. A review. In: W.C. McCallum, R. Zappoli and F. Denoth (Eds.), Cerebral Psychophysiology: Studies in Event-Related Potentials (EEG Suppl. 38). Elsevier, Amsterdam, 1986: 51–92.

Schandry, R. and Hoefling, S. Interstimulus interval length and habituation of the P300. In: H.D. Kimmel, E.H. Van Olst and J.F. Orlebeke (Eds.), The Orienting Reflex in Humans. Erlbaum, New York, 1979: 129–134.

Stowell, H. Cerebral slow waves related to the perception of pain in man. Brain Res. Bull., 1977, 2: 23–30.

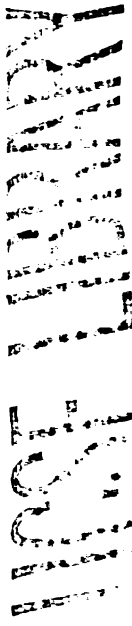
Stowell, H. Event related brain potentials and human pain: a first objective overview. Int. J. Psychophysiol., 1984, 1: 137–151.

Umino, M., Sano, H., Ohwatari, T., Oka, S. and Kubota, Y. Relationship between subjective pain estimation and somatosensory evoked potentials by electrical tooth stimulation. Bull. Tokyo Med. Dent. Univ., 1988, 35: 67–74.



CHAPTER 3

TOPOGRAPHY OF PAIN, INTENSITY AND P300 COMPONENTS IN THE PAIN EVOKED POTENTIAL



Summary

The scalp topography of evoked potential components related to pain, non-painful intensity and cognitive information processing of task-relevant stimuli (P300) were mapped using 30 EEG electrodes and compared. The components were derived using difference waves: Pain was the difference between somatosensory evoked potentials (SEPs) in response to painful stimuli vs. strong but non-painful stimuli; Intensity was the difference between SEPs to strong non-painful vs. mild non-painful stimuli; P300 was the difference between SEPs to the same stimuli under Target instructions vs. Non-target instructions. Painful stimuli were produced using intracutaneous electrical stimulation of a fingertip and two levels of non-painful stimuli were produced by superficial electrical stimulation of a neighboring fingertip.

The positive peaks in the three types of difference waves differed in latency: Intensity was earliest, then Pain, then P300. An analysis of topographic similarity using Desmedt & Chalklin's Z estimator and Lehmann's Global Dissimilarity scores showed that the positive peak of the Pain difference wave (Pain component) had a significantly different topography from the P300 component (Pain was broad and symmetrical around the vertex whereas P300 was broad with a more posterior distribution around Pz). The Pain and Intensity components were both usually broad and maximal at Cz, however there was a trend for these two components to differ in topography. Our results illustrate how the SEP to painful stimuli is a weighted combination of multiple overlapping components.

Key words: Pain; Pain evoked potential; Somatosensory evoked potential; P300; Intensity; Topographical mapping

Introduction

Over the last 20 years, research using somatosensory evoked potentials in response to painful stimuli ("pain SEPs") has established that certain SEP measures correlate highly with subjective reports of pain sensation (Stowell 1977; Carmon et al. 1978; Harkins and Chapman 1978; Chen et al. 1979; Bromm and Scharein 1982a; Fernandes de Lima et al. 1982; Umino et al. 1988). In addition, SEP measures have often been shown to parallel the effect that analgesic drugs and their antagonists have on pain sensation (for reviews see Bromm 1985; Chapman 1986; Bromm 1989; Chen 1993; Handwerker and Kobal 1993).

In a recent paper (Becker et al. 1993), we showed that the Pain SEP does not reflect a unitary process, but rather reflects the summation of a number of overlapping components. We identified three components: one related to the *intensity* of the stimulus (without regard to its painfulness), one related to a cognitive component known as the *P300* (or P3b) which reflects information processing of task-relevant stimuli, especially if they are presented infrequently and unpredictably, and one specifically related to the *painfulness* of the stimuli. Recently, Towell and Boyd (1992; 1993) have also identified a separate P300 component in the pain SEP evoked by the CO_2 laser.

Our components were derived by subtracting one SEP from another SEP in order to form "difference waves." For example, subtracting an SEP resulting from a painful stimulus *not* designated as task-relevant from an SEP to the same painful stimulus when it *is* designated as task-relevant produces a difference wave which contains a P300 component. Similarly, subtracting an SEP to a Strong but non-painful, task-relevant stimulus from an SEP to a Painful task-relevant stimulus produces a difference wave containing a Pain component. We found that activity

at two scalp sites, Cz and Pz (see Figure 1 for electrode positions), could differentiate these three components based on the latencies and amplitudes of their positive peaks. In this study, we further investigate this data set by analyzing the topography of these components using 30 scalp electrodes. Topographic mapping can be useful in determining whether neural activity at different timepoints or under different conditions is likely to arise from the same configuration of neural generators.

-- Figure 1 about here --

Figure 1. Radial projection of the 30 electrodes used. Mastoid electrodes are below the horizon, directly below CP3 and CP4.

Previous topographic mapping studies of pain-related activity have all mapped the "raw" Pain SEPs, i.e., not the components identified with difference waves. The most comprehensive topographic study using painful electrical stimuli was done by Chatrian et al. (1975) using six subjects and a montage of 20 electrodes on one hemisphere and the midline. They employed brief shocks delivered directly to the tooth pulp in drilled teeth. Their Table 1 and Figure 6 reveal three main topographies beginning about 80 msec after the stimulus: a pattern at about 82 msec with a contralateral focal negativity in the low postcentral region between C4 & T8 and a midline positivity centered between Fz and Cz (that peaked at a latency close to the peak of the focal negativity); a later broad midline negativity (N147) centered between Fz and Cz but extending over much of the scalp; and finally, a very broad midline positivity (P249) centered between Cz and Pz and extending over the entire scalp, but clearly different from the

topography of the N147. The focal negativity at 82 msec was sometimes seen bilaterally, presumably between C3 and T7 on the ipsilateral side.

Buchsbaum (1984) used 16 subjects and 16 electrodes to map four levels of intensity using the Tursky concentric stimulating electrode (Tursky et al. 1965) attached to the dorsal forearm. Information from another paper by the same research group (Lavine et al. 1976) appears to indicate that the intensities used in the 1984 paper corresponded to: 1. below or at sensory threshold; 2. distinct, but not uncomfortable; 3. unpleasant; and 4. painful. Buchsbaum's Figures 19.8 and 19.9 present the N120 and P200 topographies for each of the four levels. All maps showed a broad distribution centered at the vertex with increasing amplitudes in response to the more intense stimuli and the author commented that both the N120 and P200 components had a similar topographic distribution. However, examination of Buchsbaum's Figure 19.9 shows that the N120 might not extend as far parietally as does P200, especially for the unpleasant and painful stimuli.

To our knowledge, the only presentation of a topographic map specifically using the type of electrical stimulus used in the present study, the intracutaneous stimulus (Bromm and Meier), is a single map of the N145 (Bromm 1989 Fig. 3b). It shows a broad topography with a Cz maximum and with greater amplitude frontally than parietally, consistent with the N147 topography of Chatrian et al. (1975).

Joseph et al. (1991), in what was primarily an MEG study with three subjects, collected 14 channels of SEPs in response to moderately painful intracutaneous electrical stimulation of a finger but did not map the results. They commented that the amplitude of the N150-P250 was maximal at the vertex. Their MEG data, collected from 40 closely bunched positions on the contralateral scalp, indicated

that the magnetic counterparts to the SEP N150 and P250 had opposite polarity but both had generators localized to the same region: frontal operculum in frontal cortex. In addition, they localized activity at 90 msec to a generator in primary somatosensory cortex (SI) in two subjects. These conclusions were based on a model that assumes a spherical local geometry of the head and assumes that sources can be modeled as ideal current dipoles, i.e., point sources. The authors hypothesize that the SEPs' vertex maximum for the N150 and P250 results from bilateral sources that summate at the vertex, but also point out that subcortical sources, or cortical sources remote from the MEG measurement region, might be involved.

Four studies have examined the topography in response to cutaneous heat stimuli produced by CO_2 laser stimulation. Treede et al., (1988) found a series of components that roughly parallel the components in response to electrical stimuli, but with a delay of approximately 100 msec (attributable to both the slower conduction velocities of the peripheral afferents and to the longer activation time due to heat conduction through the skin). Twenty four subjects and 14 electrodes were used to map responses to laser stimulation of the hairy skin of the hands and feet. The maps presented were averages that included stimuli that were both below (.75X) and above (1.5X) pain threshold and so could *not* reveal differences between painful and non-painful stimuli. The first component mapped was a focal negativity (N167) centered over T4 and C4 in response to left hand stimulation and at a slightly later latency (N190) over Cz in response to foot stimulation, consistent with their respective cortical projection areas. Eighty msec later (N249 for hands; N273 for feet) appeared a Cz peak with a broad bandlike coronal distribution. A much larger positive peak (P391 for hands; P427 for feet) had a

broad symmetrical midline distribution with a peak between Cz and Pz. In a later paper (Kunde and Treede 1993), the authors replicated the topography of the negative components and suggested that the N167 resulted from activity in SII. Kakigi et al. (1989), also using CO_2 laser stimulation with ten subjects and 16 electrodes, found a widespread, vertex positive component (P320) that was comparable to Treede et al.'s P391. In contrast to Treede et al, where the positive component had the same topography for both the hands and feet, Kakigi et al. commented that the positive component in response to stimulation of the chest seemed to be more parietal than in response to hand stimulation.

While the CO_2 laser studies above appear to measure activity conducted by A delta fibers, one study (Treede and Bromm 1988) has mapped "ultralate" activity conducted by C fibers after blocking the A fibers with a pressure block. They found a positivity at roughly 1200 msec (P1200) and commented that it had a topography similar to the P391. However, they only show maps for one subject and that subject seems to have a somewhat more parietal distribution for the P1200 than the earlier positivity.

The scalp topography of *non-painful* somatosensory stimuli has been studied more extensively and systematically than the topography of painful stimuli, especially for the early components occurring during the first 60 msec (Tsuji and Murai 1986; Desmedt et al. 1987; Desmedt and Tomberg 1989; Emmert and Flügel 1989; Tomberg et al. 1989; Rossini et al. 1990; Desmedt and Tomberg 1991; García-Larrea et al. 1991; Kakigi and Shibasaki 1991; García-Larrea et al. 1992; Kakigi and Shibasaki 1992). To our knowledge, however, no studies have specifically examined the topography of the changes in the SEP that result from increases in stimulus intensity. It seems that most, if not all, of the peaks of the

SEP increase in amplitude with increases in stimulus intensity, at least up to a point (e.g., (Uttal and Cook 1964; Chen et al. 1979; Fernandes de Lima et al. 1982). For example, Wang et al. (1989) found that with electrical stimulation of the femoral nerve, the peak amplitude of the first localized scalp component (P26) increased as the stimulus intensity was increased from two times sensory threshold through six times sensory threshold before plateauing.

García-Larrea et al. (1991), using 11 subjects and 16 electrodes showed that when subjects attend to a stimulated finger, a focal negativity develops contralaterally in the C4-T8 region beginning at about 80 msec and later spreads in a coronal band across the scalp (their Fig. 7). While Desmedt and Tomberg's (1989) electrode placements and method of interpolation mostly hide the early N80 focal negativity, their data (their Fig. 14) clearly shows that from 110 msec to 140 msec this negativity spreads in a coronal band across the scalp. Beginning at about 155 msec, the negativity recedes bilaterally as a positivity swells at the vertex. In a different paper (Desmedt et al. 1987) the later components were mapped. The vertex positivity reached a maximum at 180-190 msec with a broad distribution over the scalp (their Figs. 1 & 2). These results are consistent with the maps of SEPs from non-painful median and radial nerve stimulation in Treede et al. (1988) and Kunde and Treede (1993).

A number of authors have commented that the peaks in the Pain SEP (measured specifically at one electrode: Cz) all correspond to peaks in non-painful SEPs and so are not specifically indicative of pain processing (Harkins and Chapman 1978; Fernandes de Lima et al. 1982; Bromm 1985; Miltner et al. 1989). The same appears to be true of the peak topographies identified above, at least with regard to electrical stimuli (to our knowledge, no study has yet mapped SEP

responses to *non-painful* laser stimuli). I.e., each of the pain SEP peak topographies discussed above has a counterpart in non-painful SEPs: a focal contralateral negativity at about 80 msec, a more widespread negativity with a fronto-central distribution at about 145 msec, and a large widespread positivity centered at the vertex at 200-250 msec.

The somatosensory P300 has not been studied as often as the auditory and visual P300s, but its topography appears to be very similar to the P300 in these other modalities (Desmedt et al. 1987; Onofrg et al. 1990; Giard et al. 1991; Friedman et al. 1993). Recently, Bruyant et al. (1993) have mapped the topography of the somatosensory P300 with 26 subjects and 19 electrodes. Like its counterpart in the other modalities, the peak of the P300 is very broadly localized over parietal cortex, roughly centered at Pz. The authors found that in their paradigm the topography of the early stages of the P300 is slightly contralateral while still broadly covering the midline. It becomes less lateralized as it reaches its peak. No consensus exists on the neural generators that give rise to the somatosensory P300, but Yamaguchi and Knight (1991) have shown that different cortical lesions can have different effects on the P300, supporting the existence of multiple generator sources.

All of the above studies examined the topographies of *peaks in the raw SEPs.* However, as we have demonstrated (Becker et al. 1993), since evoked potentials are made up of overlapping activity from different processes, looking at activity only at the SEP's peak latencies (i.e., at the latencies where the resultant amplitudes of the overlapping processes just happened to reach a maximum) can be inadequate. Difference waves can sometimes reveal processes that are maximally active at latencies other than the peak latencies of the raw SEPs.

In this study we mapped *the difference waves* containing the Pain, Intensity and P300 components. For each of 14 subjects, we identified and mapped the positive peak of the component found in each of seven difference waves. By using 30 electrodes that were widely spaced over the scalp (see Figure 1) we were able to identify activity that had maximal amplitude at electrodes other than Cz and Pz and that was not well recorded at those two electrodes. In addition, by allowing the peak amplitude to be located at any electrode, we were able to obtain a more accurate measure of the peak latency than would be provided by the latency at Cz or Pz.

We hypothesized that, when examined with 30 electrodes: 1. the Pain component would have a longer latency than the Intensity component; 2. the Pain component would have an earlier latency than the P300 component; 3. the Pain component's topography would be different from that of the Intensity component; and 4. the Pain component's topography would be different from that of the P300 component. We quantified the topographic differences using two measures of topographic similarity and statistically compared the differences with the amount of *within*-condition variation found among multiple examples of each component.

Methods

An analysis of latencies and amplitudes from electrodes Cz-A1 and Pz-A1 from this data set has already been reported (Becker et al. 1993). See Becker et al. 1993 for additional details on data collection methods.

Subjects

Fourteen right-handed males, aged 19-36 years, were recruited as paid volunteers from a local college. All indicated that they were in good health, had no neurological problems, and were not taking medication that affected their alertness.

Stimuli

Stimuli consisted of single unipolar electrical pulses of 1 msec duration delivered to the centers of the palmar surfaces of the distal phalanges (fingertips) of the middle or index fingers of the left hand. Fingertips were prepared by vigorously rubbing with an alcohol swab. For half of the subjects, the index finger served as fingertip #1 and the middle finger served as fingertip #2. The other half of the subjects had the opposite configuration.

Fingertip #1 was covered with a piece of plastic Tegaderm (TM) adhesive bandage with a 7 mm diameter hole in order to limit the spread of current. A Grass Gold Cup electrode filled with Grass EC2 electrode cream was used as the positive stimulating electrode. It was taped to the intact skin within the 7 mm hole.

Fingertip #2 was prepared for stimulation following a modified version of the procedure suggested for "intracutaneous pain stimuli" by Bromm and Meier (1984). An approximately 1.5 mm diameter shallow cavity in the center of the fingertip was created by gently abrading the skin with a rotating Dremel engraving

cutter burr (model #106; steam-autoclave sterilized before each use) using a high-speed moto-tool. Care was taken to avoid damage to the underlying dermis. In the rare case of bleeding, the procedure was interrupted and repeated on a neighboring skin area. The positive stimulating electrode for fingertip #2 was a custom-made blunt stainless steel pin, 1.2 mm in diameter by 1 mm in length, embedded in a plastic cover. A tiny dab of ECI Electro-gel was placed in the skin cavity and the electrode was then taped into place in the cavity. Impedance of this electrode was kept below 5 kohms (in contrast to impedances of 50-100 kohms for fingertip #1). Impedance was checked before each recording period and additional electrode jelly added, if necessary, to maintain 5 kohm impedance.

The negative stimulating electrode used for both fingertips was a Grass gold cup electrode filled with Grass EC2 electrode cream and taped to the palmar surface of the middle phalanx of finger #1. Electrode cream was rubbed into the entire palmar surface of this phalanx before applying the electrode and the entire phalanx was covered with tape. The mean impedance of this electrode was 30 kohms.

These two methods yielded very different subjective sensations (see Bromm and Meier 1984). Stimuli delivered to fingertip #1 produced sensations that at low levels were perceived as "pulsing," or "dull." As the current was increased, these sensations could become subjectively quite strong, *without being uncomfortable or painful.* As current levels were increased further, the sensation became an increasingly unpleasant paresthesia that could become very uncomfortable. However, even at high levels described as "very uncomfortable," many subjects did not describe the sensation as "painful," perhaps because it lacked the "sharp" quality often associated with "pain." Prior to the introduction of the intracutaneous

stimulation method, many studies used the above method for their "painful" electrical stimulation (e.g., (Stowell 1977; Bromm and Scharein 1982b; Bromm and Scharein 1982a).

In contrast, the intracutaneous stimulation method (fingertip #2) produced a clearly "painful" sensation. At currents just above sensory threshold, a slight tingling sensation was reported. With increasing currents, subjects soon reported painful sensation, without reporting the dull pulsing sensations elicited on fingertip #1. The subjective intensity of the pain increased with increasing currents, becoming extreme at high currents. This stimulus has been most often described as "stabbing," "sharp" and "hot."

Three levels of stimuli were individually determined for each subject (see Procedure). Two levels of *non-painful* (and not-uncomfortable) stimuli were delivered to fingertip #1. Using this method of skin preparation allowed us to deliver two levels of stimuli that were both non-painful and yet were clearly different in intensity. One level of *painful* stimuli was delivered to fingertip #2. This method allowed us to deliver stimuli that were quite painful without a strong paresthesia.

Stimulating hardware

All aspects of data collection, including stimulus generation, EEG sampling and evoked potential averaging were controlled by ERPSYSTEM software (Neurobehavioral Laboratory Software) running on an IBM compatible 80386 microcomputer. The stimulus signal from the computer's DAC was put through a Constant Current Isolation Unit (CCIU) (Frederick Haer & Co., model #74-65-1) which also amplified the current but left the computer generated wave shape intact. The output of the CCIU, from 2-90V batteries wired in series, was then put

through a custom-made, isolated switching box that directed the current to one of the fingers under computer control.

Procedure

Each subject was read an overview of the experiment and completed consent forms approved by the Committee on Human Research before the recording and stimulating electrodes were attached.

Sensory threshold, pain threshold, and pain tolerance levels were assessed using an ascending method of limits (Gescheider 1985). Subjects were informed that the intensity of stimuli to be used later in the experiment would be much lower than the high levels used in the pain tolerance assessment. As the two fingertips were prepared in different ways, they had very different threshold and tolerance levels. Series of stimuli were first delivered to fingertip #1 and then to fingertip #2, and the procedure was then repeated a second time. Only ratings from the second series were used since, after having experienced the full range of intensities, subjects were less apprehensive and much more confident in their judgments. This procedure provided reference points for the stimulus levels chosen by the subjects for the recording portion of the experiment and also served to familiarize the subject with the range of possible intensities he would experience.

For fingertip #1, subjects were given a 0 to 9 rating scale with the following points anchored: 0=Undetectable; 1=Just detectable; 2=Mild pulse; 3=Clear pulse; 5=Strong pulse; 6=Begins to be uncomfortable; 7=Clearly uncomfortable; 8=Very uncomfortable. Stimuli were first increased in .1 mA units until detection (i.e., sensory threshold) occurred. Stimuli were then increased in .5 mA increments. The lowest intensity rated a 6 was the discomfort threshold, and the

"highest level that you are willing to experience" was considered the pain tolerance level. Stimuli were discontinued at 10 mA (or at the compliance limit of the stimulator, if lower), even if the tolerance level had not been reached. No subject reached their tolerance level for fingertip # 1, with the average rating of the highest stimulus being 6.4 ("beginning to be uncomfortable") (range 4-9).

For fingertip #2, subjects were given a *different* 0 to 9 rating scale that better fit the sensations for this finger, with the following points anchored: 0=Undetectable; 1=Just detectable; 3=Faintly painful; 4=Mildly painful; 5=Moderately painful; 6=Rather painful; 7=Very painful; 8=Extremely painful. These descriptors were based on the psychometric work done by Gracely and Dubner (1987). Stimuli started below sensory threshold and were increased in units of .1 mA. The lowest intensity with a rating of 3 was considered the pain threshold. After the pain threshold was reached, subsequent stimuli were increased in .5 mA units. The "highest level that you are willing to experience" was considered the pain tolerance level. As with fingertip #1, we discontinued stimuli at a level of 10 mA (or the compliance limit, if lower). Only 2 of the 14 subjects had reached their tolerance level at that point, with the average rating of the highest stimulus being 8.7 (above "extremely painful") (range 7-9).

Determination of stimulus intensity levels used during the recording periods

Subjects were asked to choose three stimulus levels for use during subsequent recordings. Two, corresponding to ratings of 2 (mild pulse) and 5 (strong pulse), were used for fingertip #1. Since a rating of 6 indicated "begins to be uncomfortable," it was repeatedly emphasized that level 5 should be as strong as possible, but *"without being uncomfortable or painful."*

The third stimulus level, for fingertip #2, corresponded to a 6 rating: "Rather painful" (above "Moderately painful" and below "Very painful.") Subjects were informed of the frequency of painful stimuli during subsequent recording periods, and were asked to keep two things in mind in choosing the painful stimulus level: First, since the main purpose of the experiment was to analyze physiological responses to painful stimuli, it was necessary for them to choose stimuli that were clearly and definitely painful and not just mildly uncomfortable or strange. Second, we would not be able to change the levels of the stimuli during the session without starting over. Therefore, they should not choose a level that was so high that they would not be willing to finish the experiment.

To determine the "mild pulse" to fingertip #1, a stimulus corresponding to a 2 during the thresholding procedure was presented to the subject, who was given the opportunity to raise or lower that level so as to produce the best "mild pulse" in light of all of their experience with the stimuli. Levels for the other two stimuli were chosen in the same way. As a result of experiencing the range of stimuli in the threshold and tolerance assessment, subjects reported no problem in choosing stimulus intensities in this way. Furthermore, after having experienced the very high intensity stimuli in the tolerance assessment, subjects did not seem particularly anxious about the relatively lower stimulus levels used in the recording sessions.

Mean stimulus levels chosen by the subjects (based on 13 subjects with accurate calibrations) were 1.79 mA for the "2--mild pulse" and 6.32 mA for the "5--strong pulse" for fingertip #1, and 3.41 mA for the "6--rather painful" stimulus to fingertip #2. These levels for fingertip #1 corresponded to a mean of 14% and 77% of the distance from the sensory threshold to the discomfort threshold (based

on 9 subjects; 5 subjects did not reach their discomfort level for fingertip #1 before we stopped the threshold assessment procedure at 10 mA). The level for fingertip #2 corresponded to a mean of 3.7 times each subject's individual pain threshold (based on all 14 subjects; range was 1.7-6.3).

Recording periods

During each recording period one of the three stimuli was designated as the "target" by instructions on a computer screen. The subject's task was to lift his right index finger immediately after the target, with no response required for the other two stimuli. The stimulus designated as the target was changed every 5 to 6 minutes. See Table 2 for a description of the stimuli in each recording period.

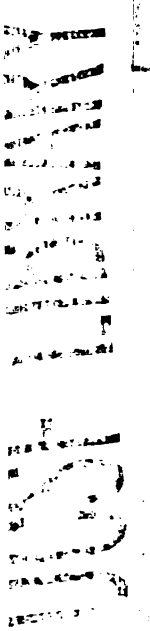


TABLE 2. STIMULI USED DURING EACH RECORDING PERIOD

Recording periods. Between blocks, subjects took short breaks of 1-2 minutes. After period B and after Period C , the electrodes were disconnected so that subjects could walk around the building to refresh themselves.

PERIOD A - Practice

2 blocks of 50 stimuli each; ISI = 5-8 sec randomly

Stimulus probability

First block		Second block	
Mild non-painful Standard	60%	Mild non-painful Standard	60%
Strong non-painful TARGET	20%	Strong non-painful Rare non-target	20%
Painful Rare non-target	20%	Painful TARGET	20%

PERIOD B

Alternating blocks of 50 stimuli each; ISI = 5-8 sec randomly

Stimulus probability

Half of blocks		Half of blocks	
Mild non-painful Standard	60%	Mild non-painful Standard	60%
Strong non-painful TARGET	20%	Strong non-painful Rare non-target	20%
Painful Rare non-target	20%	Painful TARGET	20%

The first 3 mild shocks of each block were "throw-away" stimuli that were not included in the averages. The type of block used as the first block was counterbalanced among subjects. Only the first 40 of the approx. 125 Mild non-painful Standards were used in the average. Period B continued until a minimum of 20 artifact-free trials were collected for each type of stimulus.

PERIOD C

Multiple blocks of 50 stimuli each; ISI = 5 sec fixed

Stimulus probability

Blocks 1 & 4		Blocks 2 & 3	
Mild non-painful TARGET	10%	Mild non-painful TARGET	10%
Painful Standard	90%	Strong non-painful Standard	90%

Blocks 1 & 2 began with 12 "throw-away" Standard shocks and blocks 3 & 4 began with 5 "throw-away" Standard shocks. Period C continued until a minimum of 40 artifact-free trials were collected for the Painful Standard and the Strong non-painful Standard stimuli.

PERIOD D

Exactly the same as Period B.

Trials from Periods B & D were combined so as to produce a minimum of 40 artifact-free trials for each type of stimulus.

Evoked potential recording

Evoked potentials were recorded from 31 scalp sites using the ECI Electro-Cap Electrode System (Cz, Fp1, Fp2, F7, F5, F3, Fz, F4, F6, F8, FC3, FC4, T7, C3, C4, T8, CP3, CP4, P7, P5, P3, Pz, P4, P6, P8, O1, O2, Oz, TP11 (left mastoid), TP12 (right mastoid), A1 (left earlobe)) (Electrode Position Nomenclature Committee of the American Electroencephalographic Society 1991). A1 was not used in the topographic analysis reported here. Cz was used as the reference during recording and all 30 channels were mathematically converted to an average mastoid reference for mapping. Vertical and horizontal EOG was recorded between gold cup electrodes placed above and below the left eye, and at the left and right outer canthi, respectively. Electrode impedances were kept below 3 kohms at all electrodes. Subjects were grounded with a broad grounding plate attached to the left forearm.

Signals were amplified by a Grass Model 12 Neurodata Acquisition System (half amplitude at .1 and 100 Hz). Signals were sampled at 200 Hz from 50 msec before each stimulus to 600 msec after each stimulus. From 600 msec to 1800 msec signals were sampled at 100 Hz. Only data up to 700 msec after the stimulus will be presented here. Trials contaminated by significant horizontal or vertical EOG artifact (i.e., signal excursions greater than 90 microvolts, peak-to-peak), with EEG artifact in any channel (signal excursion greater than 170 microvolts, peak-to-peak), or with incorrect or missing responses were excluded from analysis.

Generation of difference waves

Data for each subject was processed separately. First, average SEPs were computed over all non-rejected trials for each type of stimulus. Difference waves were then created by subtracting the SEP for one condition from the SEP for

another condition. The composition of the difference waves is specified in Table 3.

TABLE 3.
CALCULATION OF DIFFERENCE WAVES

For each difference wave, the second SEP was subtracted from the first.

Dif. Wave No.	1st SEP	Recorded During Periods	2nd SEP	Recorded During Periods
INTENSITY COMPONENT (Strong non-painful - Mild non-painful)				
1	Strong non-painful Standard	C	Mild non-painful Standard	B&D
2	Strong non-painful Rare non-target	B&D	Mild non-painful Standard	B&D
3	Strong non-painful Target	B&D	Mild non-painful Standard	B&D
PAIN COMPONENT (Painful - Strong non-painful)				
4	Painful Standard	C	Strong non-painful Standard	C
5	Painful Target	B&D	Strong non-painful Target	B&D
6	Painful Rare non-target	B&D	Strong non-painful Rare non-target	B&D
P300 COMPONENT (Target - Nontarget)				
7	Painful Target	B&D	Painful Standard	C
8	Strong non-painful Target	B&D	Strong non-painful Standard	C
9	Strong non-painful Target	B&D	Strong non-painful Rare non-target	B&D

Three difference waves represented the difference between the SEPs to the Strong non-painful stimuli vs. the Mild non-painful stimuli (an Intensity component). Three difference waves represented the difference between the SEPs to the Painful vs. the Strong non-painful stimuli (a pain component), when both stimuli served the same role. These three difference waves were generated under the three different task instructions: as target stimuli, standard stimuli, or rare nontarget stimuli. Finally, three difference waves represented the difference between the SEPs to the Target condition vs. non-target conditions for physically identical stimuli (a P300 component).

Analysis of component latencies

In an earlier paper (Becker et al. 1993) we showed that the three types of components differed significantly in the latencies of their positive peaks at Cz-A1 and Pz-A1, with the intensity component being the earliest followed by the pain component and then the P300 component. Here we extend that analysis to the full array of 30 electrodes which allowed the peak amplitude to be located at any electrode and therefore provided a more accurate measure of the peak latency than that found at a specific pair of electrodes.

For both the Pain vs. Intensity and the Pain vs. P300 latency analyses, for each difference wave from each subject, a computer program displayed all 30 channels of digitally filtered evoked potential traces on one screen (see Figure 2). It then checked all values in a specified latency window and automatically chose the single largest positive peak in any of the 30 channels. The size of the peak was computed relative to the zero voltage of the calibrated AC amplifier channel. Peaks were required to be inside the window, i.e., they could not be at either window edge. Both the amplitude and latency of the peak was scored by computer

and verified by individual inspection.

-- Figure 2 about here --

Figure 2. Plot of 30 electrodes used in analysis of component latencies. Latency of largest positive peak in any channel is identified.

For the analysis of the components' positive peak latencies, the Intensity component was represented by one difference wave (Strong Standard - Mild Standard; Difference Wave No. 1 in Table 3). The other two Intensity component difference waves (Waves 2 & 3 in Table 3) would be expected to contain P300 components which could be larger than the Intensity component and which could confound the analysis of latencies. The Pain component in all analyses in this paper was represented by two difference waves (Waves 4 & 5 in Table 3). The third Pain difference wave (Painful Rare non-target - Strong non-painful Rare non-target; Wave 6 in Table 3) was not used because examination of the data indicated that it was likely confounded by the presence of a P300 component in addition to the Pain component. This was likely due to differing amounts of "target value" that the painful and non-painful stimuli had during the times when they were presented only rarely (20% of the time) but were not specifically designated as a Target requiring a finger lift. The painful stimuli were very attention-catching whereas the non-painful stimuli were not (Becker et al. 1993).

For the Intensity vs. Pain latency analysis, the window used for both types of difference waves was 135-395 msec after the stimulus. For the Pain vs. P300 latency analysis, the window used for both types of difference waves was 135-695 msec after the stimulus. Peaks were scored twice, once with a digital low pass filter

with a half-amplitude cutoff of 15 Hz, and a second time with a cutoff of 7 Hz in order to parallel the analysis of topographies that also used both filters. The peak latencies were examined using PC/SAS's General Linear Model Procedure for Analysis of variance with repeated measures.

Topographic mapping methods

We modeled the scalp surface as a sphere and projected the electrode positions onto the sphere according the placement of relative electrode positions specified by the 10-20 electrode system. We followed the conventions of (Perrin et al. 1989) where Cz is at the top of the sphere, T7 and T8 (formerly named T3 and T4) (Electrode Position Nomenclature Committee of the American Electroencephalographic Society 1991) are diametrically opposite each other on the equatorial line, and Fpz and Oz are also diametrically opposite each other on the equatorial line. Each electrode is specified by two angles: the spherical angle from Cz to the electrode and the spherical angle from T8 to the electrode (moving counter-clockwise). These angles are given in Table 4. The former names of the electrodes are given in parentheses.

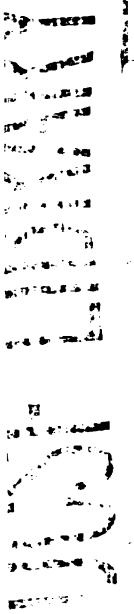


TABLE 4. SPHERICAL COORDINATES OF ELECTRODE POSITIONS

Electrode	θ	ϕ
Cz	0	0
C4	45	0
Fz	45	90
C3	45	180
Pz	45	270
F4	57.673	48.436
F3	57.673	131.564
P3	57.673	228.436
P4	57.673	311.564
T8 (T4)	90	0
F8	90	36
Fp2	90	72
Fp1	90	108
F7	90	144
T7 (T3)	90	180

Electrode	θ	ϕ
P7 (T5)	90	216
O1	90	252
Oz	90	270
O2	90	288
P8 (T6)	90	324
FC4	48.762	26.507
FC3	48.762	153.493
CP4	48.762	206.507
CP3	48.762	333.493
F6	73.747	41.694
F5	73.747	138.306
P5	73.747	221.694
P6	73.747	318.306
TP12	131.238	206.507
TP11	131.238	333.493

All interpolation for potential values between the actual electrodes was done on the sphere. Once values had been interpolated they were then projected onto a plane for display in two dimensions. We used the radial projection specified by (Perrin et al. 1989). As this projection only displays the northern hemisphere of the sphere, the mastoid electrodes TP11 and TP12, located below the equator, were not displayed. However, the values of these two electrodes were used for interpolating the values between electrodes. Figure 1 shows the 28 electrodes in the northern hemisphere using the radial projection.

Interpolation method

We used the Nearest Neighbor method of interpolation where the four nearest electrodes were used to calculate each interpolated value (Shepard 1968;

Buchsbaum et al. 1982). Each electrode's value was weighted by the inverse of the squared distance between it and the interpolation point. Unlike most Nearest Neighbor interpolations, we used the distance along the sphere--not the distance on the planar projection.

Nearest Neighbor interpolation is a conservative method that locates all minima and maxima at electrode positions. While it produces some minor discontinuities in the maps (at the points where one of the nearest neighbors switches to a different electrode) and does not produce maps that are as smooth and aesthetic as spline methods, it is not subject to the distorting effects that sharp local gradients can have on the spline methods that are constrained to pass through the data points.

In order to eliminate high frequency noise, the data was always digitally lowpass filtered before the values for the amplitudes of the 30 electrodes at a given timepoint were mapped. Different filter cutoff points were used at different times during the analysis, as specified below.

Potential values used in mapping were either relative to a *mastoid* reference (the mathematical average of the left and right mastoids) or to an *average* reference (the mathematical average of all 30 electrodes), as specified below. The mastoids are likely to be sites that are affected relatively little by the positive components studied here and thus make good references. Dowman et al. showed that with painful and non-painful sural nerve stimulation, SEPs measured with a balanced sterno-vertebral reference were approximately 10% of the amplitude at the left mastoid as they were at Cz (Dowman, 1992, , Figure 2). The pattern of their results indicated that, among their midline electrodes, current density was greatest near Cz and low near the mastoids. Similarly, Chatrian (1975), using a

noncephalic reference, showed that the positive SEP components were maximal at the midline and relatively small at far lateral sites. P300 topography, while usually more parietal than SEP vertex potentials, is maximal near the midline and also presents relatively low current density near the mastoids (Bruyant et al. 1993). Maps of the prestimulus baselines of the relevant difference waves were generated and appeared to consist of noise. Therefore, we did *not* subtract the prestimulus map from each poststimulus map.

Comparison of component topographies

In order to compare the topographies of the three components we had to first identify the latency where each component was largest in its respective difference wave. Next, we generated a topographical map for that condition at that latency, using the data from all 30 electrodes. We then quantitatively compared each pair of maps (using two methods: Desmedt's Z Score (Desmedt and Chalklin 1989) and Lehmann's Global Dissimilarity (Lehmann and Skrandies 1980; Lehmann and Skrandies 1984; Lehmann 1986; Lehmann 1987; Lehmann et al. 1987) to see how similar they were. Finally, we statistically compared the similarity of maps supposedly representing the same component (e.g., two different pain component maps from the same subject) with the similarity of maps representing supposedly different components (e.g., one pain component map and one P300 component map from the same subject) in order to determine whether the different components had topographies that were significantly more different than the amount of variation of topography within a component.

Determination of component peak latencies

After establishing in the previous analysis that the three components had different latencies (see results) we set three different but overlapping windows to search for the peak of each of the three components: Intensity 135-290; Pain 195-395; and P300 315-695 msec. A plot showing the 30 filtered channels of each difference wave was generated showing the appropriate window boundaries but not showing any identifying information about which electrode went with each trace. Two experienced EEG researchers who were not familiar with this data independently inspected these plots to determine whether there was a clear positive peak present in the window. Because many difference waves contained large amounts of alpha, it was sometimes not possible to separate a component peak from an alpha peak. In addition, very small peaks (< 3-4 μvolts), especially if they occurred as part of relatively disorganized activity across the channels, were cause for rejection of that condition. The raters also inspected for electrode artifacts and found two cases that resulted in exclusion of one electrode from the analysis of two subjects. Figure 3a shows an example of a condition with a clear positive peak and Figure 3b shows an example of a problematic condition that was eliminated from the analysis because of the absence of a clear peak.

-- Figure 3 about here --

Figure 3. 3a. Plot of 30 electrodes showing a clear component peak.
3b. Plot of 30 electrodes showing a difference wave without a clear peak.

The problem of alpha activity interfering with evoked potentials is well known (e.g. Halliday 1982) and may be related to a stimulus induced activation when a subject is in a drowsy state (Halliday 1982; Pfurtscheller 1992). Examination of the three subjects whose 15 Hz data showed the fewest clear component peaks revealed that although the alpha activity was not extremely large in the raw SEPs (compared to the SEP peaks), the alpha activity was often quite large in the difference waves *compared to the size of the (smaller) difference wave peaks.* The alpha in the difference wave was due partly to different amounts of alpha in the two raw SEPs, but was compounded by any out of phase alpha. Figure 4 shows the Cz response from two SEPs and their difference wave (the darkest trace) showing how out of phase alpha in the raw SEPs leads to very large alpha in the difference wave. The difference wave in Figure 4 is from the same subject and condition that is shown in Figure 3b.

--Figure 4 about here--

Figure 4. Alpha in difference wave compared to alpha in raw SEPs. Period shown is from -50 to 600 msec, with vertical lines every 100 msec. Data is from one subject at Cz, lowpass filtered at 15 hz. The light solid trace is the Pain Standard SEP, the light dashed trace is the Strong Standard SEP, and the dark trace is the difference wave.

The phase difference of the alpha in the two raw SEPs is not obviously related to differences in stimulus level (mild, strong, or painful) or to stimulus probability and task (standard, target, or rare non-target). Examples could even be found of phase differences when comparing SEPs created from the same type of

stimulus (e.g., Mild Standard) during two different periods in the session.

The P300 component plots were digitally lowpass filtered with a half-amplitude cutoff at 7 Hz. The vast majority of the power of this component is below the alpha range (Farwell et al. 1993) and this filter eliminated most of the alpha activity that was present in many of the plots, making the P300 peak more obvious. In order to equate the filtering parameter, the Pain component plots used in the Pain vs. P300 analysis were also filtered at 0-7 Hz. Although no studies have systematically analyzed the power spectrum of the Pain difference waves, there is evidence (Bromm 1989) that the raw SEP to painful stimuli has most of its power well below 7 Hz. In addition, this filter did not seem to overly distort the Pain components as compared with the same data filtered at 15 Hz.

The Intensity vs. Pain analysis was conducted twice, once using a 15 Hz cutoff and once using a 7 Hz cutoff. By comparing the two versions of the plots it was clear that the Intensity component peaks contained significant power above 7 Hz, as well as significant power below 7 Hz. However, by using the 15 Hz filter, it was often impossible to separate the intensity and pain components from the ongoing alpha and more plots were eliminated due to the absence of a clear peak.

The two raters independently agreed on 86% of the 7 Hz filtered plots and 69% of the 15 Hz filtered plots. They then met and came to a consensus opinion on the remaining plots. Of the 7 Hz filtered plots, 3/42 (7.1%) of the P300 plots, 11/42 (26%) of the Intensity plots and 6/28 (21.4%) of the Pain plots were rejected. The six rejected pain plots resulted from the absence of peaks in both Pain conditions for 3 of the 14 subjects. Of the 15 Hz filtered plots, 10/28 (36%) of the Pain plots (the same six as in the 7 Hz filtered plots plus one of the two Pain conditions from an additional four subjects), and 12/42 (29%) of the Intensity

plots were rejected.

A computer program automatically identified the positive peak in the appropriate window for each accepted difference wave. In order to avoid peaks due to small residual eye movements that were not rejected during data collection, peaks at Fp1 or Fp2 during the first 300 msec were ignored. In addition, for the Pain and Intensity components that were filtered at 7 Hz, if inspection revealed that there was more than one peak in the window, the peak was chosen that had the largest amplitude in the 15 Hz filtered version of the same data.

Conditions used in topographical analysis

An examination of the topographies of the grand average (across subjects) conditions led to the surprising finding that all of the difference waves created by subtracting an SEP from Period B&D from one from Period C, or vice versa, were confounded by activity related to the difference between the two types of periods. Upon further examination, this activity was found to be due to a widespread graded frontal negativity to posterior positivity in the SEPs from Period C that began even before the stimulus presentation and continued to varying degrees for at least 300 msec. This might be related to the Contingent Negative Variation (CNV) or cognitive expectancy component (Rohrbaugh et al. 1986; Tecce and Cattanach 1987), especially since Period C had an interstimulus interval (ISI) of exactly 5 seconds, as compared with a random 5-8 second ISI in Periods B&D.

Three difference waves in Table 3 (Waves No. 1, 7, 8) share this confound which could distort the topographic maps of the different components. We decided to eliminate the Strong non-painful Standard - Mild non-painful Standard difference wave (Wave No. 1) from the topographical analysis. Two other difference waves representing the Intensity component did *not* share this confound.

Although those two (Strong non-painful Rare non-target - Mild non-painful Standard and Strong non-painful Target - Mild non-painful Standard) also contained long-latency cognitive components related to their rareness and target-value in addition to the Intensity components, by restricting the window for peak picking to 135-290 msec we were able to identify the Intensity peaks.

Two of the P300 difference waves resulted from comparing Targets in Periods B&D with Standards in Period C (Waves No. 7, 8). It is not clear whether the topographies of these components were distorted by the Period B&D vs. Period C difference. The P300 components peaked at very long latencies (mostly from 400-650 msec) and had relatively large amplitudes making it less likely that the smaller difference due to Period B&D and C that was present before the stimulus would substantially affect the peak P300 topography. We included these two difference waves in the analysis, but also included the Strong non-painful Target - Strong non-painful Rare non-target difference wave (Wave No. 9). Both SEPs that went into this latter wave were from Periods B&D. Although it is conceivable that this difference wave might be distorted by the subtraction of a Rare non-target SEP as opposed to a Standard SEP due to the conceivable presence of a P3a response with a different topography than the P300 (P3b) response (Squires et al. 1975; Snyder and Hillyard 1976), we saw no evidence of a P3a component in the Rare non-targets that was different from the P300 component in the Targets. The primary difference between this difference wave and the other two P300 difference waves is that the amplitudes are smaller due to the subtraction of a small P300 component in the Rare non-target from the larger P300 in the Target. In our analysis we examined all three P300 waves and compared the results from the first two with the results from the latter one.

Although confounds were conceivable in all three P300 difference waves, Waves No. 7 and 8 were potentially confounded by a completely different process than Wave 9. If all three waves produced components with similar topographies, that would argue against the influence of the possible confounds.

One of the Pain difference waves (Wave No. 6; Painful Rare non-target - Strong non-painful Rare non-target) was excluded because examination of the data indicated that it was likely confounded by the presence of a P300 component in addition to the Pain component, as was explained under "Analysis of Component Latencies," above.

Quantitative comparisons of maps

Overview

Traditional methods of assessing topographic differences are not suited for analyzing a data set of this type that contains a large number of electrodes (30) and a relatively small number of subjects (14). The usual analysis involves assessing an electrode x condition interaction with ANOVA or MANOVA. A significant interaction indicates that the pattern of amplitudes across the array of electrodes is different in the two conditions.

MANOVA involves the fewest assumptions, however it can not be used when the number of variables (i.e., the number or electrodes times the number of conditions) is greater than the number of subjects, and in this case each comparison would involve 60 variables (30 electrodes times two conditions) and 14 subjects.

ANOVA with repeated measures can be used with more variables, however it assumes a certain variance-covariance structure that is almost certainly violated

in EEG studies with many electrodes. Adjustment factors (e.g. Greenhouse-Geisser and Huynh-Feldt) have been developed to adjust the degrees of freedom to take this violation of the assumptions into account. However when the assumptions are violated as grossly as they are likely to be in EEG studies, tests using the adjustment factors "should be interpreted cautiously" (SAS Institute Inc. 1989).

The analysis we present here follows a different strategy. Rather than directly testing the significance of the difference of two patterns of EEG topography, we perform a two step operation. First, for all maps of interest from a single subject, we generate a list of all possible pairs of maps and we compute scores that indicate *how similar* each pair of maps is. For example, in our case, for each subject, we have two maps that both represent the Pain component and this is one of the pairs that is evaluated for similarity. Ideally, these two maps should be very similar since they supposedly represent the same neural process. We also have two maps that both represent the P300 component. This pair should also be very similar. In contrast, we can also pair up Pain map #1 with P300 map #1, and if these two maps are different, we should get a low similarity score. We can also pair up Pain-1 & P300-2, Pain-2 & P300-1 and Pain-2 & P300-2. We can then compute a mean value for all four of these Pain-P300 pairs. Finally, we can compute a mean value for the amount of similarity in pairs of supposedly the same component, i.e., the mean of two pairs: Pain-1 & Pain-2 and P300-1 & P300-2. Therefore, for this one subject we have ended up with only two numbers.

The second step of this operation is to statistically compare these two numbers for each subject using a matched pairs t-test or a non-parametric test such as the Wilcoxon signed rank test. Both tests should be one tailed because the

hypothesis is unidirectional: the amount of similarity of the supposedly same maps must be *greater than* the amount of similarity of the supposedly different maps.

This approach does not assume that all subjects will have the same topography for any given component; for example it does not assume that all subjects have the same Pain component topography. It only assumes that repeated instances of the Pain component, for any given subject, will always have the same topography. This allows for individual differences in the exact position and orientation of the neural generators that give rise to the scalp topography. As electrode arrays become denser, these individual differences are likely to become more obvious and will need to be taken into account.

Methods of quantifying the similarity between pairs of maps

Two methods of quantifying the similarity between pairs of maps were used. The first method, termed the "Z estimator" was developed by Desmedt & Chalklin (1989). It expresses the similarity between two maps by a number between 1 and -1, where "1" indicates an identical topographic pattern and "-1" indicates a reverse or mirror image pattern. Z is a measure of similarity of pattern and is not affected by differences in absolute amplitude between the two maps. In its simplest form, the formula for Z is simply the formula for a correlation, with n equal to the number of electrodes. Desmedt & Chalklin also present modifications of the formula that give different weightings to different electrodes in order to emphasize areas of large or small amplitude, to emphasize areas of expected interest, or to adjust for a high or low signal-to-noise ratio. An additional optional suggested modification is to convert the maps to average referenced maps in order to focus on relatively small topographic differences that would otherwise be hidden by a large uniform potential component.

Before computing the Z estimator, we converted the maps to average reference in order to emphasize differences in maps that often looked very similar to the eye. We used the basic Z estimator formula:

$$Z = \frac{\sum_{i=1}^{n} f_i g_i}{\sqrt{\left(\sum_{i=1}^{n} f_i^2\right)\left(\sum_{i=1}^{n} g_i^2\right)}}$$

where n equals the number of electrodes (30 in this case) and f_i equals the ith electrode for the first map and g_i equals the ith electrode for the second map.

Since the Z estimator is essentially a correlation, and since the sampling distribution of correlations is not normally distributed, especially for values distant from 0, we transformed the Z estimator values to Fisher's z' which does have a nearly normal sampling distribution (Minium 1970; Cohen and Cohen 1983). The transformed values were then used in the statistical analyses. The formula for Fisher's z' (which is *not* related to the "z" in the Z estimator) is:

$$z' = \frac{1}{2}[\ln(1+r) - \ln(1-r)]$$

where r is the correlation (in this case the Z estimator).

The second method was developed by Lehmann and Skrandies in 1980 (Lehmann and Skrandies 1980) and in various later papers by Lehmann has been called "shape dissimilarity," "global dissimilarity," and "dissimilarity." The formula for computing this metric has been given in two different forms, one relating each electrode value to the mean value of that electrode averaged across both maps (Lehmann and Skrandies 1980; Lehmann et al. 1987) and another relating each electrode value directly to the comparable value at that electrode in the other map

(Lehmann and Skrandies 1984; Lehmann 1986). To make matters even more confusing, one paper (Lehmann 1987), which was Lehmann's most comprehensive review of mapping issues to that date, included a third formula which appears to be in error, as it is not in agreement with the other published formulas.

Lehmann specifies that before applying this measure, the maps must be converted to the average reference and must be normalized to equivalent amplitude (by dividing by the "global field power" (Lehmann and Skrandies 1980; Lehmann and Skrandies 1984; Lehmann 1986; Lehmann 1987; Lehmann et al. 1987) so that the measure will indicate only pattern differences and not differences due to absolute amplitude. We implemented the dissimilarity index with the following formula (Lehmann and Skrandies 1984; Lehmann 1986):

$$dissimilarity\ index = \frac{1}{2n}\sum_{i=1}^{n}\sqrt{(v_{i1}-v_{i2})^2}$$

where n is the number of electrodes (30 in this case) and v_{i1} and v_{i2} are the voltages at electrode i for map *1* and map *2*. This is equivalent to the standard deviation computed at each electrode (i.e., the square root of the average across the two paired electrodes of the squared deviations from their mean) and then averaged across the 30 electrodes. Since this is an average of standard deviations, a value of 0 indicates that two maps do not differ. The measure can not take on negative values. The size of the measure indicates the degree of dissimilarity of the pattern of voltages between the two maps.

Results

Analysis of positive peak latencies

In order to parallel the analysis of positive peak topographies, the positive peak latencies were analyzed using two different half-amplitude lowpass filters, at 7 Hz and 15 Hz.

Pain vs. P300 latency

Planned contrasts using an analysis of variance with repeated measures on the average of the positive peak latencies of the Pain difference waves (from difference waves no. 4 and 5 of Table 3) compared with the average of the positive peak latencies of the P300 difference waves (from difference waves 7 and 8) showed that the pain component (mean 329 msec) was earlier than the P300 component (mean 460 msec; mean Pain-P300 difference of 132 ± S.E. 33 msec; $F(1, 13) = 15.71$, $P = .0016$) when the latencies were identified in traces filtered with a 7 Hz half-amplitude lowpass filter or when the latencies were identified in traces filtered with a 15 Hz half-amplitude lowpass filter (Pain 305 msec, P300 449 msec; mean Pain-P300 difference 145 ± S.E. 37 msec; $F(1, 13) = 15.14$, $P = .0019$). The comparison of the average of the pain latencies with the third P300 difference wave (no. 9) was also significant with 7 Hz filtering (P300 476 msec; mean difference 148 ± S.E. 40 msec; $F(1, 13) = 13.86$, $P = .0026$) and 15 Hz filtering (P300 496; mean difference 192 ± S.E. 34 msec; $F(1, 13) = 32.26$, $P = .0001$).

However, the best estimates of the peak latencies of the Pain and P300 components were found after setting a narrower window for the identification of each peak and after excluding conditions that did not show a clear peak--which was the process used to identify peaks for the topographic analysis. This process (using

7 Hz filtering) yielded Pain (difference waves no. 4 and 5) and P300 (difference waves no. 7 and 8) latencies of 306 ± S.E. 9 msec and 496 ± S.E. 25 msec, respectively.

Pain vs. Intensity latency

Planned contrasts using an analysis of variance with repeated measures on the average of the positive peak latencies of the Pain difference waves (from difference waves no. 4 and 5) compared with the positive peak latencies of the intensity difference wave (from difference wave 1) showed that the pain component (mean 279 msec) was later than the intensity component (mean 221 msec; mean Pain-Intensity difference 58 ± S.E. 20 msec; ($F(1, 13) = 8.67$, $P = .0114$) when the latencies were identified in traces filtered at 15 Hz or when the latencies were identified in traces filtered at 7 Hz (Pain 284 msec, Intensity 239 msec; mean Pain-Intensity difference 45 ± S.E. 20 msec; $F(1, 13) = 5.34$, $P = .0378$). The Pain component latency in this analysis differs somewhat from the Pain latency in the Pain vs. P300 analysis due to the use of different windows for the two analyses (see "Analysis of component latencies" in Methods).

Again, the best estimates of the peak latencies were found using narrower windows and excluding conditions without a clear peak. This process (using 15 Hz filtering) yielded Pain and Intensity latencies of 291 ± S.E. 11 msec and 190 ± S.E. 14 msec, respectively. Using 7 Hz filtering, the latencies were 306 ± S.E. 9 msec and 210 ± 16 msec, respectively.

Topographies of Intensity, Pain and P300 difference waves

Data from all 14 subjects was averaged together to create grand average waveforms, and these waveforms were mapped at each timepoint (once every 5

msec) in order to examine the changes in topography over time associated with each difference wave. Very early peaks (earlier than approximately 50 msec) could not be examined due to their small amplitude in relation to the signal-to-noise ratio produced by averaging only 40 stimuli per average, and due to their high frequency composition which could not be well displayed using 200 Hz sampling. The grand average maps displayed in Figures 5-7 were all created after digitally filtering the data with a 30 Hz half-amplitude lowpass filter.

Incremental activity due to increased non-painful Intensity, as represented by difference wave no. 2 (of Table 3), is shown in Figure 5, but the following features are present in all three Intensity difference waves. There is an early focal negativity at about 80 msec (N80) located around the C4 electrode, in the approximate region of primary somatosensory cortex (SI). This focal negativity spreads in a coronal band across the scalp first reaching a Cz negative peak at 120 msec and then reaching an ipsilateral C3 negative peak at 130 msec. As the positive vertex component begins to emerge at about 130 msec, the negativity fades, first on the contralateral side where it began and then ipsilaterally. The broad bilateral positive component is centered at the vertex (electrode Cz) but extends over much of the scalp. This component peaks at 190 msec and then slowly fades.

Incremental activity due to Pain, as represented by difference wave no. 4 ,is shown in Figure 6. Both Pain difference waves show some focal negativity beginning at 85-90 msec, but unlike the Intensity N80, this negativity continues to grow in amplitude without moving across the scalp, reaching a peak at 135-140 msec. This negativity is also centered around the C4 area and has a similar topography as the Intensity N80. Further analysis is needed to assess whether the

Intensity N80 and the Pain N140 differ in topography. After 170 msec, the topography begins to be dominated by a developing broad positivity that is centered at the vertex. This positivity is quite pronounced by 200 msec but then fades slightly before swelling again to reach its peak at 320 msec.

P300 activity related to information processing of task-relevant stimuli, as represented by difference wave no. 9, is shown in Figure 7. Consistent with previous research, this component does not become active until approximately 300 msec. It then develops into a broad, bilateral positivity that is centered at Pz but that extends broadly over much of the central-posterior scalp. In the grand average this reaches a high amplitude by around 400 msec but stays close to the same amplitude for over 100 msec (peaking at 515 msec) before slowly fading.

-- Figures 5, 6 and 7 about here --

Figure 5. Grand average Intensity difference wave; lowpass filtered at 30 Hz; average mastoid reference.

Figure 6. Grand average Pain difference wave; lowpass filtered at 30 Hz; average mastoid reference.

Figure 7. Grand average P300 difference wave; lowpass filtered at 30 Hz; average mastoid reference.

Quantitative comparison of Intensity, Pain and P300 positive peak topographies

The topographic analysis presented here assessed whether the broad positive Pain component differed topographically from the Intensity positivity at 200 msec and the P300's positivity at 400-600 msec. Two methods of quantitative

comparison of maps were used: Desmedt's Z estimator and Lehmann's Dissimilarity Index.

The topography of the positive peak in each of the seven difference waves for each subject is displayed in Figure 8. The first two columns of this figure show the Pain components from two difference waves, the next two columns show the Intensity components from two difference waves, and the last three columns show the P300 components from three difference waves. The top row shows the topographies of the peaks in the grand average difference waves. Note that in the grand average maps, the pain components and the Intensity components both have broad peaks that are centered at Cz. The P300 maps are also broad but are located more parietally with a maximum at Pz. Inspection of the rows for the individual subjects shows that the pattern seen in the grand average holds up for most subjects: the P300 maps have peaks that are located more parietally than the Pain and Intensity maps. The Pain and Intensity maps are not obviously different from each other, although there may be subtle differences that are partially obscured by the variability (noise) within each category of maps.

-- Figure 8 about here --

Figure 8. Topographies of positive peaks in each difference wave condition, for the grand average and each subject. Maps are shown after lowpass filtering at 7 Hz, converting to average reference and normalizing by global field power; white is positive and black is negative. The first map is from difference wave #4 of Table 3: Painful Standard - Strong non-painful Std; the second map is #5: Painful Target - Strong non-painful Target; third is #2: Strong non-painful Rare non-target - Mild non-painful Std;

fourth is #3: Strong non-painful Target - Mild non-painful Std; fifth is #9: Strong non-painful Target - Strong non-painful Rare non-target; sixth is #8: Strong non-painful Target - Strong Std; and last is #7: Painful Target - Painful Std. Missing maps are due to conditions without a clear peak. Subjects 3 and 6 each had one defective electrode. Subjects are in order from most complete data to least complete data.

Pain vs. P300 topography

For this analysis, all traces were filtered with a 7 Hz half-amplitude cutoff filter before the peaks were chosen. Five subjects were excluded from this analysis due to the absence of a clear component peak in one or more of the four conditions used. Matched pairs t-tests (one-tailed) and the non-parametric Wilcoxon signed rank test (one tailed) were used to evaluate whether the degree of topographical similarity between positive peaks of conditions that represent different components was less than the degree of similarity among positive peaks of conditions representing the same components (i.e., is the between-condition similarity less than the within-condition similarity?). The average of 1.) the similarity of the two positive Pain components from difference waves nos. 3 and 4 (from Table 3) and 2.) the similarity of the two positive P300 components from difference waves nos. 7 and 8, was compared with the average of the four comparisons of a pain component with a P300 component (difference waves nos. 3 & 7, 3 & 8, 4 & 7, and 4 & 8).

The within-condition comparisons (Pain-Pain and P300-P300) produced an average Fisher transformed Z estimator score of 1.08 corresponding to a correlation of .79, whereas the between-condition (Pain-P300) comparisons produced an average Fisher transformed Z estimator score of .61, corresponding

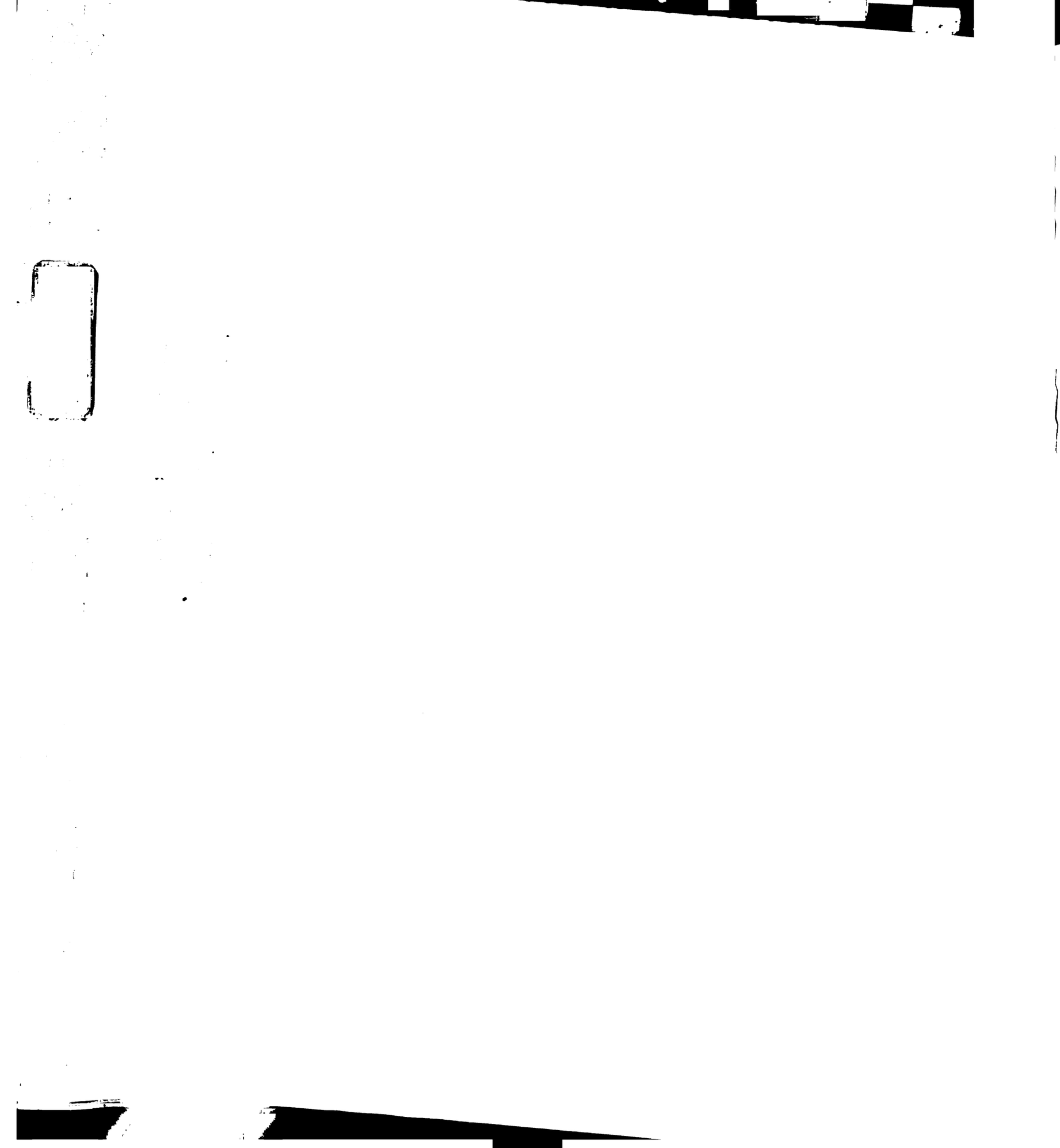
to a correlation of .54. This difference was significant with the matched pairs t-test ($t(8)=3.092$, $P=.0074$) and with the signed rank test ($P=.0137$). The Dissimilarity Index yielded a similar pattern of results ($t(8)=3.0693$, $P=.0077$; signed rank test, $P=.0117$). This comparison and others are summarized in Table 5.

The third P300 difference wave (wave no. 9) was not included in the above analysis since it was created using the same Strong non-painful Target SEP that was used in creating wave no. 8 and might artificially inflate the within-condition similarity. The topography of the positive peak of this difference wave was very similar to that of both P300 waves 7 and 8 (average Fisher transformed scores of 1.45 and 1.15, corresponding to correlations of .90 and .82, respectively). This component was also significantly different from the Pain components as assessed by comparing the within-Pain similarity (Waves 4 and 5; average Fisher transformed score of 1.05 corresponding to a correlation of .78) with the average Pain-Wave 9 similarity (i.e., the average similarity of waves no. 4 & 9 and 5 & 9; average Fisher transformed score of .58 corresponding to a correlation of .52) (Z estimator: $t(10)=2.140$, $P=.0286$, signed rank test, $P=.0337$; Dissimilarity Index: $t(10)=1.898$, $P=.0435$, signed rank test, $P=.0738$).

These results indicate that the positive peaks of the Pain difference waves and the P300 difference waves have different topographies.

Pain vs. Intensity topography

The analysis of the Pain vs. Intensity topography is more problematic. When the data was lowpass filtered with a half-amplitude cutoff of 15 Hz before mapping, only three of the 14 subjects remained in the analysis with clear component peaks in all four of the relevant difference waves. These three had marginally significantly different Pain and Intensity topographies as assessed by



comparing the within-Pain similarity (difference waves 4 and 5; average Fisher transformed score of 1.707 corresponding to a correlation of .94) with the Pain-Intensity similarity (waves no. 4 & 2, 4 & 3, 5 & 2, and 5 & 3; average Fisher transformed score of .87 corresponding to a correlation of .70). (Z estimator: $t(2)=2.564$, $P=.0622$; signed rank test, $P=.125$; Dissimilarity Index: $t(2)=5.087$, $P=.0183$; signed rank test, $P=.125$). The within-Intensity similarity (difference waves no. 2 & 3) was not used in this analysis since both of those difference waves were created using the Mild Standard SEP which might lead to an artificially high within-component similarity.

Using 7 Hz lowpass filtering reduced alpha wave interference and added an additional four subjects, but may have somewhat modified the Intensity topography since it appears to include some frequency components above 7 Hz (see Methods). These seven subjects also had Pain vs. Intensity topographies that trended towards a difference (Z estimator: $t(6)=1.688$, $P=.0712$; signed rank test, $P=.1094$; Dissimilarity Index: $t(6)=1.564$, $P=.0844$; signed rank test, $P=.1094$).

By including subjects in the analysis who had clear peaks in at least one, but not necessarily both, of the Intensity component difference waves, we were able to include 10 of the 14 subjects. The Pain-Intensity similarity scores were computed as the average of all available Pain-Intensity combinations for each subject. This increased the statistical significance of the trend (Z estimator: $t(9):=1.934$, $P=.0426$; signed rank test, $P=.0655$; Dissimilarity Index: $t(9)=1.784$, $P=.0541$; signed rank test, $P=.0801$) and yielded Fisher transformed scores for Pain-Pain and Pain-Intensity of 1.109 and .723 corresponding to correlations of .80 and .62, respectively.

These results indicate that there is a marginally significant trend for the

positive peaks of the Pain and Intensity difference waves to have different topographies. However this finding is limited by the relatively large number of difference waves where a clear component peak was not present and topographic data could not be used in the analysis (36% of the 15 Hz filtered conditions and 21% of the 7 Hz filtered conditions).

TABLE 5. SUMMARY OF STATISTICAL COMPARISONS OF TOPOGRAPHIC SIMILARITY

Values are correlations (Desmedt & Chalklin's Z estimator scores) corresponding to the mean of the Fisher transformed Z estimator scores from all subjects used in the analysis. The Pain-Pain correlations are higher than the Pain-P300 correlations and the Pain-Intensity correlation.

Correlations among pairs representing the same components	Correlations among pairs representing different components	Number of subjects	Significance
mean of (Pain-Pain & P300-P300) .79	Pain-P300 (using dif. waves 7 & 8) .54	9	<.01
Pain-Pain .78	Pain-P300 (using dif. wave 9) .52	11	<.05
Pain-Pain .80	Pain-Intensity .62	10	borderline .05

Discussion

We have shown that difference wave methodology can be used to reveal incremental processing related to non-painful Intensity, to information processing of task-relevant stimuli (the P300 response), and to Pain. Each of these three types of difference waves has a characteristic development with different topographical patterns occurring at different latencies after the stimulus (see Figures 5-7). Both the Intensity and Pain difference waves show early focal negativities which are followed by much larger widespread positivities. The P300 does not show an early negativity but also shows a widespread positivity.

These positivities are the most prominent features of the difference waves, and their latencies and amplitudes at two electrodes were analyzed in an earlier paper (Becker et al. 1993). While our data showed that many of the subjects had peaks at these two electrodes (Cz and Pz), many conditions had peaks located at other electrodes and the Cz and Pz peak latencies did not optimally represent the latency of the peak brain activity. Here, we extended the latency analysis to the 30-channel data array and confirmed that the peaks do differ in latency. The Intensity peak at about 210 msec is significantly earlier than the Pain peak (306 msec), and the Pain peak is significantly earlier than the P300 peak (496 msec).

Comparison of Pain, Intensity and P300 positive peak topographies

We compared, on a subject-by-subject basis, the 30-channel topography of the positive peaks due to Pain with the topographies due to P300 and Intensity (shown in Figure 8). We found that the Pain and P300 peaks clearly and significantly differed in topography. While the Pain peak had a vertex maximum and spread symmetrically and broadly over most of the scalp, the P300 peak had a parietal (Pz) maximum that was also symmetrical and broad but clearly more

posterior (see Figures 6, 7, 8). This topographical difference implies that the Pain component involves different neural generators than does the P300 component and that the Pain positivity is not simply an early P300.

The comparison of the Pain peak with the Intensity peak was more problematic. Examination of the grand averages of these two positive peaks appear very similar, with both showing a vertex maximum and a broad, symmetrical distribution (Figures 5, 6 and top row of Figure 8). In individual subjects, all of the pain peaks and most of the Intensity peaks also showed a widespread vertex maximum (Figure 8) but the topographic patterns were often not as symmetrical as in the grand averages. Visual inspection of Figure 8 makes it difficult to ascertain whether the Pain and Intensity component topographies differ. However, the *quantitative* analysis of the topographies found that there was a trend for the two Pain peaks of each subject to be more similar than the Pain and Intensity peaks were. This trend reached borderline statistical significance ($.05 < p < .10$), and suggests that each subject's Pain positivity may be produced by a somewhat different configuration of generators than is the Intensity positivity. However, future research is needed to confirm this trend.

Description of SEP peaks

The focus of this study was the topography of the positive components in the three difference waves. However, our data is also useful in characterizing the topography of the raw SEPs to painful and non-painful electrical stimuli. Figure 9 shows grand average maps for the three types of SEP peaks that have been noted in the studies reviewed above. The "N80" shown here is the topography at the latency of the larger of the C4 or T8 negative peaks, during the 50-100 msec window. The "Cz N150" is the topography at the largest Cz negative peak in the

SEP corresponding to the negative vertex topography described by others (Chatrian et al. 1975; Buchsbaum 1984; Bromm 1989; Joseph et al. 1991), even though, in our data, at these latencies there were more negative values at electrodes other than Cz. The "P250" is the topography at the largest positive peak in the SEP, which was always at Cz in the grand average waveforms.

-- Figure 9 about here --

Figure 9. Peaks for Grand Average SEPs (not for difference waves). N80 is the larger of the C4 or T8 negative peaks in the 50-100 msec window. "Cz N150" is the Cz negative peak. "P250" is the largest positive peak at any electrode. Lowpass filtered at 30 Hz; average mastoid reference.

Examination of Figure 9 clearly indicates that the grand average topography of the N150 is different from the P250. This result is consistent with the findings using painful electrical tooth pulp stimuli (Chatrian et al. 1975) and non-painful electrical stimulation of the finger and median nerve (Desmedt et al. 1987; Treede et al. 1988; Desmedt and Chalklin 1989), and in contradiction to the observation, although not necessarily the published maps, of Buchsbaum (1984) who used painful electrical forearm stimulation and observed that the N150 and P250 had a similar topography. The greater spatial resolution provided by our 30 channel electrode array may be responsible for the clear appearance of topographic differences.

This finding argues against using an N150-P250 peak-to-peak measure and in favor of using baseline-to-peak measures. Peak-to-peak measures apparently combine the activity of two different processes occurring at different neural

generators and complicate the interpretation of results.

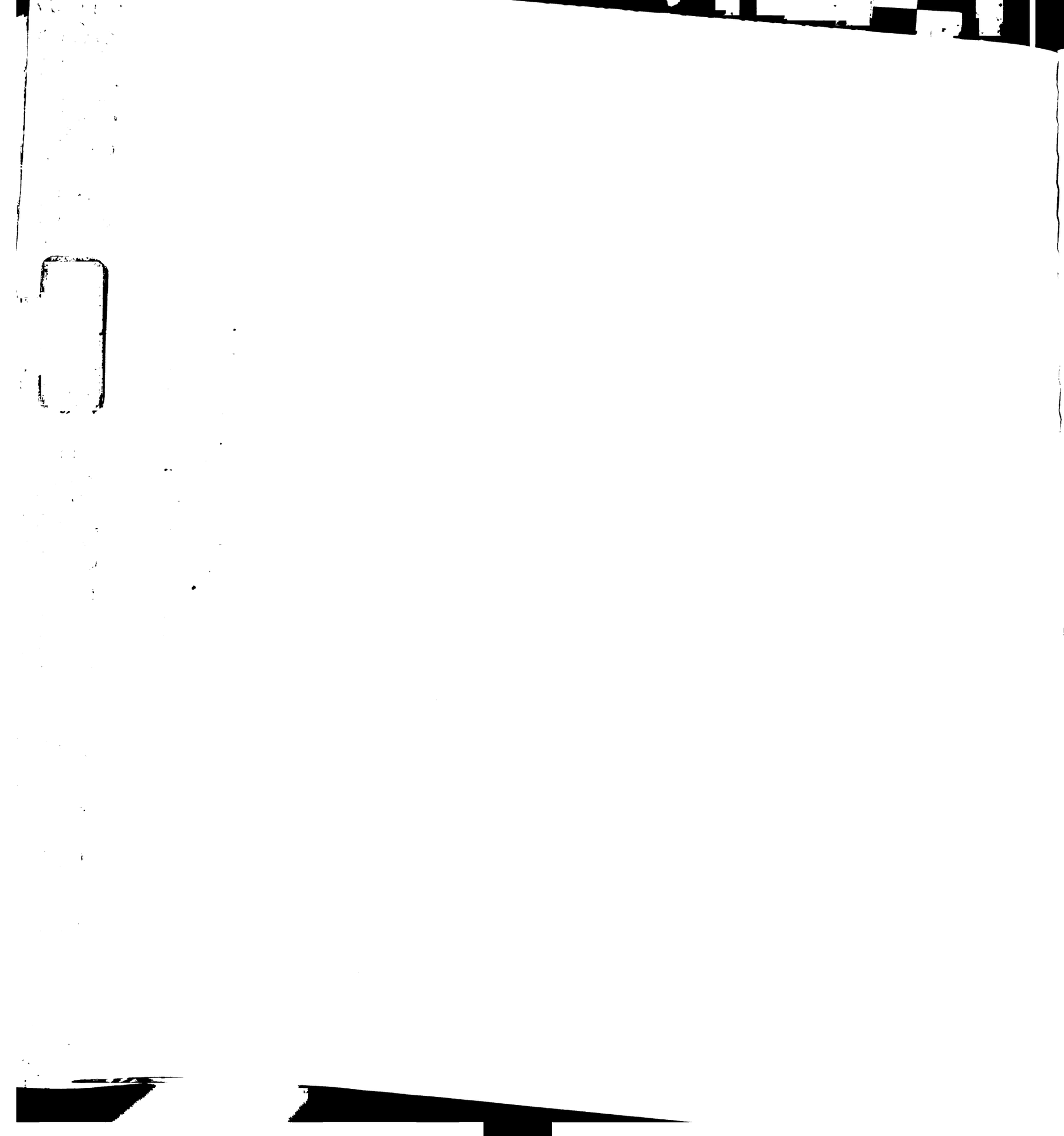
These results also qualify the interpretation of Joseph et al. (1991) who found that with intracutaneous electrical finger stimulation (the same type of stimulation used in the present study) a single neural generator, localized with their model to the frontal operculum, was active at both 150 msec and 250 msec. Our data implies that additional generators must be active at one or both of the latencies in order to produce the differing SEP topographies.

Our N80 results are consistent with studies showing a focal negativity on the contralateral side (Chatrian et al. 1975; Treede et al. 1988; García-Larrea et al. 1991; Kunde and Treede 1993). Chatrian et al., using tooth pulp stimulation, also found an ipsilateral peak (N88) in 15 cases in addition to a contralateral peak (N82) in 23 cases. The authors commented that this was to be expected in light of a high degree of bilateral representation for the orofacial apparatus as compared with other parts of the body (Netter 1986). It is consistent with animal work showing bilateral cortical activation in response to tooth pulp stimulation (Andersson and Rydenhag 1985).

An examination of the "P250" maps for the three SEPs in response to painful stimuli (the first three rows of Figure 9) illustrates how the positive peak is affected when a P300 is produced by the paradigm. The Pain Standard SEP should contain the least amount of P300 activity. The Pain Rare non-target and Pain Target would be expected to contain increasing amounts of P300 activity. Note that the SEPs' overall positive peak occurs later and the topography is more parietal as increasing amounts of the P300 component are added to the response.

Comments on neural generator anatomy

We believe it is premature to attempt to localize neural generators based on



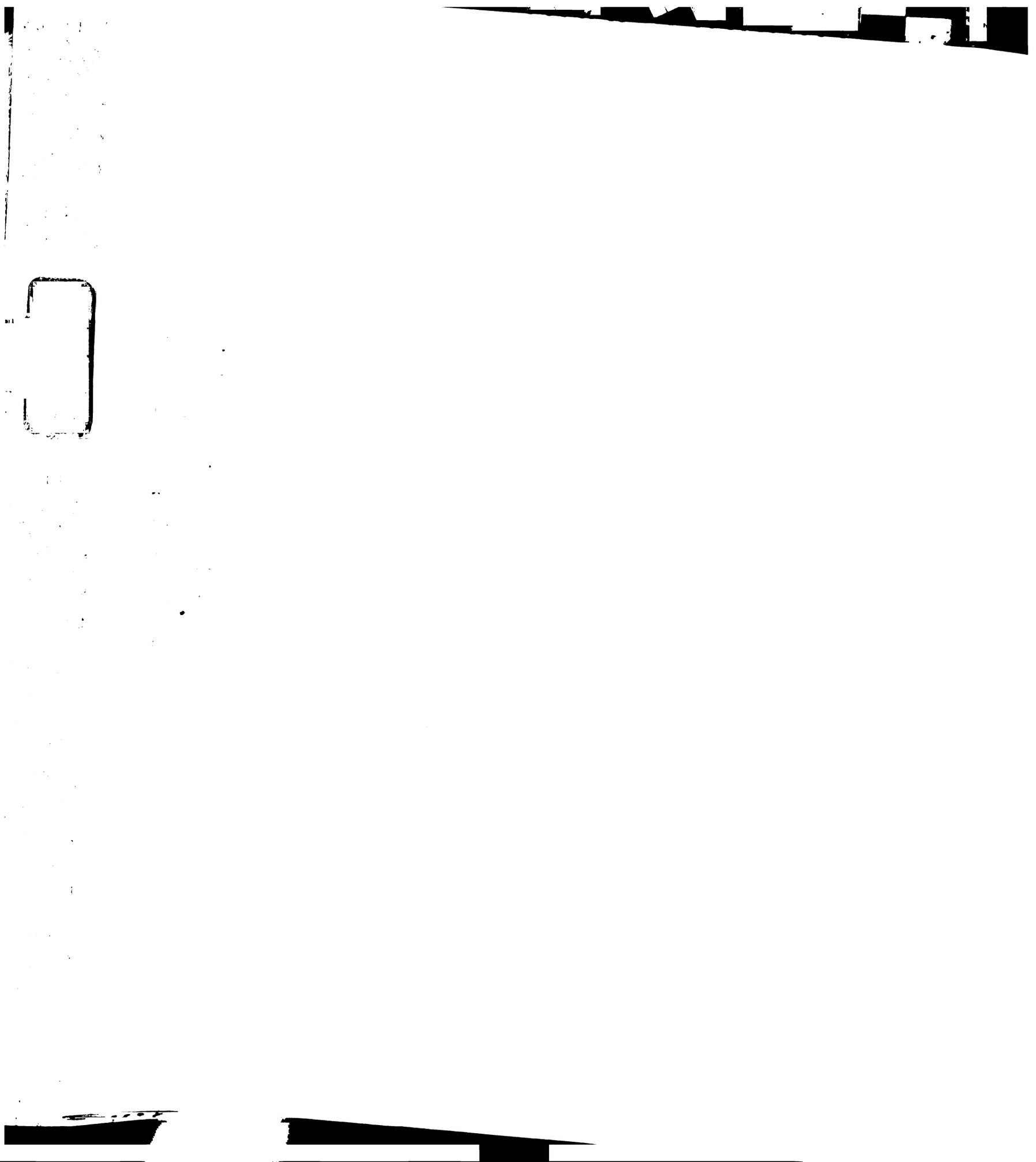
an "intuitive" or face-value interpretation of topographical maps. Many factors, including generator orientation, generator depth, current spread in skull and scalp, and overlap of multiple simultaneously active generators, complicate the interpretation of the scalp activity and have given rise to the field of "dipole localization" (Fender 1987) which attempts to mathematically model these factors and derive the three-dimensional coordinates of the generator sources. We can, however, make some basic observations about this data.

First, the early focal negativities in both the SEPs and the difference waves appear to be located in the region of the somatosensory cortices (SI and SII). Treede et al.'s (1988) finding that non-painful foot stimulation produced a slightly later (N90) and more central focal negativity than did non-painful hand stimulation (N69) is supportive of the hypothesis that this negativity reflects activity in a mapped area of somatosensory cortex.

Second, the symmetrical nature of the positive vertex components in the SEPs and difference waves and of the P300 component implies that the neural generators are either bilaterally symmetrical or located at the midline. In addition, the large amplitude of these positive components indicates that they are likely to be of cortical origin, and in all likelihood are produced by relatively large sections of cortex, and not by small point sources (Rockstroh et al. 1989).

Directions for future work

Future research should take into account four factors that complicated the interpretation of our results. First, alpha activity in the difference waves sometimes made it impossible to separate the Intensity and Pain peaks from ongoing alpha activity. Hopefully, this can be reduced by maintaining the subjects' state of arousal at a higher level. Second, there was a certain amount of variation



in the topography of each subject's different examples of the Pain and Intensity components that might be attributed to noise. Including more than 40 trials per average should produce a higher signal to noise ratio. Third, we found that there were systematic topographic differences attributable to the subjects' state in Periods B and D vs. the subjects' state in Period C. If SEPs from different Periods are used in the same difference wave, care should be taken to equate the subjects' state in the two periods. Finally, future electrode arrays should focus on specific regions of interest. More electrodes around Cz might help differentiate the Pain and Intensity positivities, and might help determine whether an apparent midline positivity results from overlapping bilateral sources. More electrodes around C4 and T8 might help determine whether the early focal negativities in the Pain and Intensity difference waves share the same topography, and might help to determine whether these negativities reflect activity in SI as opposed to SII.

Conclusion

Our results show that difference waves can be used to produce positive components that are specifically related to Pain, Intensity and P300 activity, and that the three components can be differentiated from each other based on latency. The Pain and P300 components can also be differentiated based on scalp topography. Future work is needed to determine whether the observed trend for topographical differences between the Pain and Intensity components will be supported.

This ability to differentiate Pain processing from non-pain processing using difference waves stands in contrast to the *inability* of the raw SEP peaks to differentiate painful and non-painful stimuli. The painful and non-painful raw SEPs both have peaks at about the same latencies, and the topographies at those

peaks results from a combination of overlapping generators. The pain-related generators may provide only a small contribution to the total activity at the raw peak. A further complication with the use of raw SEPs to painful stimuli is that since a P300 can be present to varying extents as part of the late positivity, any changes seen in response to experimental interventions (such as analgesic drugs or changes in attention) are confounded by their effect on the P300. The usual measures of the positivity response (peak amplitude, integrated area under the curve, and the spectral power of low frequencies) are all subject to this confound. We encourage others who are interested in evoked potential activity specifically related to pain to adopt the difference wave methodology.

CHAPTER 4

OVERALL DISCUSSION

My dissertation research has shown that although the usual methods of measuring SEPs are inadequate and confound different processes, there is SEP activity that seems to be specifically related to CNS processing of pain. This is an important finding. I have shown that there is a pain component that differs from two other components: one related to changes in (non-pain) intensity and one related to cognitive processing of task-relevant stimuli (the P300).

With regard to the specific hypotheses listed in Chapter One, I showed in Chapter Two that:

1. The Pain component has a significantly later latency than the Intensity component at Cz and Pz.
2. The Pain component has a significantly earlier latency than the P300 component at Cz and Pz.
3. The Pain component and P300 component have significantly different topographies at Cz and Pz, with the Pain component larger at Cz and the P300 component larger at Pz.

In Chapter Three, using the full array of 30 electrodes, which is better able to identify the true latencies of maximal activity, I showed that:

1. The Pain component has a significantly later latency than the Intensity component.
2. The Pain component has a significantly earlier latency than the P300

component.

3. The Pain component and P300 component have significantly different topographies, with the Pain component having a very broad symmetrical distribution centered at Cz and the P300 component having a broad bilateral distribution centered at Pz.

4. Both the Pain and the Intensity components have broad symmetrical distributions centered at Cz. However, there is a suggestive but non-significant trend ($.05 < p < .10$) for the two components to subtly differ.

Reconciliation of SEP components with PET results

The early negative peaks in the difference waves, the Pain N140 (see figure 6) and the (non-pain) Intensity N80 (see figure 5) both showed clear maxima at electrode C4, consistent with activation of the hand region of contralateral SI (Homan et al. 1987). It is also possible, but less likely, that the Pain N140 or Intensity N80 might be generated in SII or the insula. The electrode array that was used in this study was designed to broadly cover the entire scalp and, unfortunately, does not have the spatial resolution to better localize these components. This can be easily remedied in future studies using different electrode placements and additional electrodes.

Increased activity in contralateral SI would be expected as a result of an increase in non-pain Intensity. In addition, almost all of the PET comparisons showed increased SI activity in response to painful stimuli, making it possible that the later Pain N140 corresponds to the PET SI activation.

The later SEP pain component, the broad positivity peaking at 320 in the grand average, is more difficult to reconcile with the PET results. The clearly

symmetrical distribution of this component implies either a midline generator or bilateral generators that overlap at the midline. The large amplitude of the component implies that it is generated by relatively large areas of cerebral cortex, and not by deeper structures including the thalami, lentiform nuclei or midbrain nuclei that do not possess open field configurations. While the cingulate cortices are located on the medial surfaces of the cerebral hemispheres deep inside the longitudinal fissure, it seems unlikely that the orientation of their pyramidal cells is such that activation of the cingulate cortex on only one hemisphere would give rise to a bilaterally symmetrical field distribution on the scalp. Only one of the PET comparisons found significant *ipsi*lateral cingulate activation, although it is conceivable that other comparisons may have shown ipsilateral cingulate activation that was not quite strong enough to reach statistical significance.

Perhaps it is more likely that the Pain P320 is generated by relatively *small* activations of *large* regions of cortex, and that these small activations would not be identified by the statistical approach used in the PET studies. That approach is used to identify large activation increases in individual voxels, not small increases in many voxels. The long latency of the P320 makes it possible that it reflects a widespread *cortical activation* in response to an earlier "evaluation" of the stimulus as painful.

Another speculation is that the P320 represents a widespread *cortical inhibition* of specific cortical regions that are not needed to process a response to the stimulus which has already been evaluated as painful. The cellular mechanisms underlying large, slow, positive potentials are not well understood and so it is difficult to know even if the potentials are generated by EPSPs or IPSPs (Rockstroh et al. 1989). If the Pain P320 is generated by cortical inhibition it

would also be missed by the PET studies, since it appears that they are only looking for regions of activation (Jones et al. 1991; Talbot et al. 1991). The one study that did examine increases *and* decreases (using SPECT) (Apkarian et al. 1992) did find an area of decrease.

Are the pain component generators specifically related to cortical processing of pain?

The above analysis suggests that the P320 may be related to activation or inhibition of widespread regions of cortex. Are these the same widespread regions that also underlie the Intensity P190? If they are the same, it implies that the P320 generators are not *specifically* related to cortical processing of *pain*. If they are different, it implies that the P320 is a correlate of a specific stage of pain processing.

Unfortunately, the research presented here is not able to resolve this question. Superficial examination of the topographical maps, especially of the grand averages (Figure 8) shows that the Intensity P190 and the Pain P320 look very similar. However, the statistical analysis using data from individual subjects showed a strong trend for the two examples of the pain component to be more similar to each other than they were to the intensity components. If the pain and intensity components were produced by the same cortical generators, the pain topography vs. intensity topography similarity should be as high as the pain topography vs. pain topography similarity.

A similar question exists with regard to the Intensity N80 and the Pain N140. The topographical similarity of these components will be investigated in the future. Hopefully, this analysis will reveal an unambiguous answer, although the small number of electrodes in the region of interest in the current data set may impede

the search for topographic differences.

The relationship of the SEP pain components to laser-evoked potentials

The CO_2 laser evoked potentials presented by Treede et al. (1988) show a focal negativity at T4 and C4 at 167 msecs. They suggest that this negativity is analogous to the N69 focal negativity at C4 that they see in response to non-painful electrical stimulation, and that the delay is due to both the slower conduction of A delta (in comparison to A beta) fibers and to the delayed receptor activation as a result of heat transmission through the skin.

The Pain N140 focal negativity seen in this dissertation research could conceivably be comparable to Treede et al.'s A delta N167, but is earlier because the intracutaneous electrical stimulation used here would not be subject to the same heat transmission delays. Similarly the Pain P320 (following 180 msec after the N140) might be comparable to Treede et al.'s P391 (following 224 msec after the N167). The topography of Treede et al.'s P391 shows a maximum between Cz and Pz which may indicate that this peak contains a substantial P300 component. A P300 component would probably delay the peak latency, as discussed earlier for the three different pain components in Figure 9, indicating that if the P300 component was not present, the P391 peak might occur earlier, with an N167 to positive peak interval closer to the 180 msec seen between the Pain N140 and Pain P320 peaks.

On the other hand, arguing against equivalence of the Pain N140 and the laser N167 is the finding that Treede et al.'s focal negativity in response to hand stimulation (N167) shows a clearly larger response at T4 than at C4, whereas the Pain N140 (in response to finger stimulation) reported here is clearly larger at C4.

The possible parallel between the two studies may suggest that the Pain N140 seen here differs from the Intensity N80 primarily due to the different conduction velocities of the A beta and A delta fibers. Similarly, the Pain P320 that follows the Pain N140 could conceivably be a widespread activation or inhibitory response that exactly parallels the Intensity P190 that follows the Intensity N80. This argument, if valid, implies that the Pain N140 and P320 may not be *specifically* related to cortical structures that process *pain*; i.e., they may simply reflect a cortical response to sensory information arriving on a relatively slow fiber system.

As discussed above, further topographical work with more focused electrode arrays and better signal to noise ratios will hopefully provide an unambiguous resolution of the question of whether the Intensity N80 and P190 are produced by different configurations of neural generators than are the Pain N140 and P320.

The relative value of EEG evoked potential mapping in comparison with other functional imaging methods

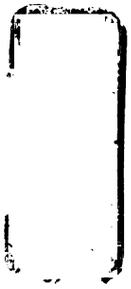
In addition to the well established clinical uses of evoked potentials (Chiappa 1983; Bromm and Treede 1991), evoked potential mapping as used in this dissertation, is also a research tool for functional imaging, along with PET, functional MRI (fMRI), and magnetoencephalography (MEG). Each of these approaches has its strength and weaknesses.

The main strength of PET and fMRI is their very good spatial resolution. For example, the Montreal group's PET study (Talbot et al. 1991) had a voxel size of 5 x 5 x 6.5 mm, and recent fMRI work used a similar voxel size of 4 x 4 x 5 mm (Rao 1994). While this resolution is currently close to the best possible resolution for functional imaging in humans, even it may not be able to differentiate activity

in very closely related structures such as the insula, SII, area 7b, and retroinsular cortex, especially if structural MRI is not used to assess individual differences in structure and/or if there are no gross anatomical structures to separate the regions in the structural MRI image (since SII and area 7b are contiguous areas of cortex on the inner bank of the frontoparietal operculum, their border probably can not be identified with structural MRI). For the present, only animal research is able to make fine discriminations among small bordering structures

As for time resolution, PET is relatively poor. For example, the Talbot (1991) study results were an average of regional cerebral blood flow (rCBF) activity over a 60 second period. Functional MRI's time resolution is much better and is part of what makes this technique so exciting. Regular fMRI can collect a 20 slice brain image in about 2 seconds (Kwong 1994), while echo-planar fMRI can collect a 16 slice sample in only 40 *msec*! However, this short sample time is somewhat misleading since the underlying physiological process that fMRI measures (rCBF) is a relatively sluggish process. There is a 4-5 *second* delay from the time of a stimulus to the maximal rCBF response (Kwong 1994). It seems likely to me that over this long a period of time there is likely to be a great deal of temporal blurring such that information about the relative sequencing of structures (i.e., the order of activation during the first 200 *msec* after a stimulus) is likely to be mostly lost.

EEG mapping and MEG mapping are complementary methods that both measure fields (electrical and magnetic fields respectively) produced by current flow in the vicinity of cortical pyramidal cells. The strength of both of these methods is their excellent temporal resolution. They can sample activity in a fraction of a msec, and each sample is a measure of the brain's electrical fields at



that point in time and is not subject to a lag time as is fMRI. Activity in response to a time-locked stimulus can be followed and the sequence of patterns of activity charted, as was done in Figures 5-7 of this paper.

Maps such as the ones used in this paper show a view of the field pattern on the scalp. Both EEG and MEG studies generate this type of map. However, this is only a first step in using EEG and MEG to image brain function. To localize neural activity, both of these methods rely on an indirect approach whereby the locations of sources are inferred based on data collected from a limited number of sites on the scalp. Mathematical modeling of these sources ("dipole localization" modeling) is currently an active area of research and the most sophisticated models take into account the subjects' actual head shape (using structural MRI) and the different conductivities of brain, skull and scalp. Since MEG models can be somewhat simpler than EEG models, they may ultimately have a somewhat better ability to localize sources. Although the work reported in this dissertation did not utilize this kind of modeling, my planned work over the next few years will.

As a result of basic electromagnetic properties, MEG is blind to currents that are oriented radially to the scalp surface, and is best able to discern sources that are located in cortical sulci and oriented tangentially to the surface. In contrast, EEG is best able to discern radial sources, but is also able to localize tangential sources by using multiple electrodes (i.e., any given source will not be tangential to all electrodes). Currently, most MEG recording is limited to a small number of channels, with the expense of each channel being the limiting factor. The pain MEG study mentioned earlier (Joseph et al. 1991), used only one channel but moved it to 40 different positions on the scalp in order to map the brain activity. This approach assumes that the neural process will be the same the first time it is

measured and the 40th time it is measured (and in this study each of the 40 positions involved 200 moderately painful shocks!). While this may be a reasonable assumption for certain types of processes, for responses to painful stimuli and their cognitive reactions, it is questionable.

EEG mapping studies can employ more channels and can simultaneous record from all electrodes. Fifteen channels seems to be the current minimum number used for mapping, while as many as 128 have been used (Crease 1993). Using many recording channels will of course help the spatial resolution of both EEG and MEG, however there are still very significant modeling problems to solve in terms of dealing with 1. realistic head shapes; 2. multiple, simultaneously active sources; and 3. large cortical sources that are not well modeled as point dipoles, and are better modeled as sheets of dipoles. In the meantime, these models are best applied to relatively focal sources (e.g. the contralateral N140 in Figure 6) rather than broad sources such as the late positivity that was the main subject of this dissertation. In addition, experimental strategies that limit the number of simultaneously active sources in the map (e.g. by using difference waves to isolate a single process) will help lead to more valid localization.

Can EEG mapping contribute insights into brain functioning that other methods can not?

Yes. Ideally, EEG and MEG mapping would always be used together since they could be used with the same protocols and data could be collected simultaneously, yet they would provide complementary information about source localization. However, either one of them alone has the ability to localize certain types of neural sources and to sequence the activation of those sources. Even with their relatively poor level of spatial resolution, it should still be possible to

determine, for example, which EEG or MEG patterns correspond to the activation of the different structures identified with PET or fMRI as being involved with pain processing (at least those structures with pyramidal cells, such as anterior cingulate, SI, and the combined lateral sulcus region (SII, 7b, insula and retroinsula). Once this correspondence is determined, it should be possible to determine the order and precise timing of activation of these structures.

EEG mapping and dipole localization modeling by themselves are less likely to contribute to *anatomical* insights than they are to *physiological* insights. However, even with their limited ability to localize sources, they may generate hypotheses for anatomical insights that could be investigated more extensively with other techniques.

Another unique contribution of EEG and MEG mapping is that most of the activity they measure directly results from EPSP and IPSP activity in real time, and not from a time-lagged response in glucose metabolism or regional cerebral blood flow.

While EEG and MEG mapping have the strategic advantages mentioned above, EEG mapping in particular has one very important practical advantage--it's cheap! For example, a complete 64 channel EEG mapping system with computer costs less than $40,000. MEG systems cost over $1,000,000 and just the *upgrade* from conventional fMRI to echo-planar fMRI is over $500,000 (Crease 1993). EEG systems are also available at almost every university and hospital, in dramatic contrast to the very few PET and MEG facilities *in the world.* This cost factor makes it possible to conduct research that might not be funded if the cost was close to $1,000 for every subject studied. As I am interested in studying *psychological* processes, I am particular sensitive to the relatively low priority given to funding

this work.

Of course, the ideal solution, since each of these technologies has its strengths and weaknesses, is to use many of them, perhaps even simultaneously. An upcoming June 1994 workshop on "Multimodal registration: Combining MRI, EEG, PET & MEG" will deal with exactly that problem.

I am personally enthusiastic about working with EEG mapping and modeling. I believe that EEG can make a contribution to functional imaging in general, and pain functional imaging in particular. I believe that EEG mapping can provide confirmatory data for the identification of structures using PET and fMRI, and, along with MEG, can provide data about the sequencing of activation of different structures that can *not* be provided by PET or fMRI. EEG may also be able to provide data relevant to physiological modulatory effects that may be invisible to PET and fMRI. Finally, EEG may be the most cost effective way to study the effect of different interventions on pain physiology, e.g., analgesic drugs and psychological interventions such as distraction, placebo or hypnosis, and to study the correlation of subjective responses with brain physiology.

Conclusion

This dissertation research has clearly shown that the difference wave methodology used here is superior to previously used methods for research using somatosensory evoked potential in response to painful stimuli. It has shown that the raw SEP includes activity due to multiple functional sources, including a cognitive response associated with task-relevant stimuli (P300 component), a response reflecting an increase in non-painful intensity (Intensity component) and a response reflecting the difference between painful and non-painful stimuli (Pain response). The amplitude of the raw SEP peaks (used by most previous research)

results from the overlap of the multiple components and does *not* reflect the amount of pain-related activity. Future work should employ the difference wave methodology when examining pain-related activity.

A statistical comparison of topographic maps of the late positive components in each difference wave has shown that the P300 component has a different topography from the Pain component, indicating that these components are generated by different sets of neural generators. The Pain and Intensity components appear similar in the grand averages but when examined in individual subjects, show a strong ($.05 < p < .10$) trend to differ. Further work is needed to determine whether the Pain and Intensity components differ in topography.

BIBLIOGRAPHY

Andersson, S.A. and Rydenhag, B., Cortical nociceptive systems, Phil. Trans. R. Soc. Lond. B, 308 (1985) 347-355.

Apkarian, A.V., Stea, R.A., Manglos, S.H., Szeverenyi, N.M., King, R.B. and Thomas, F.D., Persistent pain inhibits contralateral somatosensory cortical activity in humans, Neuroscience Letters, 140 (1992) 141-147.

Arendt-Nielsen, L., Zachariae, R. and Bjerring, P., Quantitative evaluation of hypnotically suggested hyperaesthesia and analgesia by painful laser stimulation, Pain, 42 (1990) 243-251.

Backonja, M. and Miletic, V., Responses of neurons in the rat ventrolateral orbital cortex to phasic and tonic nociceptive stimulation, Brain Research, 557 (1991) 353-355.

Becker, D.E., Yingling, C.D. and Fein, G., Identification of pain, intensity and P300 components in the pain evoked potential, Electroencephalography and clinical Neurophysiology, 88 (1993) 290-301.

Berthier, M., Starkstein, S. and Leiguarda, R., Asymbolia for pain: A sensory-limbic disconnection syndrome, Ann Neurol, 24 (1988) 41-49.

Brennum, J. and Jensen, T.S., Relationship between vertex potentials and magnitude of pre-pain and pain sensations evoked by electrical skin stimuli, Electroencephalography and clinical Neurophysiology, 82 (1992) 387-390.

Bromm, B., Pain-related components in the cerebral potential: Experimental and multivariate statistical approaches, In: B. Bromm (Eds.), Pain measurement in man: Neurophysiological correlates of pain, Elsevier Science Publishers B.V., 1984, pp. 257-290.

Bromm, B., Evoked cerebral potential and pain, In: H.L. Fields, R. Dubner and F. Cervero (Eds.), Advances in Pain Research and Therapy, Vol. 9, Raven Press, New York, 1985, pp. 305-329.

Bromm, B., Laboratory animal and human volunteer in the assessment of analgesic efficacy, In: C.R. Chapman and J.D. Loeser (Eds.), Issues in pain measurement, Raven Press, New York, 1989, pp. 117-143.

Bromm, B. and Meier, W., The intracutaneous stimulus: A new pain model for algesimetric studies, Methods and Findings in Experimental and Clinical Pharmacology, 6 (1984) 405-410.

Bromm, B. and Scharein, E., Principal component analysis of pain-related cerebral potentials to mechanical and electrical stimulation in man, Electroencephalography and clinical Neurophysiology, 53 (1982a) 94-103.

Bromm, B. and Scharein, E., Response plasticity of pain evoked reactions in man, Physiology & Behavior, 28 (1982b) 109-116.

Bromm, B. and Treede, R.D., Laser-evoked cerebral potentials in the assessment of cutaneous pain sensitivity in normal subjects and patients, Rev. Neurol. (Paris), 147 (1991) 625-643.

Bruyant, P., García-Larrea, L. and Mauguière, F., Target side and scalp topography of the somatosensory P300, Electroencephalography and clinical Neurophysiology, 88 (1993) 468-477.

Buchsbaum, M.F., Quantification of analgesic effects by evoked potentials, In: B. Bromm (Eds.), Pain measurement in man. Neurophysiological correlates of pain, Elsevier Science Publishers B.V., 1984, pp. 291-300.

Buchsbaum, M.S., Rigal, F., Coppola, R., Cappelletti, J., King, C. and Johnson, J., A new system for gray-level surface distribution maps of electrical activity, Electroencephalography and clinical Neurophysiology, 53 (1982) 237-242.

Carmon, A., Dotan, Y. and Sarne, Y., Correlation of subjective pain experience with cerebral evoked responses to noxious thermal stimulations, Experimental Brain Research, 33 (1978) 445-453.

Casey, K., Higher central nervous system mechanisms of pain, Annual meeting of the American Pain Society, November 4-7, 1993, Orlando, Florida, 1993.

Chapman, C.R., Evoked potentials as correlates of pain and pain relief in man, Agents and Actions Supplements, 19 (1986) 51-73.

Chatrian, G.E., Canfield, R.C., Knauss, T.A. and Lettich, E., Cerebral responses to electrical tooth pulp stimulation in man: An objective correlate of acute experimental pain, Neurology, 25 (1975) 745-757.

Chen, A.C.N., Human brain measures of clinical pain: A review: I. Topographic mappings, Pain, 54 (1993) 115-132.

Chen, A.C.N., Chapman, C.R. and Harkins, S.W., Brain evoked potentials are functional correlates of induced pain in man, Pain, 6 (1979) 365-374.

Chiappa, K.H., Evoked Potentials in Clinical Medicine, Raven Press, New York, 1983, 340 pp.

Chudler, E.H., Anton, F., Dubner, R. and Kenshalo, D.R., Jr., Responses of nociceptive SI neurons in monkeys and pain sensation in humans elicited by noxious thermal stimulation: Effect of interstimulus interval, Journal of Neurophysiology, 63 (1990) 559-569.

Chudler, E.H., Dong, W.K. and Kawakami, Y., Cortical nociceptive responses and behavioral correlates in the monkey, Brain Research, 397 (1986) 47-60.

Coghill, R.C., Talbot, J., Evans, A., Gjedde, A., Meyer, E., Duncan, G.H. and Bushnell, M.C., Human cerebral processing of noxious and innocuous stimuli, Annual Meeting of the American Pain Society, October 22-25, 1992, San Diego, California, 1992.

Cohen, J. and Cohen, P., Applied Multiple Regression/Correlation Analysis for the Behavioral Sciences, Lawrence Erlbaum Associates, Hillsdale, New Jersey, 1983, 545 pp.

Condés-Lara, M., Zapata, I.O., León-Olea, M. and Sánchez-Alvarez, M., Dorsal raphe and nociceptive stimulations evoke convergent responses on the thalamic centralis lateralis and medial prefrontal cortex neurons, Brain Research, 499 (1989) 145-152.

Crease, R.P., Biomedicine in the age of imaging, Science, 261 (1993) 554-561.

Cruccu, G., Fornarelli, M., Inghilleri, M. and Manfredi, M., The limits of tooth pulp evoked potentials for pain quantification, Physiology & Behavior, 31 (1983) 339-342.

Desmedt, J.E. and Chalklin, V., New method for titrating differences in scalp topographic patterns in brain evoked potential mapping, Electroencephalography and clinical Neurophysiology, 74 (1989) 359-366.

Desmedt, J.E., Nguyen, T.H. and Bourguet, M., Bit-mapped color imaging of human evoked potentials with reference to the N20, P22, P27 and N30 somatosensory responses, Electroencephalography and clinical Neurophysiology, 68 (1987) 1-19.

Desmedt, J.E. and Tomberg, C., Mapping early somatosensory evoked potentials in selective attention: critical evaluation of control conditions used for titrating by difference the cognitive P30, P40, P100 and N140, Electroencephalogr Clin Neurophysiol, 74 (1989) 321-46.

Desmedt, J.E. and Tomberg, C., The search for 'neutral' conditions for recording control event-related potentials in order to assess cognitive components to both irrelevant and relevant stimuli: Evidence fro short-latency cognitive somatosensory effects, In: C.H.M. Brunia, G. Mulder and M.N. Verbaten (Eds.), Event-Related Brain Research (EEG Suppl. 42), Elsevier Science Publishers, B. V., 1991, pp. 210-221.

Desmedt, J.E., Tomberg, C., Zhu, Y. and Nguyen, T.H., Bit-mapped scalp field topographies of early and late cognitive components to somatosensory (finger) target stimuli, In: R. Johnson Jr., J.W. Rohrbaugh and R. Parasuraman (Eds.), Current trends in event-related potential research, Elsevier Science Publishers B.V., 1987, pp. 170-177.

Dong, W.K., Salonen, L.D., Kawakami, Y., Shiwaku, T., Kaukoranta, E.M. and Martin, R.F., Nociceptive responses to trigeminal neurons in SII-7b cortex of awake monkeys, Brain Research, 484 (1989) 314-324.

Dowling, J., Autonomic measures and behavioral indices of pain sensitivity, Pain, 16 (1983) 193-200.

Duncan, G.H., Bushnell, M.C., Talbot, J.D., Evans, A.C., Meyer, E. and Marrett, S., Pain and activation in the thalamus, Trends in Neuroscience, 15 (1992) 252.

Electrode Position Nomenclature Committee of the American Electroencephalographic Society, American electroencephalographic society guidelines for standard electrode position nomenclature, Journal of Clinical Neurophysiology, 8 (1991) 200-202.

Emmert, H. and Flügel, K.A., Topographic mapping of somatosensory representation areas, In: K. Maurer (Eds.), Topographic Brain Mapping of EEG and Evoked Potentials, Springer-Verlag, Berlin, 1989, pp. 383-389.

Farwell, L.A., Martinerie, J.M., Bashore, T.R., Rapp, P.E. and Goddard, P.H., Optimal digital filters for long-latency components of the event-related barin potential, Psychophysiology, 30 (1993) 306-315.

Fender, D.H., Source localization of brain electrical activity, In: A.S. Gevins and A. Rémond (Eds.), Methods of Analysis of Brain Electrical and Magnetic Signals, EEG Handbook (revised series, Vol. 1), Elsevier Science Publishers, B.V., 1987, pp. 355-403.

Fernandes de Lima, V.M., Chatrian, G.E., Lettich, E., Canfield, R.C., Miller, R.C. and Soso, M.J., Electrical stimulation of tooth pulp in humans. I. Relationships among physical stimulus intensities, psychological magnitude estimates and cerebral evoked potentials, Pain, 14 (1982) 207-232.

Fields, H.L., Pain, McGraw-Hill, New York, 1987, 354 pp.

Friedman, D., Simpson, G. and Hamberger, M., Age-related changes in scalp topography to novel and target stimuli, Psychophysiology, 30 (1993) 383-396.

García-Larrea, L., Bastuji, H. and Mauguiere, F., Mapping study of somatosensory evoked potentials during selective spatial attention, Electroencephalography and clinical Neurophysiology, 80 (1991) 201-214.

García-Larrea, L., Bastuji, H. and Mauguière, F., Unmasking of cortical SEP components by changes in stimulus rate: A topographic study, Electroencephalography and clinical Neurophysiology, 84 (1992) 71-83.

Gescheider, G.A., Psychophysics: Method, Theory and Application (2nd ed.), Lawrence Erlbaum, Hillsdale, NJ, 1985, pp.

Giard, M.H., Perrin, F. and Pernier, J., Scalp topographies dissociate attentional ERP components during auditory information processing, Acta Otolarngol. (Stockh); Suppl., 491 (1991) 168-175.

Gingold, S.I., Greenspan, J.D. and Apkarian, A.V., Anatomic evidence of nociceptive inputs to primary somatosensory cortex: Relationship between spinothalamic terminals and thalamocortical cells in squirrel monkeys, The Journal of Comparative Neurology, 308 (1991) 467-490.

Gracely, R.H. and Dubner, R., Reliability and validity of verbal descriptors scales of painfulness, Pain, 29 (1987) 175-185.

Greenspan, J.D. and Winfield, J.A., Reversible pain and tactile deficites associated with a cerebral tumor compressing the posterior insula and parietal operculum, Pain, 50 (1992) 29-39.

Guilbaud, G., Benoist, J.M., Condes-Lara, M. and Gautron, M., Further evidence for the involvement of SmI cortical neurons in nociception: Their responsiveness at 24 hr after carrageenin-induced hyperalgesic inflammation in the rat, Somatosensory and Motor Research, 10 (1993) 229-244.

Guilbaud, G., Benoist, J.M., Levante, A., Gautron, M. and Willer, J.C., Primary somatosensory cortex in rats with pain-related behaviours due to a peripheral mononeuropathy after moderate ligation of one sciatic nerve: Neuronal responsivity to somatic stimulation, Experimental Brain Research, 92 (1992) 227-245.

Halliday, A.M., The visual evoked potential in healthy subjects, In: A.M. Halliday (Eds.), Evoked Potentials in Clinical Testing, Chruchill Livingstone, Edinburgh, 1982, pp. 71-120.

Handwerker, H.O. and Kobal, G., Psychophysiology of experimentlaly induced pain, Physiological Reviews, 73 (1993) 639-671.

Harkins, S.W. and Chapman, C.R., Cerebral evoked potentials to noxious dental stimulation: Relationship to subjective pain report, Psychophysiology, 15 (1978) 248-252.

Head, H., Sensation and the cerebral cortex, Brain, 41 (1918) 57-253.

Hillyard, S.A. and Picton, T.W., Electrophysiology of cognition, In: F. Plum (Eds.), Handbook of physiology: Sec. 1. The nervous system: Vol. 5. Higher functions of the brain, Amercan Physiological Society, Bethesda, MD, 1987, pp. 519-584.

Homan, R.W., Herman, J. and Purdy, P., Cerebral location of international 10-20 system electrode placement, Electroencephalography and clinical Neurophysiology, 66 (1987) 376-382.

Hummel, T., Livermore, A., Hummel, C. and Kobal, G., Chemosensory event-related potentials in man: Relation to olfactory and painful sensations elicited by nicotine, Electroencephalography and clinical Neurophysiology, 84 (1992) 192-195.

Iadarola, M., Higher central nervous system mechanisms of pain, Annual meeting of the American Pain Society, November 4-7, 1993, Orlando, Florida, 1993.

Jones, A.K.P., Do 'pain centres' exist?, British Journal of Rheumatology, 31 (1992) 290-292.

Jones, A.K.P., Brown, W.D., Friston, K.J., Qi, L.Y. and Frackowiak, R.S.J., Cortical and subcortical localization of response to pain in man using positron emission tomography, Proceedings of the Royal Society of London, Series B, 244 (1991) 39-44.

Jones, A.K.P., Friston, K. and Frackowiak, R.S.J., Localization of responses to pain in human cerebral cortex, Science, 255 (1992) 215-216.

Joseph, J., Howland, E.W., Wakai, R., Backonja, M., Baffa, O., Potenti, F.M. and Cleeland, C.S., Late pain-related magnetic fields and electric potentials evoked by intracutaneous electric finger stimulation, Electroencephalography and clinical Neurophysiology, 80 (1991) 46-52.

Kakigi, R. and Shibasaki, H., Effects of age, gender, and stimulus side on scalp topography of somatosensory evoked potentials following median nerve stimulation, Journal of Clinical Neurophysiology, 8 (1991) 320-330.

Kakigi, R. and Shibasaki, H., Effects of age, gender, and stimulus side on the scalp topography of somatosensory evoked potentials following posterior tibial nerve stimulation, Journal of Clinical Neurophysiology, 9 (1992) 431-440.

Kakigi, R., Shibasaki, H. and Ikeda, A., Pain-related somatosensory evoked potentials following CO_2 laser stimulation in man, Electroencephalography and clinical Neurophysiology, 74 (1989) 139-146.

Kalliomäki, J., Weng, H.-R., Nilsson, H.-J. and Schouenborg, J., Nociceptive C fibre input to the primary somatosensory cortex (SI). A field potential study in the rat, Brain Research, 622 (1993) 262-270.

Kenshalo, D.R., Chudler, E.H., Anton, F. and Dubner, R., SI nociceptive neurons participate in the encoding process by which monkeys perceive the intensity of noxious thermal stimulation, Brain Research, 454 (1988) 378-382.

Kenshalo, D.R. and Isensee, O., Responses to primate SI cortical neurons to noxious stimuli, Journal of Neurophysiology, 50 (1983) 1479-1496.

Kenshalo, D.R., Jr. and Perkins, W.C., Organization of primate SI cortical nociceptive neurons, Pain Supplement, 2 (1984) S312.

Kenshalo, D.R., Jr. and Willis, W.D., Jr., The role of the cerebral cortex in pain sensation, In: A. Peters (Eds.), Cerebral Cortex, Vol. 9, Plenum, New York, 1991, pp. 153-211.

Kobal, G., Hummell, C., Nuernberg, B. and Brune, K., Effects of pentazocine and acetylsalicylic acid on pain-rating, pain-related evoked potentials and vigilance in relationship to pharmakokinetic parameters, Agents and Actions, 29 (1990) 342-359.

Kozlov, A.Y., Reactions of neurons of the somatosensory cortex of the rabbit to nociceptive stimuli of varying genesis, Neuroscience and Behavioral Physiology, 21 (1991) 181-2.

Kunde, V. and Treede, R.-D., Topography of middle-latency somatosensory evoked potentials following painful laser stimuli and non-painful electrical stimuli, Electroencephalography and clinical Neurophysiology, 88 (1993) 280-289.

Kwong, K., Minding the human brain by functional MRI, AAAS Annual Meeting, February 1994, San Francisco, CA, 1994.

Lamour, Y., Guilbaud, G. and Willer, J.C., Rat somatosensory (SmI) cortex: II. Laminar and columnar organization of noxious and non-noxious inputs, Experimental Brain Research, 49 (1983a) 46-54.

Lamour, Y., Willer, J.C. and Guilbaud, G., Neuronal responses to noxious stimulation in rat somatosensory cortex, Neuroscience Letters, 29 (1982) 35-40.

Lamour, Y., Willer, J.C. and Guilbaud, G., Rat somatosensory (SmI) cortex: I. Characteristics of neuronal responses to noxious stimulation and comparison with responses to non-noxious stimulation, Experimental Brain Research, 49 (1983b) 35-45.

Lavine, R., Buchsbaum, M.S. and Poncy, M., Auditory analgesia: Somatosensory evoked response and subjective pain rating, Psychophysiology, 13 (1976) 140-148.

Leandri, M., Campbell, J.A. and Lahuerta, J., Effect of attention on tooth-pulp evoked potentials, In: H.L. Fields, R. Dubner and F. Cervero (Eds.), Advances in Pain Research and Therapy, Vol. 9, Raven Press, New York, 1985, pp. 331-336.

Lehmann, D., Spatial analysis of human evoked potentials, In: R.Q. Cracco and I. Bodis-Wollner (Eds.), Evoked Potentials, Alan R. Liss, New York, 1986, pp. 3-14.

Lehmann, D., Principles of spatial analysis, In: A.S. Gevins and A. Remond (Eds.), Methods of Analysis of Brain Electrical and Magnetic Signals, EEG Handbook (revised series Vol. 1), Elsevier Science Publishers, B.V., 1987, pp. 309-354.

Lehmann, D., Ozaki, H. and Pal, I., EEG alpha map series: Brain micro-states by space-oriented adaptive segmentation, Electroencephalography and clinical Neurophysiology, 67 (1987) 271-288.

Lehmann, D. and Skrandies, W., Reference-free identification of components of checkerboard-evoked multichannel potential fields, Electroencephalography and clinical Neurophysiology, 48 (1980) 609-621.

Lehmann, D. and Skrandies, W., Spatial analysis of evoked potentials in man--A review, Progress in Neurobiology, 23 (1984) 227-250.

Matsumoto, N., Sato, T., Yahata, F. and Suzuki, T.A., Physiological properties of tooth pulp-driven neurons in the first somatosensory cortex (SI) of the cat, Pain, 31 (1987) 249-262.

Meier, W., Klucken, M., Soyka, D. and Bromm, B., Hypnotic hypo- and hyperalgesia: Divergent effects on pain ratings and pain-related cerebral potentials, Pain, 53 (1993) 175-181.

Miltner, W., Johnson, R.J., Braun, C. and Larbig, W., Somatosensory event-related potentials to painful and non-painful stimuli: effects of attention, Pain, 38 (1989) 303-12.

Minium, E.W., Statistical Reasoning in Psychology and Education, John Wiley & Sons, Inc., New York, 1970, 465 pp.

Netter, F.H., The CIBA Collection of Medical Illustrations: Vol. 1. Nervous System: Part 1. Anatomy and Physiology, CIBA, West Caldwell, NJ, 1986, 237 pp.

Onofrg, M.C., Ghilardi, M.F., Fulgente, T., Nobilio, D., Bazzano, S., Ferracci, G. and Malatesta, G., Mapping of event-related potentials to auditory and visual odd-ball paradigms, In: P.M. Rossini and F. Mauguière (Eds.), New Trends and Advanced Techniques in Clinical Neurophysiology (EEG Suppl. 41), Elsevier Science Publishers, B.V., 1990, pp. 183-201.

Penfield, W. and Boldrey, E., Somatic motor and sensory representation in the cerebral cortex of man as studied by electrical stimulation, Brain, 60 (1937) 389-443.

Perrin, F., Pernier, J., Bertrand, O. and Echallier, J.F., Spherical splines for scalp potential and current density mapping, Electroencephalography and clinical Neurophysiology, 72 (1989) 184-187.

Pertovaara, A., Morrow, T.J. and Casey, K.L., Cutaneous pain and detection thresholds to short CO_2 laser pulses in humans: Evidence on afferent mechanisms and the influence of varying stimulus conditions, Pain, 34 (1988) 261-269.

Pfurtscheller, G., Event-related synchronization (ERS): An electrophysiological correlate of cortical areas at rest, Electroencephalography and clinical Neurophysiology, 83 (1992) 62-69.

Rainville, P., Feine, J.S., Bushnell, M.C. and Duncan, G.H., A psychophysical comparison of sensory and affective responses to four madalities of experimental pain, Somatosensory and Motor Research, 9 (1992) 265-277.

Rao, S., Minding the human brain by functional MRI, AAAS Annual Meeting, February 1994, San Francisco, CA, 1994.

Robinson, C.J. and Burton, H., Somatic submodality distribution within the second somatosensory (SII), 7b, retroinsular, postauditory and granular insular cortical areas of M. fascicularis, Journal of Comparative Neurology, 192 (1980) 93-108.

Rockstroh, B., Elbert, T., Canavan, A., Lutzenberger, W. and Birbaumer, N., Slow cortical potentials and behaviour, Urban & Schwarzenberg, Baltimore, 1989, 267 pp.

Rohrbaugh, J.W., McCallum, W.C., Gaillard, A.W.K., Simons, R.F., Birbaumer, N. and Papakostopoulos, D., ERPs associated with preparatory and movement-related processes: A review, In: W.C. McCallum, R. Zappoli and F. Denoth (Eds.), Cerebral Psychophysiology: Studies in Event-Related Potentials (EEG Suppl. 38), Elsevier Science Publishers, B.V., 1986, pp. 189-229.

Rösler, F., Sutton, S., Johnson, R., Jr., Mulder, G., Fabiani, M., Gorsel, E.P.-V. and Roth, W.T., Endogenous ERP components and cognitive constructs: A review, In: W.C. McCallum, R. Zappoli and F. Denoth (Eds.), Cerebral psychophysiology: Studies in event-related potentials (EEG Suppl. 38), Elsevier Science Publishers B.V., 1986, pp. 51-92.

Rossini, P.M., Paradiso, C., Zarola, F., Mariorenzi, R., Traversa, R., Martino, G. and Caramia, M.D., Bit-mapped somatosensory evoked potentials and muscular reflex responses in man: Comparative analysis in different experimental protocols, Electroencephalography and clinical Neurophysiology, 77 (1990) 266-276.

SAS Institute Inc., SAS/STAT User's Guide, Version 6, Fourth Edition, Volume 2, SAS Institute Inc., Cary, NC, 1989, 846 pp.

Shepard, D.A., A two dimensional interpolation function for irregular-spaced data, Proc. ACM Nat. Conf., (1968) 517-524.

Sikes, R.W. and Vogt, B.A., Nociceptive neurons in area 24 of rabbit cingulate cortex, Journal of Neurophysiology, 68 (1992) 1720-1732.

Snow, P.J., Lumb, B.M. and Cervero, F., The representation of prolonged and intense, noxious somatic and visceral stimuli in the ventrolateral orbital cortex of the cat, Pain, 78 (1992) 89-99.

Snyder, E. and Hillyard, S.A., Long-latency evoked potentials to irrelevant, deviant stimuli, Behavioral Biology, 16 (1976) 319-331.

Squires, N.K., Squires, K.C. and Hillyard, S.A., Two varieties of long-latency positive waves evoked by unpredictable auditory stimuli in man, Electroencephalography and clinical Neurophysiology, 38 (1975) 387-401.

Stowell, H., Cerebral slow waves related to the perception of pain in man, Brain Research Bulletin, 2 (1977) 23-30.

Stowell, H., Event related brain potentials and human pain: A first objective overview, International Journal of Psychophysiology, 1 (1984) 137-151.

Sweet, W.H., Cerebral localization of pain, In: R.A. Thompson and J.R. Green (Eds.), New Perspectives in Cerebral Localization, Raven Press, New York, 1982, pp. 205-242.

Swerdloff, S.J., Ruegsegger, M. and Wakai, R.T., Spatiotemporal visualization of neuromagnetic data, Electroencephalography and clinical Neurophysiology, 86 (1993) 51-57.

Talbot, J.D., Marrett, S., Evans, A.C., Meyer, E., Bushnell, M.C. and Duncan, G.H., Multiple representations of pain in human cerebral cortex, Science, 251 (1991) 1355-1358.

Tecce, J.J. and Cattanach, L., Contingent negative variation (CNV), In: E. Niedermeyer and F. Lopes da Silva (Eds.), Electroencephalography: Basic Principles, Clinical Applications and Related Fields, Urban & Schwarzenberg, Baltimore, 1987, pp. 657-679.

Tomberg, C., Desmedt, J.E., Ozaki, I., Nguyen, T.H. and Chalklin, V., Mapping somatosensory evoked potentials to finger stimulation at intervals of 450 to 4000 msec and the issue of habituation when assessing early cognitive components, Electroencephalogr Clin Neurophysiol, 74 (1989) 347-58.

Towell, A.D. and Boyd, S.G., The CO_2-laser-evoked cerebral potential in humans is not a P300 oddball potential, Journal of Physiology, 452 (1992) 281P.

Towell, A.D. and Boyd, S.G., Sensory and cognitive components of the CO_2 laser evoked cerebral potential, Electroencephalography and clinical Neurophysiology, 88 (1993) 237-239.

Treede, R.-D. and Bromm, B., Reliability and validity of ultra-late cerebral potentials in response to C-fibre activation in man, In: R. Dubner, G.F. Gebhart and M.R. Bond (Eds.), Proceedings of the Vth world conference on pain, Elsevier Sceince Publishers BV, 1988, pp. 567-573.

Treede, R.-D., Kief, S., Hölzer, T. and Bromm, B., Late somatosensory evoked potentials in response to cutaneous heat stimuli, Electroencephalography and clinical Neurophysiology, 70 (1988) 429-441.

Tsuji, S. and Murai, Y., Scalp topography and distribution of cortical somatosensory evoked potentials to median nerve stimulation, Electroencephalography and clinical Neurophysiology, 65 (1986) 429-439.

Tursky, B., Watson, P.D. and O'Connell, D.N., A concentric shock electrode for pain stimulation, Psychophysiology, 1 (1965) 296-298.

Umino, M., Sano, H., Ohwatari, T., Oka, S. and Kubota, Y., Relationship between subjective pain estimation and somatosensory evoked potentials by electrical tooth stimulation, Bull Tokyo Med Dent Univ, 35 (1988) 67-74.

Uttal, W.R. and Cook, L., Systematics of the evoked somatosensory cortical potential: A psychophysical-electrophysiological comparison, Annals of the New York Academy of Sciences, 112 (1964) 60-80.

Vin-Christian, K., Benoist, J.M., Gautron, M., Levante, A. and Guilbaud, G., Further evidence for the involvement of SmI cortical neurons in nociception: Modifications of their responsiveness over the early stage of a carrageenin-induced inflammation in the rat, Somatosensory and Motor Research, 9 (1992) 245-261.

Wang, J., Cohen, L.G. and Hallett, M., Scalp topography of somatosensory evoked potentials following electrical stimulation of femoral nerve, Electroencephalography and clinical Neurophysiology, 74 (1989) 112-123.

Wright, A. and Davies, I.a.I., The recording of brain evoked potentials resulting from intra-articular focused ultrasonic stimulation: A new experimental model for investigating joint pain in humans, Neuroscience Letters, 97 (1989) 145-150.

Wright, A., Davies, I.a.I. and Riddell, J.G., Intra-articular ultrasonic stimulation and intracutaneous electrical stimulation: Evoked potential and visual analog scale data, Pain, 52 (1993) 149-155.

Yaksh, T.L. and Hammond, D.L., Peripheral and central substrates involved in the rostrad transmission of nociceptive information, Pain, 13 (1982) 1-85.

Yamaguchi, S. and Knight, R.T., Anterior and posterior association cortex contributions to the somatosensory P300, J Neurosci, 11 (1991) 2039-54.

Zachariae, R., Bjerring, P., Arendt-Nielsen, L., Nielsen, T. and Gotliebsen, K., The effect of hypnotically induced emotional states on brain potentials evoked by painful argon laser stimulation, The Clinical Journal of Pain, 7 (1991) 130-138.

Figure 1. Radial projection of electrodes

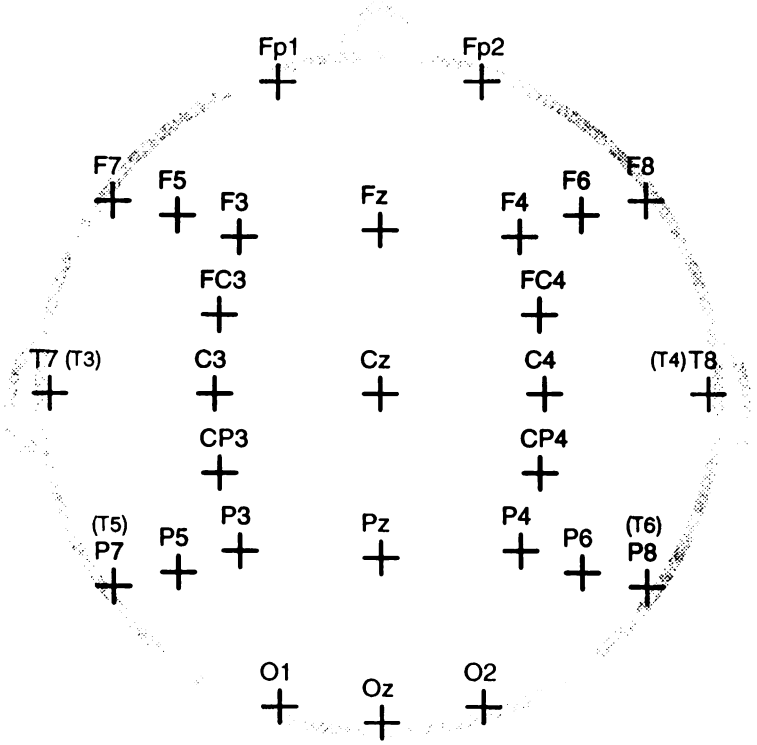


Figure 2. Plot of 30 electrodes used in analysis of component latencies

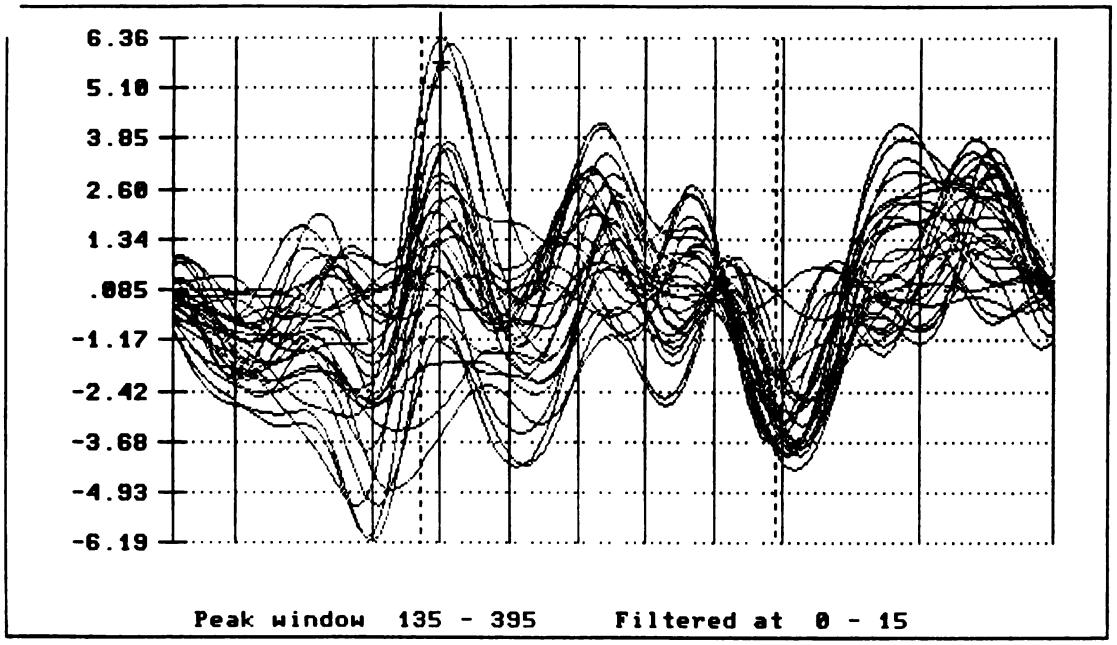


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Figure 3a. Plot of 30 electrodes showing a clear component peak

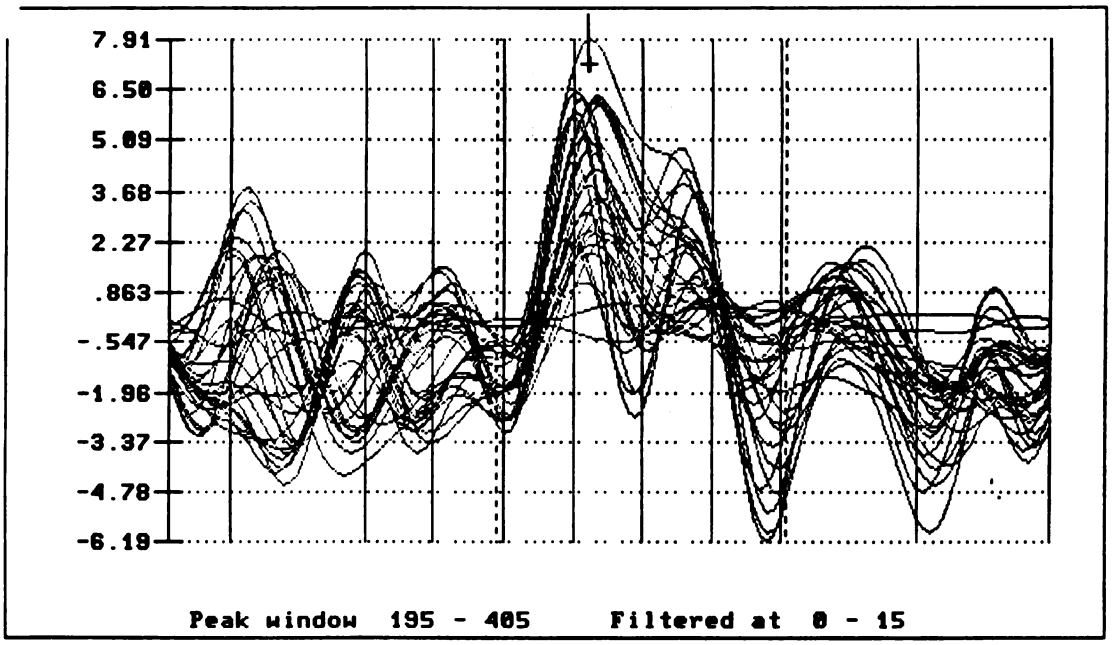


Figure 3b. Plot of 30 electrodes without a clear peak

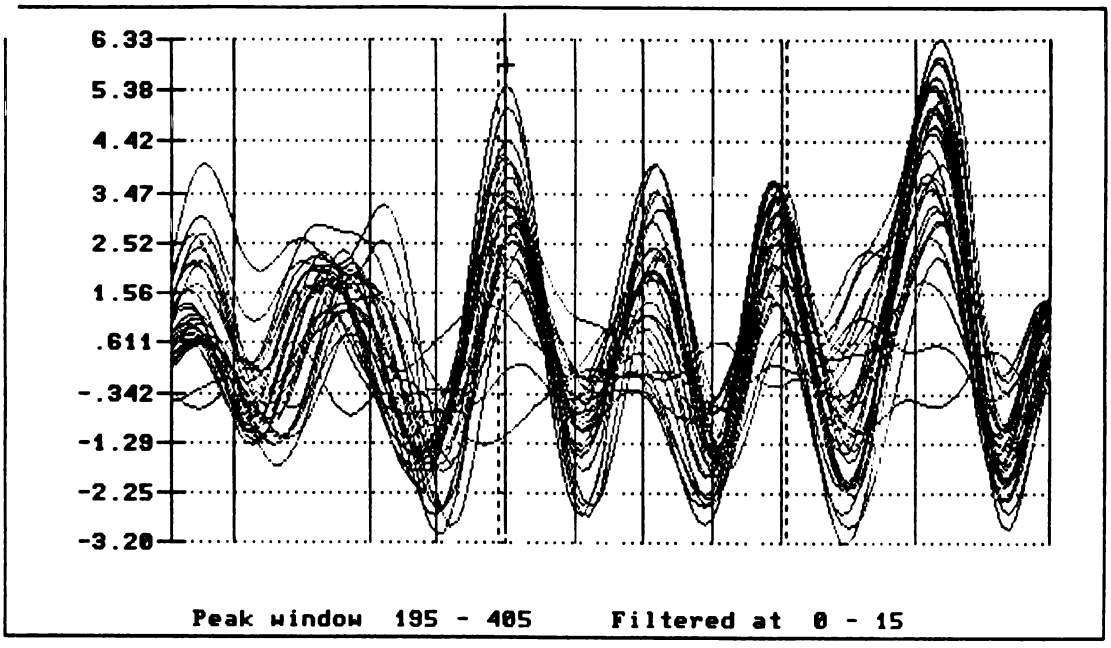


Figure 4. Alpha in difference wave compared to alpha in raw SEPs

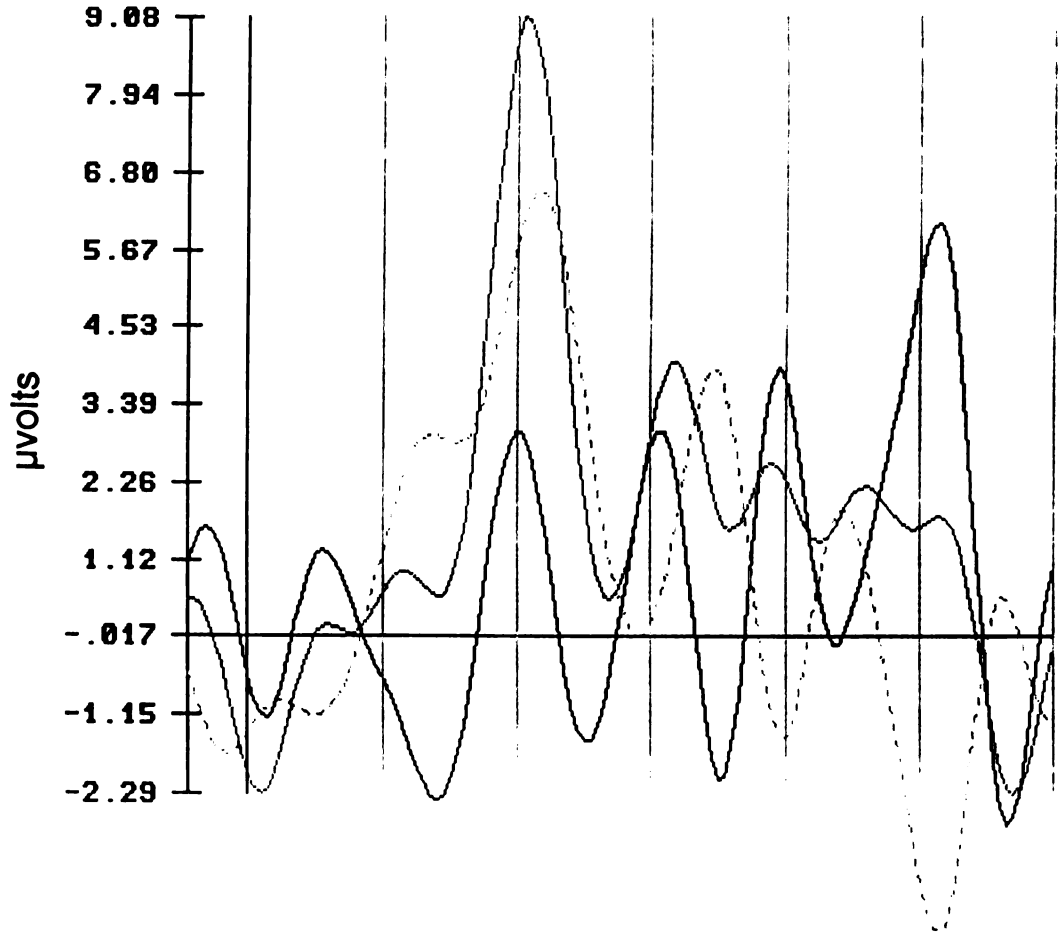


Figure 5. Grand Average Intensity Difference Wave

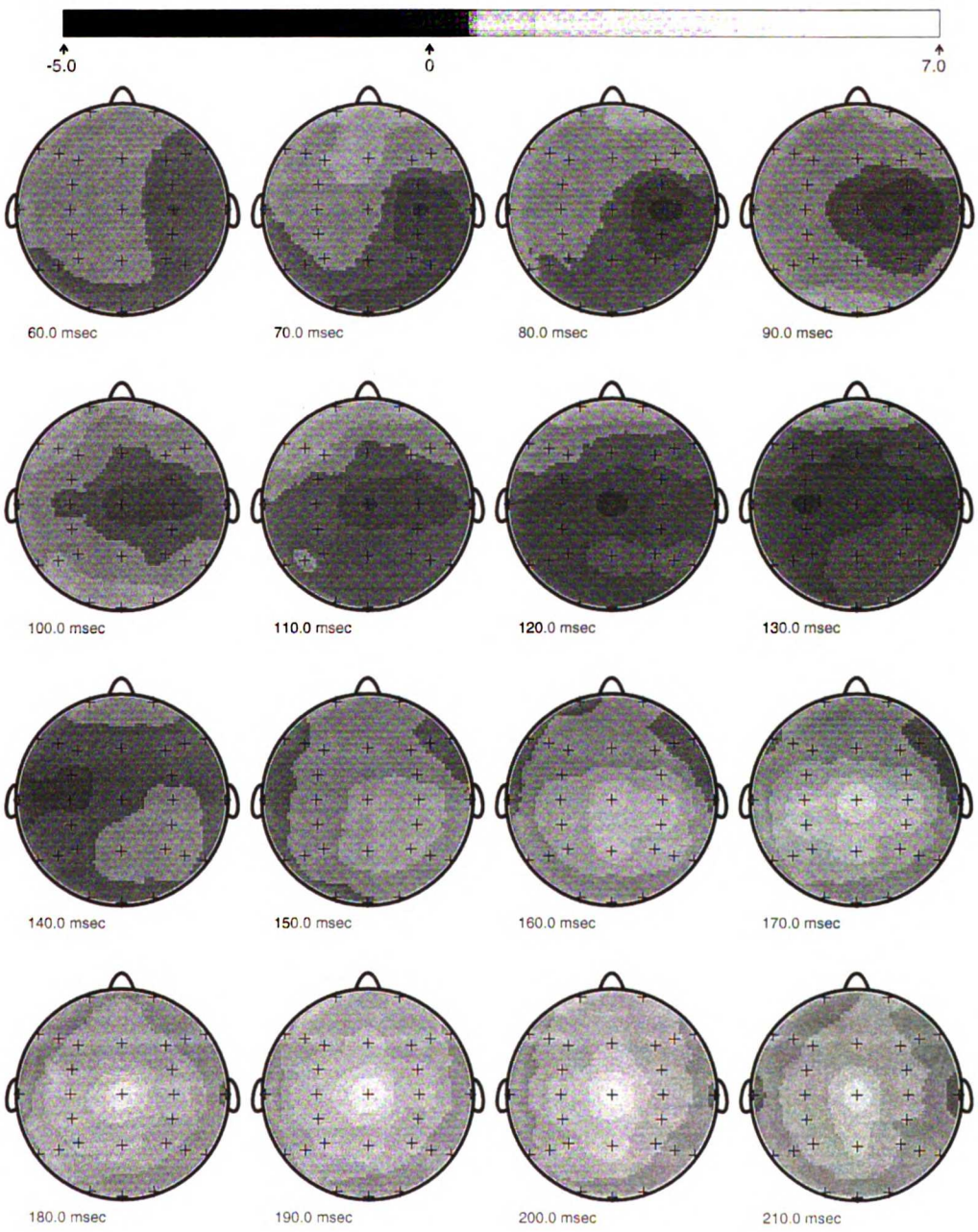


Figure 6. Grand Average Pain Difference Wave

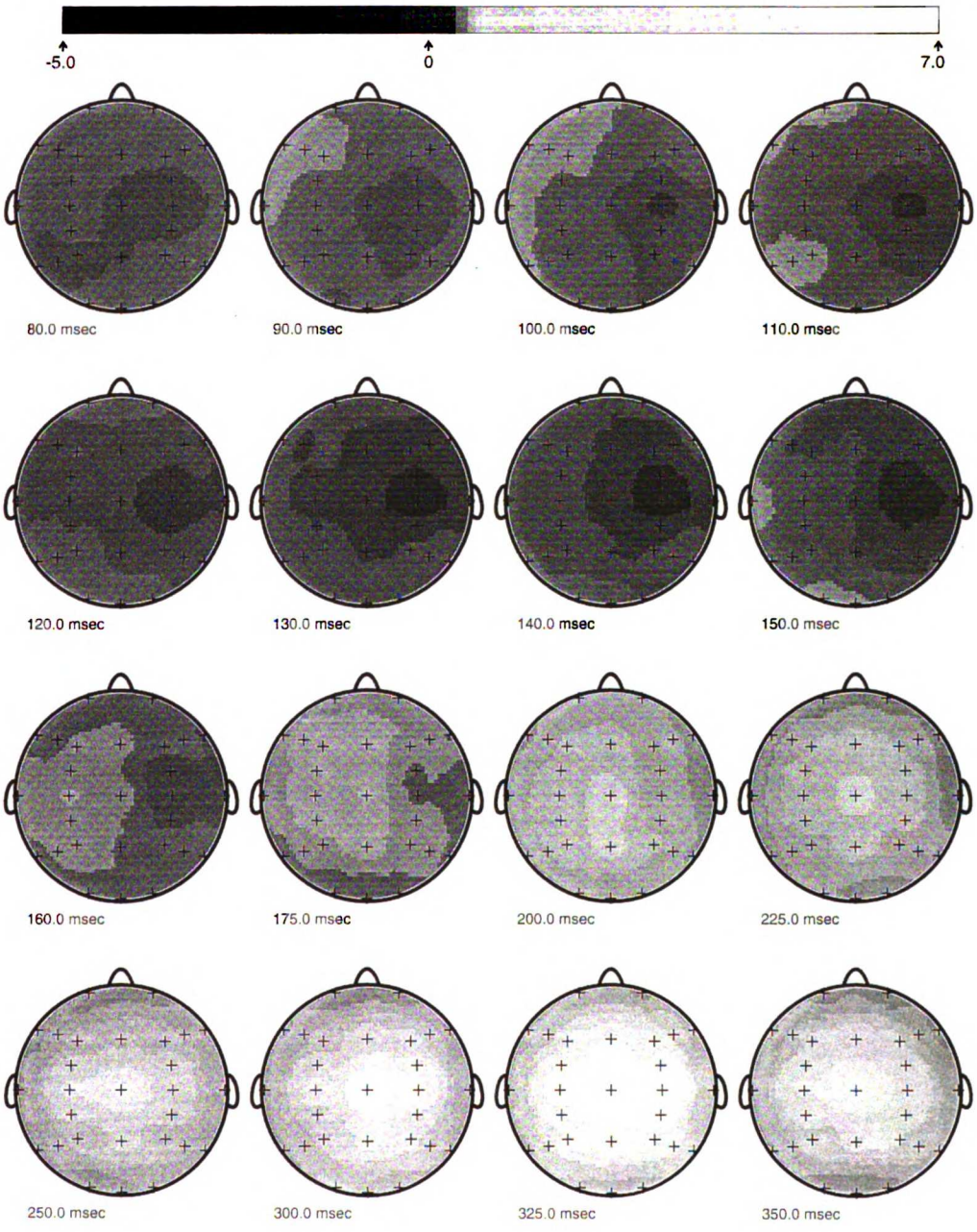


Figure 7. Grand Average P300 Difference Wave

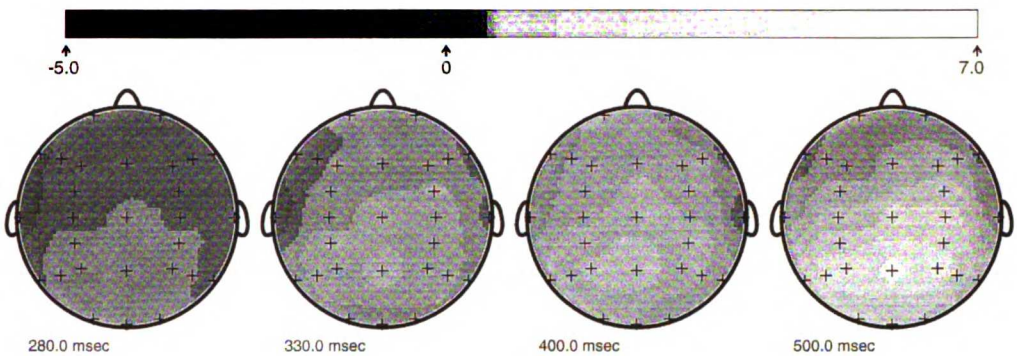
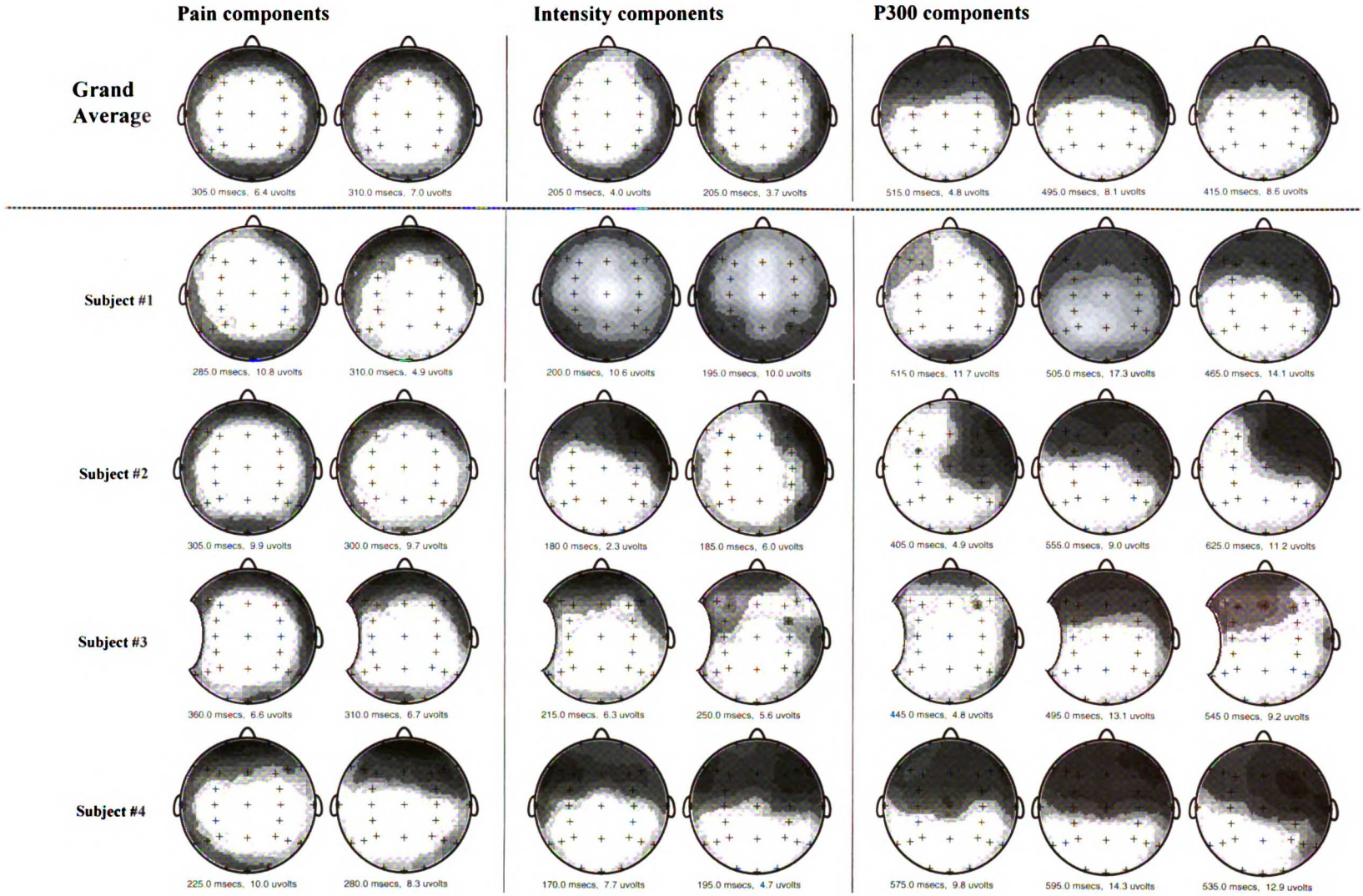


Figure 8. Topographies of difference wave positive peaks, for each subject



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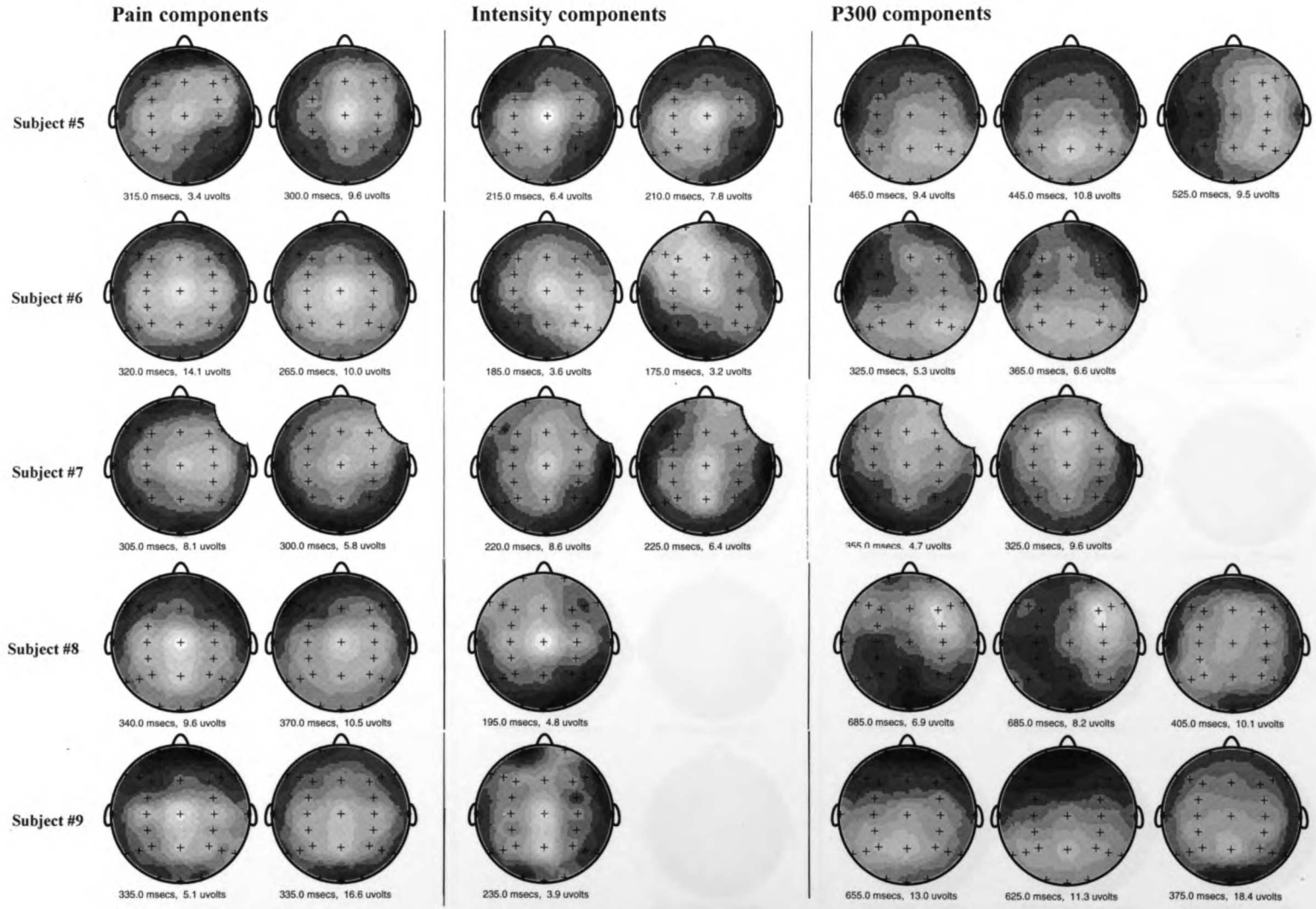

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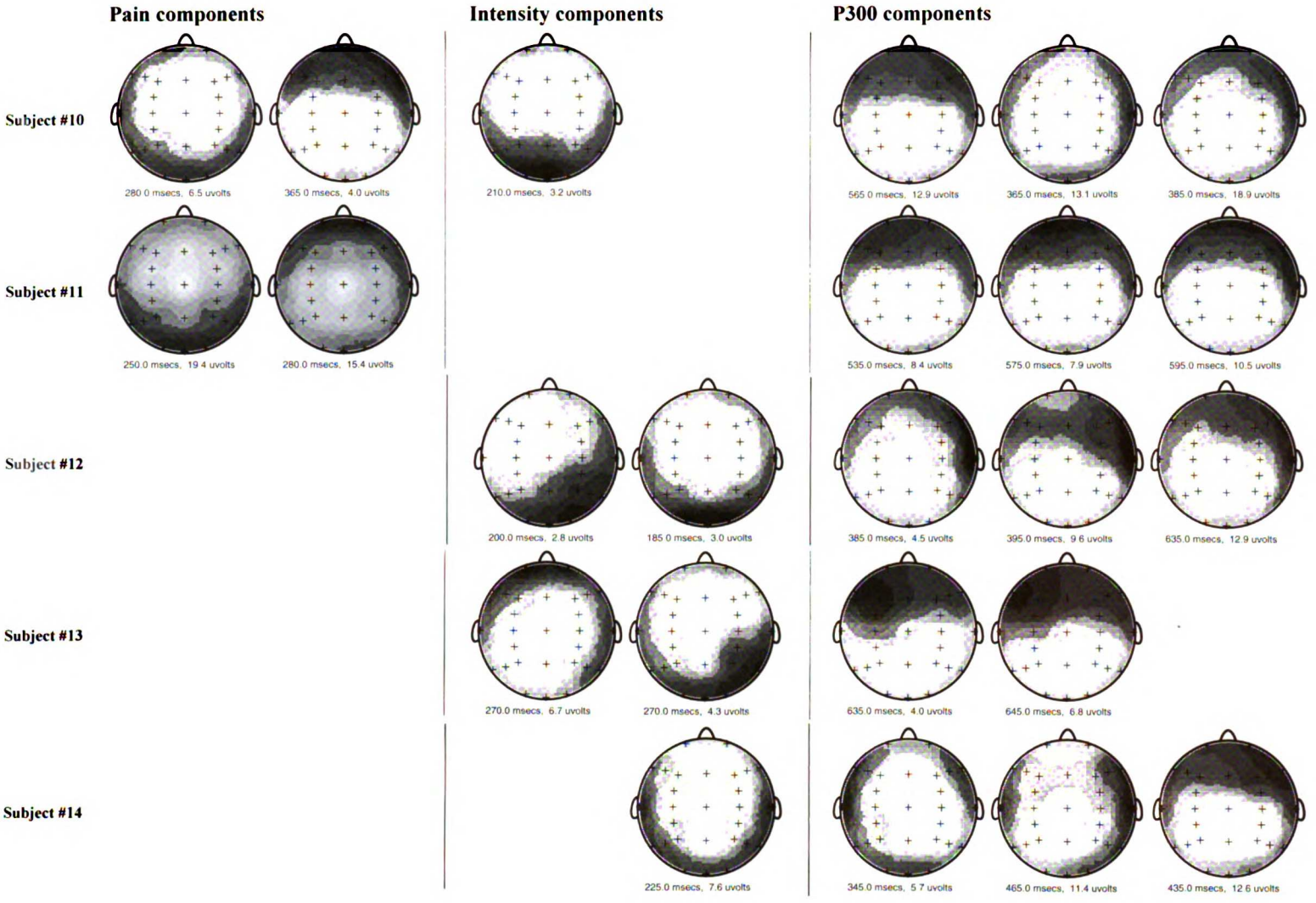

Figure 9. Peaks of Grand Average SEPs (not difference waves)