FOCUSED ATTENTION MODULATING PAIN PERCEPTION IN PEOPLE WITH CHRONIC PAIN: AN EVENT-RELATED POTENTIAL STUDY

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Focused Attention Modulating Pain Perception in People with Chronic Pain: An Event-related Potential Study

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CERTIFICATE OF ORIGINALITY

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ABSTRACT

People with chronic pain were shown to have difficulty to direct attention away from pain as in distraction due to hypervigilance to pain. Focused attention, a mental strategy which directs individuals' focus on the objective aspects of pain, was found to be effective for down-regulating pain intensity among people with chronic pain. This study can extend our understanding of the mental processes underlying focused attention that modulates nociceptive perception. This study aimed (1) to investigate the neural processes associated with focused attention through imagery of sub-nociceptive sensation; (2) to examine modulation of pain perception due to sub-nociceptive imagery in pain-free subjects and chronic pain patients; (3) to investigate the neural processes associated with modulation of pain perception using sub-nociceptive imagery and compare these processes between pain-free subjects and chronic pain patients.

Seventeen patients with chronic low back pain (mean age=41.53 years; pain history years=4.05 years) and eighteen pain-free subjects (mean age=35.78 years). After familiarization training on 5 levels of sub-nociceptive and nociceptive stimuli, the subjects were asked to participate in a perception/imagery experiment with concurrent 128-channel electroencephalogram recording. In the perception trials, the participants mentally maintained and rehearsed the nociceptive images. They then rated the recalled nociceptive images. In the imagery trials, the participants received the nociceptive stimulations, and mentally generated and rehearsed nociceptive

images that had previously learnt. They were then to rate the recalled nociceptive images.

Though no significant between-group differences were revealed by three-way repeated measures ANOVA, post-hoc t-test showed significant difference in pain normalized pain rating between two conditions in Level 2 pain in chronic pain group ($t(16)=-2.208$, $p<0.050$). Significant differences in normalized pain rating were found between two conditions in Levels 1-3 pain ($t(17)=-2.630$ to -3.223, $p<0.050$) in pain-free group. Two-way (midline sites) and three-way (lateral sites) repeated measures ANOVA showed more positive amplitudes in P2 ($p<0.01$), P3 ($p<0.01$] and P600 ($p<0.01$) and less negative N400 ($p<0.01$) in Imagery task among pain-free group. Three-way and four-way repeated measures ANOVA revealed significant between-group differences in midline and lateral electrode sites of P2, P3 and P600. Further analysis revealed that some chronic pain patients (n=6) ("respondents") showed an ability to attenuate pain when compared to the others (n=11) ("non-respondents"). ERP analyses confirmed that the respondent group has significantly larger amplitude of P2 component in the respondents.

Behavioral data suggested that the magnitude of down-regulation was shown to be lessened in chronic pain group, reflecting hypervigilance to pain possibly due to plastic cortical changes. Neurophysiologically, it was shown that some chronic pain people were able to modulate pain perception using somatosensory imagery technique. Fronto-central P2 component was shown to be the key marker for successful focused attention to nociceptive stimulation that would lead to pain attenuation. The sub-

nociceptive somatosensory image was generated, as reflected by frontal N400 component. The results support that the somatosensory imagery technique has the potential to be a therapeutic technique for some patients with chronic pain to down-regulate nociceptive perception.

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CHAPTER ONE

INTRODUCTION

The first chapter provides an overview of the research study on the effect and neural processes of somatosensory imagery on pain perception among people with chronic pain. The chapter begins with a statement of purpose, followed by the background of the study and the rationale for conducting the study. This chapter ends with a description of the organization of the thesis.

STATEMENT OF PURPOSE

People with chronic pain have been shown not only to have impaired cognitive functions but also to have difficulty in modulating perception and appraisal of the pain. This study aimed to investigate how the mental strategy of focused attention on objective aspects of nociceptive stimulus through somatosensory imagery could mediate the perception of nociceptive sensation in people with chronic low back pain. A perception/imagery mixed-trial paradigm design was used. One group of patients with low back pain and another group of pain-free individuals were asked to generate pre-learned sub-nociceptive image after perceiving different levels of nociceptive stimuli generated from an electrical stimulator. They then gave a rating of the recalled nociceptive image (imagery task). This contrasted with maintaining the nociceptive image after perceiving a nociceptive stimulus and rating the recalled nociceptive image (perception task). The rationale was that, since pain perception and attention-demanding tasks share the same attentional resources, generating a sub-nociceptive

image would modulate the processing of the nociceptive stimuli and hence the perception of the pain sensation. The event-related potentials (ERPs) associated with the imagery and perceptual processes were captured to understand better the possible neural processes underlying modulation of pain perception.

There were three objectives for the study:

1. To investigate the neural processes associated with focused attention through sub-nociceptive imagery which would modulate the perception of nociceptive sensation;
2. To examine modulation of pain perception due to focused attention through sub-nociceptive imagery in pain-free subjects and chronic pain patients; and
3. To investigate the neural processes associated with modulation of pain perception using focused attention through sub-nociceptive imagery and compare these processes between pain-free subjects and chronic pain patients.

BACKGROUND AND JUSTIFICATION

Pain sensation is often related to perilous situations. Acute nociceptive signals from the peripheral nervous system reach somatosensory cortices that constitute a discriminative aspect of the sensation. They also heighten the activities of other cortical substrates that mediate the cognitive and affective aspects of the pain experience, such as the anterior cingulate gyrus and prefrontal cortex (Ohara et al., 2005). The saliency of pain inherently demands attention to allow us to respond to the threatening situation (Eccleston & Crombez, 1999). In the case of chronic pain, pain persistently consumes attentional resources leading to cognitive deficits including

attentional, working memory and decision making (Hart et al., 2000; Dick, 2003 & 2007, Lorenz et al., 2007a & b; Wiech et al., 2005).

Pain perception can also be modulated by attention-demanding tasks. Neurophysiological studies have investigated two main types of pain modulation approaches, i.e. distraction or focused attention. Distraction requires subjects either to perform concurrent cognitive tasks (Seminowicz et al., 2004; Veldhuijzen et al., 2006) or to direct attention away during the nociceptive stimulation (e.g. García-Larrea et al., 1997). The distraction strategy is based on the assumption that attentional resources may be limited and the processing of the pain sensation arising from the painful site would diminish when the attention was diverted or re-allocated to other cognitive tasks (Eccleston & Crombez, 1999). Other researchers looked into the effects of focused attention on modulating the perception of nociceptive sensation. The fundamental difference between these cognitive strategies is that pain perception is modulated by orienting attention towards the nociceptive stimulation. The idea behind focused attention is that it enables people to extract the objective / cognitive component of nociceptive sensation (e.g. intensity and location) and set aside the subjective / emotional component (e.g. anxiety). The fact that focused attention directly involves a nociceptive sensation makes this process more goal-relevant (Moseley et al., 2008; Nouwen et al., 2006). Previous studies have found that focused attention was effective in modulating pain sensation among healthy participants (Roelofs et al., 2004) and people with chronic pain (Moseley et al., 2008; Nouwen et al., 2006). There are a number of drawbacks for attentional modulation using distraction when compared to focused attention strategy. First, the amount of attention shift between distraction and attention is difficult to control and therefore its

attribution to pain modulation can be uncertain (Quevedo et al., 2007; Wiech et al., 2008). Second, and most importantly, attentional modulation processes do not address well how pain perception is inhibited in a top-down manner. Third, the distraction approach relies on other sensory modalities to elicit pain down-regulation, and this means pain sensation lacks goal-relevance. The saliency of pain regulation thus becomes weakened. Other studies have suggested that directing attention away from pain might not be as effective in people with chronic pain due to their hypervigilance to pain (Crombez et al., 2005) and their impaired ability in down-regulating pain by re-orienting attention away from the nociceptive site (Wiech et al., 2008).

The focused attention approach might benefit from down-modulating perception of nociceptive sensation among people with chronic pain since, they have a tendency of hypervigilance to pain and are not required to orient attention away from the nociceptive stimulation site. This cognitive approach was established on a parallel treatment model (Leventhal & Everhart, 1979), in which it was postulated that a nociceptive sensation can be processed in an objective or affective manner. This suggests that pain control could be induced by generating a top-down cognitive representation or schema of pain based on sensation intensity to form a more objective schema to re-interpret the nociceptive sensation. This in turn lowers the affective representation of the pain sensation. Some behavioral studies have suggested that focused attention towards the intensity of painful stimuli and discriminating tactile sensation around the painful site have shown a down-regulation effect on pain perception (Moseley et al., 2008; Nouwen et al., 2006; Roelofs et al., 2004). Yet, the neurophysiological evidence is still limited, and the effect of focused attention on nociceptive perception in people with chronic pain still requires further investigation.

Findings of neural processes of response inhibition (Dowman, 2007a; Hatem et al., 2007; Legrain et al., 2002), that refers to an ability to exert top-down inhibitory control over executive behaviors or overt mental processes, may shed light on the neural processes of focused attention. It is because response inhibition also requires the allocation of attention to a target stimulus in order to modulate concurrent somatosensory sensation, e.g. a nociceptive sensation. In terms of neural processes, in a Go condition, subjects attend to a stimulus with a specific characteristic. In a Nogo condition, subjects apply a top-down inhibitory process to interfere with the flow of sensation. During the Nogo condition, attention is drawn to a target nociceptive stimulus (i.e. focused attention) to execute a certain action required by the paradigm, which in turn imposes a modulatory effect on the perception of a nociceptive sensation. For example, using a Go/Nogo design, Hatem et al. (2007) asked subjects to respond to a nociceptive laser stimulus and refrain from responding to the electrical stimulus in half of the trials. In the other half of the trials, subjects were asked to respond in an opposite way. In other studies, Dowman (2007a & b) adopted cross-modal cuing to elicit response inhibition on nociceptive evoked potential and pain perception. In validly cued trials, a visual cue for an upcoming pain stimulus appeared before the nociceptive electrical stimuli. In invalidly cued trials, another visual cue for upcoming visual stimulus came from two colored lights before the nociceptive stimuli. Pain down-regulation effect was obtained in the invalidly cued condition. Two event-related potentials related to inhibitory response were elicited at fronto-central sites: N2 (150-400 ms) and P300 (300-500 ms). Generally, the P2 (250-350 ms) at central sites accounts for spatial reorientation of attention toward the nociceptive stimulus and the P300 (350–550 ms) at parietal sites would be

related to sensory evaluation and event categorization involving access to long term memory (Dowman, 2007a; Friedman et al., 2001). In other words, the P2 component signifies focusing attention of target nociceptive stimulus. Source analysis from other studies on electroencephalogram (EEG) or magnetocencephalogram (MEG) data indicated that the Nogo components could be located dorso-lateral of the frontal lobe and medial aspect of prefrontal cortex, around the anterior cingulate area (Bekker et al., 2005; Bokura et al., 2001; Hatem et al., 2007).

The current study set out to explore the neural processes associated with using a self-generated sub-nociceptive image for influencing the perception of nociceptive sensation. The objective was to modulate the perception of the nociceptive sensation. The sub-nociceptive image is generated by getting access to working memory and maintaining the platform of working memory. Instead of appraising the nociceptive sensation generated from a nociceptive stimulus, the subject has to access and rehearse on the sub-nociceptive image before appraising the nociceptive sensation presented before the imagery.

Although neurophysiological evidence is limited, two key electrophysiological markers are hypothesized to signify the processes of focused attention (Dowman, 2004a & 2007a & c; Hatem et al., 2007; Legrain et al., 2002). First, the fronto-central P2 component in the imagery condition when attention is oriented from an external stimulus to the internally sub-noceptive image to be generated. Second, the actual generation of sub-nociceptive image is indicated by the frontal N400 component.

HYPOTHESIS AND SIGNIFICANCE

Among pain-free subjects, it was hypothesized that the amplitude of fronto-central P2, signifying reorienting attention from a nociceptive stimulus to a sub-nociceptive image, would increase under sub-nociceptive imagery trials when compared to the perception trials. Further, N400 component, signifying mental rehearsal of the sub-nociceptive image, would decrease in terms of amplitude. Besides, behaviorally, it was hypothesized that the pain ratings on the recalled nociceptive images would be significantly higher after the generation of the sub-nociceptive images. In order words, the pain modulation effect (pain $\text{rating}_{\text{Imagery}}$ − pain $\text{rating}_{\text{Perception}}$) would be larger in the imagery trials than in the perception trials. The amplitudes of P2 and N400 components were hypothesized to be correlated to pain modulation effect (pain $\text{rating}_{\text{Imagery}}$ − pain $\text{rating}_{\text{Perception}}$).

Among people with chronic pain, it was hypothesized that the differences in amplitudes of P2 and N400 components between imagery and perception trials would be diminished compared to those of the pain-free group. This was based on an assumption that participants with chronic pain with the tendency of hypervigilance to pain would less readily engage in focused attention after perceiving the incoming nociceptive sensation than the pain-free counterparts. Furthermore, it was hypothesized that the difference between the pain ratings on the recalled nociceptive images after the generation of the sub-nociceptive images and after simple perception of the nociceptive perception would be less in the chronic pain participants. The correlations between the amplitudes of P2 and N400 components and the pain

modulation effect (pain rating$_{Imagery}$ − pain rating$_{Perception}$) would be less strong in chroninc pain group compared to the pain-free group.

ORGANIZATION OF CHAPTERS

The thesis is composed of nine chapters, and the present one is the Introduction. Chapter 2 is the literature review on acute and chronic pain mechanism and pain modulation. Theories related to chronic pain, pain modulation, and attention and frontal lobe functions will be discussed. Chapter 3 describes the methods and results of the pilot study on test-retest reliability of sub-painful and painful sensation rating, followed by the discussion of the results. Chapter 4 is the procedures used in the two studies on modulation of pain perception using somatosensory imagery in pain-free subjects and patients with chronic pain. Data analysis used for each study is also described in this chapter. The results of two studies on somatosensory imagery in pain-free subjects and patients with chronic pain will be reported in Chapter 5. The findings obtained from the two main studies and general discussion will be discussed in Chapter 6. The thesis is concluded in Chapter 7.

CHAPTER TWO

LITERATURE REVIEW

PAIN AND NOCICEPTION: DEFINITION

Pain is a form of sensation that allows us to elicit fight-or-flight behavioral manifestations in order to evade a perilous situation or to minimize further tissue damage. This protective sense has been extensively studied in the past (Craig, 2002; Merskey, 1986; Ohara et al., 2005; Treede, 1999). Early research studies focused on pain pathways going from the peripheral nervous system to the central nervous system. Evidence now supports two separate principle entities in pain: a sensory component and an emotional component. The International Association for the Study of Pain (IASP) currently defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage (Kopf, 2010, p. 368)." The sensory component is termed "nociception", which "encompasses the peripheral and central neuronal events following the transduction of damaging mechanical, chemical, or thermal stimulation of sensory neurons (nociceptors) (Kopf, 2010, p. 366)." Thus, an external "nociceptive stimulus" transduces signals to the receptors, nociceptors, in the peripheral nervous system, which in turn transmits the signals to the neurons along pain neural pathways. The signals eventually reach the primary sensory cortex to form a "nociceptive sensation". This is a bottom-up process. Furthermore, the nociceptive sensation is then further processed through associative somatosensory and related areas and is interpreted based on an individual's knowledge and constitutes a nociceptive perception

(Goldstein, 2010). Pain, does not only refer to the unpleasant sensation itself but also is composed of an emotional component. As will be further elaborated in the upcoming section, the nociceptive signals also reach the affective cortex, including the limbic system that forms emotional experiences of "painful sensation". The knowledge-based interpretation of the painful sensation becomes "painful perception".

Furthermore, evidence has indicated that the pain network is more than intensity, discrimination and location of pain, i.e. sensory-discriminative aspect (IASP, 2011). Rather, it also includes affective-motivational and cognitive-evaluative components (Melzack & Casey, 1968; Ohara et al., 2005; Treede et al., 1999). The sensory-discriminative component of pain refers to the lateral nociceptive system, which transmits to the cortical level through the lateral thalamic nuclei. This component is related to specific pain intensity and discrimination. The affective-motivational component, on the other hand, involves the medial nociceptive system via the medial thalamic nuclei. It relates to the emotion aspect of the painful experience which is mediated by different cortical regions, such as anterior cingulate gyrus and limbic systems. The cognitive-evaluative, relatively less understood, involves a higher executive centre especially the prefrontal lobe cortex, which modulates pain perception in a top-down manner. The current study is mainly concerned with how pain perception could be modulated through the generation of sub-nociceptive imagery. It will relate more to the sensory-discriminative and cognitive-evaluative rather than the affective-motivational aspects of pain perception.

CONVENTIONAL PAIN PATHWAYS

Advances in neuroimaging technology have enriched our knowledge of the conventional nociceptive pathways related to pain (Figure 2.1). Two pathways have been proposed for explaining incoming nociceptive sensation which induces acute pain (Ohara et al., 2005). The peripheral nociceptive pathway starts at nerve endings that receive nociceptive sensation. There are two types of free pain-related nerve endings, namely small diameter non-myelinated C fibers and thinly myelinated Aδ fibers. Their central branch terminates the dorsal horn of the spinal cord. The second-order neurons in the lateral system ascend contralaterally to form the spinothalamic tract (lateral system), which in turns ends at the various thalamic nuclei, including ventral posterior lateral (VPL) and ventral posterior medial (VPM) nuclei. Some of the fibers also go to the relay center at the brainstem. The pathways terminate at the primary and secondary somatosensory cortices in the frontal cortices. In the medial system, the nerve fibers go to the posterior part of ventromedial (VMpo)

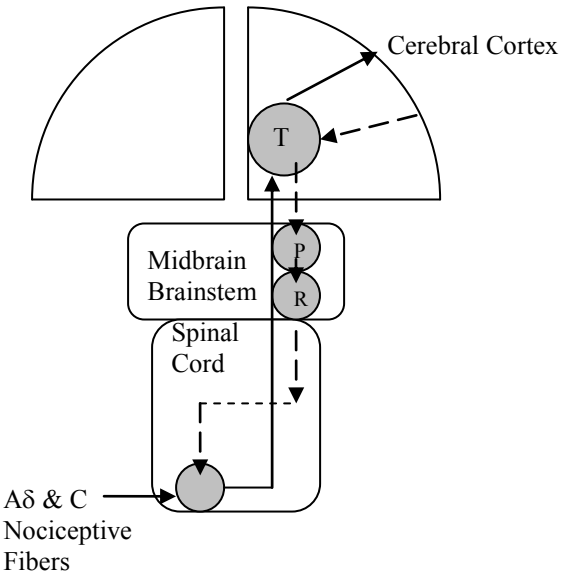


Figure 2.1 Ascending pain pathway (solid line) and descending pain modulatory pathways (dotted line). T: Thalamus; P: Periaqueductal Gray: R: Raphe Nuclear & Locus Coeruleus

and ventrocaudal part of medial dorsal (MDvc), and parafascicular (Pf) nuclei. This system mainly ends at the insular and anterior cingulated gyri, associated with the limbic system (Treede et al., 1999; Peyron, 2000; Ohara et al., 2005). There is also a parallel pathway, from which the spinal cord projections terminate at the parabrachial nucleus situated in the brainstem (Ohara et al., 2005). This subcortical nucleus then projects the pain signal to SII, insula and cingulate gyri via thalamus (medial group). Thus, there are multiple neural substrates at the cortical level which are related to pain sensation and perception. As brain imaging technology has advanced various neural substrates were identified to be the "family members" of the pain network or pain matrix as defined by Melzack (2001). The most identified regions are primary somatosensory cortex (S1), secondary somatosensory cortex (S2), insular cortex (IC), anterior cingulated cortex (ACC), and prefrontal cortex (PFC). Subcortically, thalamus, cerebellum and periaqueductal grey matter at the brainstem region are also shown to be in the pain network (Apkarian et al., 2005; Ohara et al., 2005; Schnitzler et al., 2000; Treede et al., 1999). As mentioned previously, there is a multidimensionality of pain processes in the brain and the complexity of the central pain network supports this concept. The accumulating neuroimaging evidence unravels the functions of the brain network in relation to pain processes. It has been shown that S1 and S2 are related to spatial, temporal and intensive aspects of innocuous and noxious somatosensory stimuli and they could subserve the sensory-discriminative dimension of pain processing (Bushnell et al., 2006; Schnitzler et al., 2000; Treede et al., 1999). S2 has been found to have sensory integration and spatial directed attention (Treede et al., 1999; Ohara et al., 2005). Yet the functions of IC in terms of nociceptive processing are inconclusive. It received afferents from ventral

medial nucleus of the thalamus, which appear to be related to thermal and nociceptive stimuli. While the posterior aspect has connections with somatosensory, auditory and visual cortices, the anterior portion is linked with limbic and viceroy-autonomic functions. This neural subtraction in the temporal is now regarded to be related to autonomic and affective reactions to the nociceptive stimuli, visceral sensory and motor integration, pain-related memory and learning (Schnitzler et al., 2000). ACC has been traditionally regarded as a part of the limbic system (Schnitzler et al., 2000), and it is associated with the affective-motivational dimension of pain (Apkarian et al., 2005; Peyron, 2000; Schnitzler et al., 2000). Rainville et al.'s (1997) study suggested that ACC has a role for modulation of pain-evoked activity after hypnotic suggestions for changes in pain unpleasantness, and it was correlated with subjects' ratings of pain unpleasantness. ACC is consistently found to be associated with affect, emotion and memory of pain experiences (Petrovic et al., 2002; Treede et al., 1999). A study by Albanese et al. (2007) also showed that the central neural substrates are not only responsible for incoming nociceptive stimuli, but also retained memory traces of pain. It was also shown that, after the introduction of cutaneous pain, the SI and posterior parietal cortex retain short-term memory of the spatial and intensity aspects of noxious stimuli.

Event-related potential (ERP) is one of the common neuroimaging techniques to investigate temporal processes underlying acute pain perception. There are several ways to apply nociceptive stimuli in experimental studies, including laser pain (Forss et al., 2005) and thermal pain (including hot and cold pain) (Nouwen et al., 2006; Wiech et al., 2005). Results of previous research related to electrical evoked potential are the focus of the following section, especially the use of nociceptive stimuli that

are also used in the current study. Nociceptive evoked potentials induced by cutaneous electrical stimulation at finger tip sites have mainly elicited N1 (N140 peak) and P2, with peak latencies appearing at about 100 to 150 milliseconds (ms) and 200 to 250 ms, respectively (Dowman, 2007a; Kakigi et al., 2000; De Pascalis et al., 1999, 2001 & 2008; Zachariae et al., 1994). These components peaked at central sites, with P1 somewhat more frontally distributed. Dipole sourcing analysis based on MEG data when train pulses of electrical stimuli were applied to the hand area showed that the N1 component (100-150ms post stimulus) was generated in the S2 and insula bilaterally and the P1 was originated from bilateral S2 and cingulate gyrus (Howland et al., 1995; Kitamura et al., 1995, 1997; Hoshiyama et al., 2000; Yamasaki et al., 2000). This is consistent with the differences in the transmission speed between nociceptive Aδ-fibers and C-fibers and the lateral and medial nociceptive pathways previously discussed (Arendt-Nielsen, 1990, Bragard et al 1996, Bromm & Treede, 1983, Iannetti et al 2003, Tran et al, 2002). This suggests that the nociceptive signals are transmitted to the cortices bilaterally before reaching the cingulate area. The amplitudes of N1 and P2 components of electrical evoked potentials were shown to be reduced under cognitive tasks or distraction in other studies on attention to pain (De Pascalis et al., 1999, 2001 & 2008; Dowman 2007a & b; Yamasaki et al., 2000; Zachariae et al., 1994).

Since nociceptive and sub-nociceptive electrical stimuli were applied to the cutaneous region posterior to the right lateral malleolus supplied by the sural nerve in this study, the ERP components related to the sural nerve are reviewed here. The work of a research team led by Dowman and colleagues (2007a & b) provided a good foundation of somatosensory evoked potential (SEP) in relation to the sural nerve

(Dowman, 2004a & b; 2007a & b). A series of ERP components with mid-latency were consistently revealed in their studies. There were three stable periods (SP) based on the topographies, namely SP1, SP2 and SP3. There is a transition between SP3 and P1. The ERP epochs were defined based on the transition period between these stable periods. This resulted in a negativity over the central scalp at 70-110 ms post-stimulus (CN70-110) corresponding to SP1 and SP2 transition (SP1-2). There were two overlapping epochs with different topographical distributions corresponding to SP3 and P1 transition (SP3/P1): a contralateral temporal negativity at 100–180 ms (CTN100-180), a fronto-central negativity at 130–200 ms (FCN130-200). They are followed by a positive potential at 270–340 ms (labeled as P2) and another at 349-409ms (labeled as P3a). The first three negative components, i.e. CN70-110, CTN100-180 and FCN130-200, form a complexity which is equivalent to N1 reported in other SEP-related studies. The one difference is that the amplitudes of these mid-latency ERP were found to be smaller when attention is voluntarily directed toward the site of stimulation at the sural nerve than when directed to other tasks (Dowman, 2004a & b, 2007a & b). This signifies automatic, intermodal orienting toward a threatening somatosensory stimulus. The P2 component is the positive potential with duration of P270–340 ms. This component was shown to increase with painful intensity (Bromm & Lorenz, 1998; Dowman, 1996), when the subject is engaged in a distraction task from the sural nerve stimulation (Dowman, 2004a and 2007a). Since this component was not found to increase in an intermodal task, it was suggested that it is related to spatial attention re-orientation toward nociceptive stimuli. The P3 component was also identified in relation to sural nerve evoked potentials. This component increased with increased stimulus intensity. This is equivalent to the P3a

in oddball or Go/Nogo experiments and it tends to be anteriorly distributed while attending towards infrequent and deviant stimuli (Friedman et al., 2001; Polich, 2003). On the other hand, the posterior scalp of the P3a reflects stimulus evaluation and updating (Friedman et al., 2001; Goldstein et al., 2002). Dowman (2007a) showed that the P3a component could also be obtained in invalidly cued condition regardless of stimulus occurrence probability. Table 1.1 summarizes nociceptive ERP components of the sural nerve and related mental processes and generators (Dowman, 2007a & b).

While the various higher-center substrates receive afferent nociceptive signals from the periphery, there are two levels of systems that send out efferent signals to modulate pain: the descending pain modulatory system and the "top-down" pain modulatory system. The former involves the midbrain substrates that send out inhibitory signals. The key substrates of the descending pain modulation pathway are the periaqueductal grey (PAG) and rostral ventromedial medulla (RVM) situated at the midbrain region acting as an inhibitory system to suppress ascending nociceptive signals (Bingel & Tracey, 2008; Bushnell et al., 2006; Schnitzler et al., 2000; Treede et al., 1999; Wiech et al., 2008). Both PAG and RVM exert inhibitory influences back to the dorsal horn of the spinal cord. This in turn results in a down-modulation effect on pain perception. This descending pain modulation pathway also has a connection with higher level neural substrates which form the top-down modulation system. Although the processes are still uncertain at this stage, both rostral ACC and lateral PFC have been shown to play roles in top-down pain modulation in recent studies (Bingel et al., 2008; Petrovic et al., 2002; Tracey et al., 2008). This network forms the core components of the cognitive-evaluative aspect of pain experiences. As

mentioned before the medial aspect of PFC, including rostral ACC, was associated with increased pain perception and unpleasantness (Petrovic et al., 2002, Baliki et al., 2006). It has been reported that its activation is related to increased nociceptive perception as it brings attention towards the source of the pain (Apkarian et al., 2009; Begel et al., 2006; Wiech et al., 2008). The lateral aspect, especially dorsolateral prefrontal cortex (DLPFC), could be the cortical region for pain modulation (Apkarian et al., 2009; Bingel et al., 2008; Tracey 2007 & 2008; Wiech et al., 2008) when pain is down-modulated during spatial attention reallocation and reappraisal of pain perception. In a review article, Wiech et al. (2008) also suggested three pain modulation neural mechanisms which appear to be controlled by dorsolateral and ventrolateral regions of PFC: attention, reappraisal and expectation. The attention mechanism would be the most relevant to this study and it could involve DLPFC and ACC. These regions are shown to have an inhibitory influence on the descending pain system via the ACC, thalamus and PAG in midbrain (Rainville et al., 1997; Wiech et al., 2008). The temporal processes of these cortical substrates in relation to pain modulation are yet to be identified.

Table 1.1 Nociceptive ERP components of the sural nerve and related mental processes and sources (Dowman 2004 a & b; 2007 a & b)

ERP	Distribution & Duration	Mental Processes	Sources
SP1-2	Central negativity at 70–110ms (CN70-110)	- Automatic process to detect and reorient attention toward the sural nerve stimulation site - decreases when attention is directed towards the sural stimulation site (intermodal)	Primary somatosensory & supplementary (medial wall of parietal cortex)
SP3/P1	Centro-temporal negativity at 100–180 ms (CTN100-180)		Somatosensory association areas located in the parietal operculum (e.g., second somatosensory cortex, Brodmann area 7b, insula)
SP3/P1	Frontocentral negativity at 130–200 ms (FCN130-200)		Medial prefrontal cortex (including the supplementary motor area and anterior cingulated cortex (ACC)), and primary somatosensory cortex
P2	Fronto-central positivity (FCP270–340 ms)	- Reflects non-pain-specific cognitive processes (Arendt-Nielsen 1994; Bromm & Lorenz 1998) - Increase with increasing painful intensity & attention is oriented away from other task & toward the evoking stimulus to sural nerve (spatial) - Amplitude decreases when engaging in a distraction task	Inferior posterior parietal cortex (e.g. Brodmann area 40 & temporal parietal junction)
P3a	Frontocentral positivity (P349-409)	- Elicited by infrequent and irrelevant stimulus, indexing involuntary orienting response (Friedman et al., 2001; Polich, 2007)	Dorsolateral and medial prefrontal (ACC) cortices
	Parietal positivity (P349-409)	- Stimulus evaluation and categorization	Inferior parietal cortex, and the posterior hippocampus

CHRONIC PAIN: NEUROIMAGING AND NEUROPHYSIOLOGICAL PERSPECTIVES

Definition of Chronic Pain

In contrast to acute pain, chronic pain appears to be more complex since its perception is beyond the tissue damage at the peripheral sites. Depending on definitions and populations, studies have revealed that the prevalence of chronic pain ranged from 10 to over 50% (Elliott et al., 1999; Melzack, 2001; Neville et al., 2008; Smith et al., 2001). In Hong Kong, similar statistics of 10.8% was reported (Ng et al., 2002). The International Association for the Study of Pain (IASP) (1986) defines chronic pain as "pain that persists beyond normal tissue healing time, which is assumed to be 3 months (p. S1)." Hart et al. (2000) argued that chronic pain persists typically 6 months after injury due to unclear etiology and ineffective medical interventions. It can lead to avoidant behavior, reduced activities and various emotional and psychological distresses (Hart et al., 2000; Morone, 2007). There are six major causes of chronic pain (IASP, 2011): musculoskeletal (e.g. arthritis, spinal stenosis), cancerous and neuropathic pain (e.g. post-stroke pain, peripheral neuropathy). There are four main types of chronic pain: nociceptive (somatic and visceral), neuropathic, psychogenic and idiopathic pain. Nociceptive pain is detected at somatic tissues (such as muscles), visceral (such as small intestine) by nociceptors. Neuropathic pain is caused by the nerves at which the physiological changes at the nerve occur. Psychogenic pain is usually associated with psychological disorder, such as depression. Thus, there are no observable tissue damages since the the pain sensation is perceived at the higher cortical level. Idiopathic pain has no known

obvious physical or psychological causes. In this study, the kind of pain the participants with chronic pain experience would be somatic pain as low back pain is musculoskeletal origin. It is assumed that the peripheral nerve is functional and intact and does not lead to neuropathic pain.

Cortical Changes in People with Chronic Pain

Neurochemical changes have been reported in various review articles (Apkarian et al., 2009; Bolay et al., 2000; Neugebauer et al., 2009; Zhuo et al., 2008). During tissue healing processes, some chronic pain appears to be related to heightened activities of the glutamate N-methyl-D-aspartate (NMDA) receptors located at the postsynaptic portion of the dorsal horn at the spinal cord level (Bolay et al., 2000; Brook, 2005; Rosenow et al., 2003) and cortical substrates (especially ACC) (Zhuo, 2008). Activation of NMDA leads to an increased calcium ion (Ca^{+}) released intracellularly to trigger a series of long-term potentiation at the postsynaptic end. The details of the cellular mechanisms are beyond the scope of this study. But this persistent altered neuronal activation at the spinal level eventually causes central sensitization along the nociceptive pathways and even reorganizations in neural substrates at the cortical level (Bolay et al., 2000; Rosenow et al., 2003; Zhuo, 2008). At this stage, pain condition is considered to become “cortical”. Recent neuroimaging studies give a clearer view on the cortical representation of chronic pain. A meta-analysis study also concluded that the hypersensitive condition under chronic pain could be due to amplification of the thalamus, insular, and S2 cortices responses, along with concurrent decreased cerebral blood flow in ACC (Peyron, 2000). Abnormal cerebral blood flow was found in the thalamus, caudate and ACC in people

with fibromyalgia syndrome (Staud et al., 2001). The reorganization or at least plasticity changes within thalamocortical pathways projecting to S1, S2 and ACC was reported in a group with trigeminal neuralgia (Rainville et al., 2001; Zhuo, 2008) or phantom pain (Birbaumer et al., 1997; Flor et al., 1995). These morphological changes in neural substrates in the pain matrix were also revealed in people with low back pain. Changes in somatotopic organization in the primary somatosensory cortex (S1) were found among people with phantom pain or low back pain (Flor et al., 1997; Rainville et al., 2001). Another study highlighted that sustained pain may lead to increased activity in the medial PFC covering the rostral ACC under a sustained high level of low back pain (Baliki et al., 2006). Two neuroimaging studies specifically related to people with low back pain. Using morphometric analysis methods, Apkarian et al. (2004) found low back pain is associated with decreased gray matter density in the bilateral DLPFC and right thalamus (by 11%). Another study found similar gray matter decrease pattern in DLPFC with additional decrease in dorsolateral pons and somatosensory cortex (Schmidt-Wilcke et al., 2006) though an increased activity in thalamic gray matter was revealed.

Although there are still inconsistencies across studies on the altered activity level in different cortical substrates among people with chronic pain, several review papers suggested that persistent bottom-up pain might lead to long-term plastic changes or even neurodegeneration at different regions of the cortex, especially at the DLPFC, the ACC and the subcortical thalamic region (Apkarian et al., 2004 & 2009; Iadarola et al., 1995; Ducreux et al., 2006; May, 2008; Neugebauer et al., 2009; Wiech et al., 2008; Zhuo, 2008). Apkarian et al. (2009) proposed a working model in which there might be an imbalance phenomenon occurring between the lateral and medial pain pathways, in which the former is more related to cognitive and affective

aspects of the pain perception. It is regarded that the lateral pathway constitutes objective aspects of the nociceptive signal, such as intensity and location, whilst the medial pathway is more related to the emotional or affective aspect of the pain experience. It was stipulated that, under chronic pain, inhibition of lateral pathways on the medial counterpart has been impeded. This leads to a decreased afferent input through the lateral pain pathway via the lateral and posterior thalamus, i.e. VPL and VPM nuclei, which is related to tactile sensation. This reciprocally leads to an increased activity in the medial nucleus, i.e. MDvc nucleus. As the medial pathway has stronger connectivity with cortical substrates such as amygdala and ACC, the affective component of the pain perception has become aberrantly active (Apkarian et al., 2009; Rainville et al., 2001). This would develop "sub-nociceptive pain" or central pain (Rainville et al., 2009, p. 134). The diminished activity in the cognitive aspect of the pain matrix, especially the DLPFC, which is more connected to the lateral pain pathway, concurs with the imbalance phenomenon. Findings suggested that the DLPFC is the substrate for executive functions to "keep pain out of mind" as previously discussed (Apkarian et al., 2009; Lorenz et al., 2003; Ohara et al., 2005; Wiech, 2008). Thus, it is probably that people with chronic pain condition would have an impaired ability in performing top-down pain modulation (mediated by the lateral pathway) via the PAG descending pain modulatory system and at the same time, the increased activities in affective components (mediated by the medial pathway) might explain the emotional instability (Hart et al., 2000).

Behavioral and Neurophysiological Studies on Chronic Pain

Various behavioral and neurophysiological studies also revealed impaired

cognitive functions in people with non-malignant chronic pain (Hart et al., 2000; Dick 2003 & 2007, Lorenz et al., 2007a & b) although there are a relatively limited number of related studies. This could be because of the heterogeneous nature of chronic pain suffered by the individuals participating in the studies. Among various cognitive dysfunctions, such as memory or decision making, attention deficit has been studied the most among people with chronic pain (Apkarian et al., 2009; Hart et al., 2000). Eccleston (1995) found that people with a higher intensity of chronic pain performed more poorly than pain-free counterparts in a numerical searching task and dual demand processing tasks in terms of reaction time. This indicated that chronic pain affects the efficiency of sustaining and shifting attentional abilities. Impaired attentional performance was found to lead also to poorer cognitive performances in people with chronic pain. For instance, Dick et al. (2007 & 2008) used a computerized interface to test working memory of a group of people with LBP and with fibromyalgia. The group with chronic pain obtained scores in the impaired range. This could be because people experienced difficulty to sustain a memory trace under the influence of chronic pain. In addition, Apkarian et al. (2004) investigated people with low back pain and CRPS using the Iowa Gambling Task, which measures higher-level cognitive functions of emotional decision-making with limited knowledge about the penalty and reward. People with LBP selected fewer advantageous card decks than the pain-free controls. Furthermore, due to the fact that there might be reorganization in the S1 in people with chronic pain, their tactile acuity was shown to be adversely affected (Moseley et al., 2008). The degree of acuity impairment was related to the intensity of pain among people with complex regional pain syndrome (CPRS) (Förderreuthe et al., 2004; Maihöfner et al., 2006; Pleger et al., 2006, Moseley et al., 2008). Yet, these behavioral studies did not address the

processes of how chronic pain affected the cognitive functions and did not differentiate deficits across chronic pain type.

Apart from behavioral studies, a collection of studies adopted event-related designs to look at the neural processes which could be altered or impaired under the chronicification of pain. A majority of these studies adopted oddball designs to examine the effect on the attention-related P3 component. Generally, these studies found that the amplitude of P3 decreased with experimentally induced or endogenous chronic pain (Houlihan et al., 2004; Lorenz & Bromm, 2007c; Veldhuijzen et al., 2006). This could be attributed to equivocation (Houlihan 2004) with the notion of a limited amount of attentional resources. Task difficulty appeared to be the parameter to affect the amplitude of the P3 component. A good example is the study conducted by Lorenz and Bomm (1997c). In this ERP study, experimental pain was induced by an upper-arm tourniquet. Using an oddball experimental design, the subjects were presented with a concurrent memory search task with different levels of task difficulty. The amplitude of P3 component, that reflects the attention to the cognitive task, was reduced under pain stimulation. This indicates that the induced pain consumes attentional resources. Similar findings of diminished P3 amplitude were also reported in other cognitive demanding tasks under pain condition (Dick et al., 2003; Houlihan et al., 2004; Chen et al., 2007). Lorenz and Bomm (2007a & b) used a pharmaceutical approach to study the effect of P300 during auditory attention tasks under the induction of morphine analgesia. It was found that increased P300 amplitude was increased when chronic pain was reduced by morphine. It was also found that amplitudes of the long latency LEP positivity (P400) and N170 were attenuated among people with chronic pain after application of morphine. These neurophysiological changes under morphine indicated that a disruptive effect on

perception and concentration could be transiently improved (Lorenz et al., 2007a).

Other studies revealed increased amplitude of P3 components among people with chronic pain, reflecting heightened attentional activities to achieve the same level of cognitive performance due to deficits in attention allocation. In an ERP study by Veldhuijzen et al. (2006), subjects with chronic pain were asked to participate in easy and difficult visual attention tasks. The speed-accuracy trade-off was not shown in pain subjects. The healthy subjects showed decreased P300 amplitude at Oz site in the difficult task whereas the decrease was not observed in pain subjects. This suggested that people with chronic pain might have deficits in "tuning" an optimal amount of attention resources according to task difficulty. Karl et al. (2004), adopting a visual oddball task, also showed similar increased amplitude in P300 among people with phantom pain. It was suggested that people with phantom pain might require more attention resources for successful performance in the oddball tasks and at the same time they exerted effort to turn away from the persistent pain. The increased P300 amplitudes might also reflect the manifestation of heightened perceptual sensitivity due to cortical reorganization after amputation.

PAIN MODULATION AMONG HEALTHY AND CHRONIC PAIN PEOPLE

While painful perception and perhaps experiences hinder cognitive function, especially attention, attention control could reciprocally modulate pain perception. As discussed before, there are subcortical structures, including the periaqueductal grey situated in the midbrain, functioning as a descending inhibitory system on nociceptive signals. On the other hand, evidence suggests that the higher cortical centre, including the dorsolateral prefrontal cortex, could be involved with the down-regulatory effect

on pain perception (Wiech et al., 2008). According to the Eccleston and Crombez's model (1999) previously described, engaging in a cognitive task requires attentional resources that in turn down-regulates the attention towards noxious perception due to a reciprocal relationship between attention on pain and on cognitive tasks. In other words, allocating attention on the non-painful site or other cognitive events could decrease the intensity of pain perception.

Neurophysiological studies have revealed the neural processes of attention, which may account for pain modulation. A number of studies attempted to create the effect of down-regulation of pain perception by requiring subjects to engage in a certain cognitive task (Seminowicz et al., 2004; Veldhuijzen et al., 2006; Yamasaki et al., 2000) or to orient attention spatially away from a painful site (Eimer et al., 2003; Eccleston 1995; Gutierrez-Martinez et al., 2010, Hodes et al., 1990). For example, in the study by Veldhuijzen et al. (2006), the subjects were required to perform a high- or low-demand visual search task while a cold painful stimulus were given to the non-dominant hand. It was shown that there was an increase in negativity in 350 to 450ms time window in high-load visual search, reflecting inhibition processes on pain. Another experimental design directed subjects to attend or be distracted from pain stimulation sites (García-Larrea et al., 1997). In the experiment, the subjects were asked to count the number of painful stimulations (attention) or to detect a deviant noise (distraction). The attention-related N220-P350 complex was shown to be reduced in amplitude under the distraction condition. Pain perception was shown to be reduced in these studies though substantial evidence of how inhibition processes in this top-down manner is lacking (Quevedo et al., 2007; Wiech et al., 2008).

Although the distraction approach might seem to be a reasonable means to down-modulate pain perception, its effect appears to be indirect in modulating pain

perception. In other words, attention is redirected to an attribute that is not a part of the painful stimulus (Van Damme et al., 2010). Instead, visual (Bruin et al., 2002; Eimer, 1993; Eimer et al., 2003), auditory (Falkenstein et al., 1999), or somatosensory modalities (Bokura et al., 2001; Nataka et al., 2004) were used to draw attention away from nociceptive stimuli. Nonetheless, there are several drawbacks of using distraction for modulating pain perception. First, the assumption that there are limited attentional resources in humans and hence diverted attention would result in diminishing pain perception process has not been well supported (Eccleston et al., 1999; Van Damme et al., 2010). Second, the extent to which attention can be divided and shifted between the distraction and attention attributes for pain modulation has been shown to be hard to control (Quevedo & Coghill, 2007; Wiech et al., 2008). Third, most the attentional reorientation designs in previous studies used concurrent stimulus, which is not-somatosensory in nature, for modulating pain perception. This could limit the motivation to modulate pain perception as the concurrent stimulus with another type of modality is not goal-relevant (Van Damme et al., 2010).

In contrast, focused attention, in which one attends to a painful site for modulation, might be an optimal alternative for pain modulation (Moseley et al., 2008; Nouwe et al., 2006; Roelofs et al., 2004). Focused attention has the advantage over distraction as the nociception to be modulated becomes goal-relevant. In other words, the nociceptive stimulus becomes the aim of the tasks. Besides, focused attention does not require divert attention to other attributes. The parallel treatment model on pain is one of the well accepted models to postulate the process of focused attention (Leventhal & Everhart, 1979). The model is supported by a series of empirical studies conducted by Leventhal and colleagues (Johnson et al., 1974; Leventhal et al., 1979; Levanthal & Everhart, 1979; Leventhal et al., 1989), in which the subjects were

required to bring attention to the nociceptive sites and interpret the sensation in terms of cognitive / objective aspect, instead of affective / subjective aspect. This model was proposed based on the fact that there are two exclusive parallel systems (Logan et al., 2005) in the pain networks that carry discriminative and emotional nociceptive information. As described previously, it consists of the lateral system that constitutes the cognitive aspect of the nociceptive signals, such as location and intensity in the somatosensory cortices, and the medial system that carries affective signals to the emotional systems, including ACC. This model is distinctly different from other distraction models (Eccleston et al., 1999), in which concurrent cognitive demand of a task is regarded as competing with the attention demand for pain processing.

In the parallel treatment model, pain perception can be altered by separating the objective schema from the subjective counterpart, and deciding which schematic orientation to adopt. Thus, a focused attention strategy enables pain modulation through focusing on the objective representation of pain (such as intensity) and setting aside the affective and subjective representation (Moseley et al., 2008; Nouwen et al., 2006; Roelofs et al., 2004). This could encourage a habituation effect on emotional schemata embedded in the nociceptive stimuli and extraction of the objective schemata for pain perception reinterpretation. With focused attention, the subject is "distracted" away from the affective/subjective aspect of the nociception but stays focused on the cognitive/objective aspect of the nociceptive stimulus. This confines the processes to the same sensory modality, and painful perception becomes more goal-relevant. It is also suggested that attending to pain in a more objective way could also reduce pain and the related psychological threat (Moseley et al., 2008; Roelofs et al., 2004). Relatively few behavioral studies have been conducted to investigate the effectiveness of focused attention in pain-free subjects (McCaul et al., 1982 & 1984;

Roelofs et al., 2004). In a more recent study (Roelofs et al., 2004), the healthy subjects were given cold-pressor pain while they were asked to apply either a distraction or a focused attention technique. In the latter, they were trained to focus mainly on the physical sensations being experienced and then reported what they felt. It was shown that distraction worked among those with a lower level of fear whereas focused attention appeared to be more effective among the more fearful group.

Neurophysiological or neuroimaging evidence on focused attention appears to be scarce. Studies on pain modulation via response inhibition would shed light on the possible mental processes underlying focused attention as they share similar mental processes. Response inhibition could be defined as a top-down voluntary inhibitory control over overt motor execution or covert mental processes when there is a change of context (Falkenstein et al., 1999; Hatem et al., 2007; Nakata et al., 2004). A classical example was employing Go/Nogo with oddball design tasks, in which the subjects were requested to give a motor execution (usually pressing a button) while detecting a target stimulus (Go trial) and to withhold the motor execution when detecting a non-target stimulus or irrelevant stimulus (Nogo trial) (Eimer, 1993; Falkenstein et al., 1999; Polich, 2007). A majority of studies investigated its effects on visual (Bokura et al., 2001; Bruin & Wijers, 2002; Kiefer et al., 1998; Kok et al., 1986; Vallesi et al., 2008; Pfefferbaum et al., 1988) or auditory (Eimer, 1993; Falkenstein et al., 1999) evoked potentials by withholding motor action.

Response inhibition on somatosensory stimuli including nociceptive sensation has also been studied. Inhibition of the responses share similar mental processes with focused attention as it also requires focusing the attention on the target stimuli. In a Go condition, the subject attends to and perceives a somatosensory stimulus without any mental interference. In a Nogo condition, the subject focuses attention to and

perceives somatosensory stimulus followed by a top-down inhibitory process, usually withholding a certain motor execution (Hatem et al., 2007). Previous studies have investigated the role of response inhibition and its effects on nociceptive sensation (Dowman, 2007b; Nakata et al., 2004) or sensori-motor modalities (Bokura et al., 2001; Bruin & Wijers, 2002; Falkenstein, 2006; Vallesi et al., 2008). Only a few studies were related to regulation of pain sensation (Dowman, 2007a; Hatem et al., 2007; Legrain et al., 2002). For example, in Hatem et al.'s study (2007), the subject was asked to press a button while perceiving an electrical pain (electrical Go) and withholding the button press action while perceiving a laser pain (laser Nogo). In the Nogo trials, the most consistently found event-related potential (ERP) associated with inhibitory responses were the Nogo-N2 (150-400ms) and Nogo P300 (300-500ms). These two components elicited from the fronto-central regions of the scalp, including dorsalateral prefrontal region, were associated with response conflict (Dowman, 2007a; Hatem et al., 2007; Legrain et al., 2002). Another group of studies adopted a cue validity that could also elicit an inhibition process.

In Dowman's study (2007a & b), subjects were given valid and invalid visual cues for eliciting inhibitory responses when perceiving a nociceptive stimulus. In validly cued trials, a congruent visual cue "P" indicating "an upcoming pain" preceded a painful electrical stimulus, whereas, in the invalidly cued trials, the incongruent visual cue "V" indicating "an upcoming visual stimulus" preceded the painful electrical stimulus. The subjects were required to rate pain perception after each trial. A validity cueing design has also been shown to induce inhibitory processes. The processes are somewhat different from the Go/Nogo design. In the invalid cueing condition, the more positive P2 and P3 components were elicited. The former, which is centrally located, is related to spatial reorientation of attention

toward the evoked stimulus from another modality (such as visual cue). The latter could be distributed anteriorly and posteriorly. The anteriorly distributed P3 (labeled P3a) reflects attention to infrequent and deviant stimuli involving the working memory found in other studies when additional attention is drawn to a target stimulus (Dowman, 2007a; Friedman et al., 2001). A posterior distribution P3 (also labeled P3b) would reflect involvement of sensory evaluation, event categorization and processing capacity (Donchin & Coles, 1988; Friedman et al., 2001; Goldstein, Spencer & Donchin, 2002; Kok, 2001; Legrain et al., 2002). A conceptual model proposed that both P3a and P3b components were actually hand-in-hand subcomponents of a broader process (Polich, 2007). It has been suggested that P3a reflects the ongoing monitoring of distractor stimuli mediated by ACC in the platform of working memory, whilst the later coming P3a is referred as the process of transferring the signals to the temporal-parietal area where it was compared and evaluated.

These neurophysiological studies suggested the fronto-central P2 component is the key component to indicate the initiation of focused attention to the target somatosensory (or even nociceptive) stimulus. Regardless of the nature of the following action, e.g. performing cognitive-demanding task or withholding an overt action, the P2 elicitation might indicate response inhibition processes that in turn might mediate perception of nociceptive sensation.

Although dipole analysis might not provide the accurate sources of a certain component due to its relatively poor spatial resolution, other neuroimaging methods can offer insights into the locations of the sources of the P2 and P3 components. The information will provide a reliable reference for the dipole sourcing analysis to be conducted in this study. There is convergent evidence suggesting that P2 and anterior

P3 components are likely to originate from DLPFC and ACC (Falkenstein et al., 1999; Hatem et al., 2007; Vallesi et al., 2008). The parietal P3, on the other hand, was proposed to originate from temporal regions, including parahippocampus, when the attended stimulus was compared with long-term memory (Bokura et al., 2001; Bekker et al., 2005). In other words, ACC and DLPFC play an important role in pain modulation processes (Apkarian et al., 2009; Ohara et al., 2005; Wiech et al., 2008). The ACC or the medial aspect of PFC is consistently reported to be the neural substrate or the "pain control center" for pain perception and processing. The ACC was found to be the neural substrate to store the affective component, such as unpleasantness, of the nociceptive sensation since avoidance behavior was elicited by a similar environment in which the pain sensation occurred even though no painful sensation was given (Casey et al., 1994; Peyron et al., 1999; Tölle et al., 1999; Albanese et al., 2007). A study by Ohara et al. (2005) showed that placebo analgesia after induction of laser-induced nociceptive stimuli depended on the heightened activity of the rostral ACC. In fact, it has been suggested that the ACC was involved in the memory of affective aspect of pain. For DLPFC, on the contrary, it is considered to be the "pain control centre" as its activation was shown to lead to pain attenuation in a top-down fashion (Wiech et al., 2008). It is suggested that it down-regulates pain perception through its connectivity with the ACC, which in turns exerts pain inhibitory effect through PAG and the descending inhibitory system (Al Amin et al., 2004; Baliki et al., 2003; Lorenz et al., 2003; Ohara et al., 2005; Tracey, 2008; Wiech et al., 2005 & 2008). It appears that response inhibition is mediated by the control exerted from DLPFC, which appear to govern attentional orientation (Hatem et al., 2007; Dowman, 2007a, Ohara et al., 2006). Its role in focused attention requires further investigation. Results of these brain imaging studies provide useful

information for guiding the dipole sourcing analyses to be conducted on the ERP data obtained for this study.

Pain Modulation under Chronic Pain

Existing evidence on neural processes underlying high-level pain modulation mainly comes from pain-free subjects. How well these models and processes can apply to and explain the phenomena among those who have chronic pain requires further deliberation. Studies on pain modulation among people with chronic pain are limited. This limits the generalizability of the findings across different diagnostic populations and pain conditions. Besides, most of these studies addressed the behavioral aspect of nociceptive sensation and pain perception. Similar to studies involving healthy counterparts, research on pain perception modulation among chronic pain subjects mostly employed spatial distraction. In contrast to the findings in pain-free subjects (Eccleston, 1995; McCaul et al., 1982; Rode et al., 2001; Wack & Turk, 1984; Morone et al., 2007), the effectiveness of distraction strategy on modulating pain perception in people with chronic pain is more inconclusive (Nouwen et al., 2006; Johnson, & Petrie, 1997; Rode et al., 2001). For instance, inconsistent findings were reviewed between studies reported in Kóbor et al. (2009), Rode et al. (2001), and Wiech et al. (2005) and those reported in Johnson et al. (1997) and Snijder et al. (2010). Eccleston and Crombez (1999) concluded that the effect of distraction was not clear among people with chronic pain. They further explained that this could be due to the hypervigilance to pain which made it difficult for people with chronic pain to shift attention spatially away from the nociceptive site. Van Damme et al. (2010) speculated that it was the saliency of pain down-regulation which could

have hindered the process as the distraction task used was not goal-relevant in tackling pain perception. Following this line of thought, it could be beneficial for people with chronic pain to apply focused attention for initiating down-regulation process when perceiving nociceptive sensation (McCaul et al., 1982 & 1984; Nouwen et al., 2006). Under a focused attention approach, people with chronic pain, who tend to be "pain-vigilant", would not need to be "distracted" from nociceptive sensation. Rather, they only need to focus on the objective portion of the same nociceptive signals. Besides, it is stipulated that focused attention also exposes people with chronic people directly to painful perception, which in turns would reduce pain and its related affective manifestation (Moseley et al., 2008).

Findings from a number of behavioral studies revealed the effectiveness of focused attention in modulating pain perception (Moseley et al., 2008; Nouwen et al., 2008). For example, Nouwen et al. (2006) compared the effects of attention focusing and distraction on cold-induced pain in chronic LBP people. Under the focused attention condition, subjects were required to verbalize the sensation when the arm was submerged in cold water. The results indicated that the subjects with chronic pain reported a higher level of pain intensity during the initial phase of the exposure (first 16 seconds) (mean pain intensity = 60.8 out of 100) when compared to distraction strategy (mean pain intensity = 48.7). The pain intensity reported was found to decrease gradually towards the end of the exposure session which lasted for seven minutes (mean pain intensity = 57.0). It was further concluded that the focused attention strategy was more effective when the duration of the pain perceived by the subjects was longer, while the distraction strategy might be more effective if the pain exposure was shorter. In other words, focused attention can be effective on down-regulating painful perception which is persistent in nature. Some trend of pain

attenuation was shown across time, indicating it might have a longer lasting effect on pain perception. Nouwen et al. (2006) cautioned that the methods used in the study might not be effective for selected individuals with chronic LBP. They further explained this perhaps was due to the more intensified perception of the nociceptive sensation and the discomfort felt as a result of the perceptual process which could be less than tolerable among some subjects. From a clinical perspective, those who are used to being exposed to a painful sensation would more likely benefit from focused attention due to their higher tolerance to undergo the higher initial painful intensity. Another example is a study conducted by Moseley et al. (2008) requiring subjects with complex region pain syndrome (CRPS) to discriminate different diameters or locations of tactile stimuli applied on the dorsum of the hand (vs simply perceiving tactile stimulation) and aimed to examine the effect of this cognitive task on clinical chronic pain. In spite of the etiology difference from chronic LBP, the discrimination task was shown to attenuate pain perception (mean VAS = 24 mm (16-32 mm)) when compared to simple tactile stimulation (mean VAS = 54 ± 11 mm). The mean effect size (95% CI) was computed to be 27 mm (14-40 mm). The authors concluded that people with chronic pain experienced less painful perception via focused attention since they were asked to attend to the painful area in an objective way. Besides, the reduction of pain intensity via focused attention is achieved by exposing people with chronic pain to nociceptive sensation about which they felt apprehensive. This directed them to focus on the discriminative aspect of the pain in order to minimize the affective effects. The authors also attributed pain attenuation to cortical reorganization. Table 1.2 summarizes findings of some studies on the effect of focused attention on pain perception.

Table 1.2 Summary of selected studies on focused attention (FA)

Authors	Methods	Effects	Conceptualization
McCaul et al., 1982	39 male healthy subjects received 4-minute cold-pressor trial (7°C). They were asked to describe the sensation at hand in FA condition and viewing face pictures in distraction trials.	Attention to sensations appeared to be a better for the last 2 minutes while distraction would be more effective during the earlier period.	Parallel process of objective and distressing sensations was proposed.
Roelofs et al., 2004	272 healthy female university students participated in a cold pressor experiment. In FA trials, they were instructed to focus on sensation at hand and write down what was felt whereas in	FA led to reduced pain ratings in high fearful subjects whilst the distraction might be more beneficial for low fearful ones.	Sensory focusing method facilitates the subjects to sensory aspects of the pain experience rather than the emotional aspect. FA may also enhance perceived control over pain.

	distraction task, they participated in a tone-discrimination task while receiving cold pressor pain		
Nouwen et al., 2006	41 chronic back pain patients and 41 healthy control participants were instructed to complete 7-minute cold pressor test. Under FA, they were asked to continually describe the feeling of the forearm. Under distraction, they were asked to name as many as forenames beginning with a particular alphabet	FA strategy appeared to be effective when pain duration was longer (mean pain intensity = 60.8 out of 100), and distraction might be more effective for shorter periods of pain (mean pain intensity = 48.7).	FA enables pain control by generating a cognitive representation of pain based on intensity and produce habituation of emotional schemata.

Moseley et al., 2008	13 complex region pain syndrome patients received either tactile stimulation at hand dorsum (control task) or discriminate tactile stimuli applied on the hand dorsum based on the diameter or location.	Discrimination (mean VAS = 24 mm (16-32 mm)) between the type and location of stimuli could decrease pain more than simple tactile stimulation (mean VAS = 54 ± 11 mm).	Discrimination may distract attention away from emotional to more objective aspect, expose patients to sensation (especially nociceptive) which is fearful to them and have the effect through normalization cortical reorganization for tactile and nociceptive sensations

THEORIES RELATED TO MODULATION OF PERCEPTION OF NOCICEPTIVE SENSATION

Two attention theories that would help explain attention mediated pain modulation are reviewed in this section. They include Posner's Attentional Network (Posner et al., 1990; Posner, 1994), and the Functional Model of Interruption of Pain and Attention (Eccleston et al., 1999). The first one was related to three fundamental attentional functions of the brain network. The second one tapped attentional aspects of chronic pain.

The Attention System of Human Brain

The model of Attentional Network proposed (Posner et al., 1990, 1994 & 2006) that attentional function involves the whole brain area, both cortically and sub-cortically. With extensive research support, it has been shown that the attentional network governs three main functions: (1) vigilance, (2) orienting to sensory stimuli and (3) executive control for conflict resolution. The first function of vigilance is related to maintenance of high sensitivity to upcoming stimuli. This function is thought to be varied by warning signals prior to the appearance of a target. Modulated by norephinephrine, the neural substrates for visual stimuli are found to be locus coeruleus, parietal cortex and right frontal region (Posner et al., 2007). Furthermore, orienting function involves aligning attention to upcoming stimulus from the background. Several neural substrates are consistently found to be related to an orienting function, including frontal eye field, pulvinar and superior colliculus. Acetylcholine is shown to be the key neurotransmitter (Posner et al., 2007). This

process could be elicited by cuing, which indicates a location where a stimulus is about to appear. In case of a stimulus appearing in an uncued area, an individual needs to disengage attention from the cued location and re-position the attention to where a target stimulus appears. The third attentional function is executive control. This function is elicited when the subject needs to resolve stimulus conflicts, such as the Stroop Task (Stroop, 1935; Stuss et al., 2001), in which attention needs to be maintained on a stimulus with a certain attribute and ignoring another with a different attribute. Dopamine was regarded to be the key neurotransmitter, and the executive control was shown to be governed by prefrontal cortex and anterior cingulate cortex.

Although these attentional functions are more related to visual stimuli, these three principle functions are also applicable to other sensory modalities. In the context of pain modulation using focused attention, it would involve orientation to the objective component of a nociceptive stimulus and also requires a subject's executive control to resolve the affective component from the objective counterpart. Yet the temporal processes and the involved cortical area would be different from the attentional network for visual stimulus.

The Functional Model of Interruption of Pain and Attention

The Functional Model of Interruption of Pain and Attention (Eccleston et al., 1999) is also an attention-based model. Its distinctiveness is that the model introduces the relationship between attention and chronic pain. This model takes the ontogenetical and evolutionary significance of pain into account, in which pain alerts us to naturally interrupt attention for cognitive-demanding tasks in order to react in a perilous situation. In turn, a restoration effort has to be paid to complete the action

interrupted by pain. There are seven components in this model: 1) environment, 2) multiple demands arising from the environment, 3) sensory system, 4) action programs, 5) focal task, 6) threat mediation and 7) moderating factors. In the pain-free condition, the sensation which is relevant to a purposeful action enters the system from the environment. The attention would be allocated to the relevant sensation for a focal task while the interruption by threat as a moderator would be minimal. The action programs are then executed. Pain sensation would increase attention in response to the influence of the threat as the moderator and simultaneously weaken the attention for other focal tasks. In case of acute pain, the action programs would be related to escape and focal tasks might be halted until the acute pain subsides or is habitualized. In case of chronic pain, the attention for focal tasks might be persistently "consumed" on the noxious sensation. The performance of purposeful action programs might be compromised.

Since perception of nociceptive sensation and task demands are shown to draw upon the same limited attentional resources, they are regarded as interrupting attention resources. The interruptive function is dependent on pain-related parameters and environmental demands. Persistent perception of nociceptive sensation would consistently consume the attentional resources for high demanding tasks. This would result in so-called attentional deficits among people with chronic pain. Also Ecclestion (1999) has proposed a switching mechanism in which one needs to split or switch attention between demands of task and pain source. As the task becomes more demanding the switching process would become more difficult. This explains the longer reaction time in tasks which were cognitively more demanding and at the same time showed decreased P3 amplitude (Apkarian et al., 2004; Dick et al., 2003 & 2007; Houlihan et al., 2004; Lorenz et al., 1997c).

Crombez et al. (2005) further proposed the concept of hyperviligance in pain that enhanced the applicability of the Model of Interruption Function of Pain (Eccleston et al., 1999). It was suggested that there were two characteristics of hypervigilance. The first is that an individual under the influence of hypervigilance tends to appraise bodily sensation as dangerous in such a way that it is often related to escaping from the pain. This makes the individual catastrophize the nociceptive sensation and its negative impact upon their life and health. This would result in anxiety and fear. The second characteristic is that hypervigilance is "unintentional and efficient". In other words, it tends not to be under controlled processes. The individual tends to process the pain in a rather automatic manner even though the pain is irrelevant to a particular task. Thus, counteracting the effect of hypervigilance requires attentional cost if it is put in the context of the mode of the interruptive function of pain (Crombez et al., 2005).

The neuroimaging study findings provide a better understanding about the morphological and functional differences of people with chronic pain. The current view is that the cortex undergoes neuroplasticity or even neurodegeneration under the chronicification of pain (Apkarian et al., 2009; Wiech et al., 2008). Functionally, this cortical network or representation appears to perform high-demanding tasks less efficiently. The principle reason seems to do with attentional deficiency as persistent pain continually "consumes" the attentional resources which are needed for processing high-demanding tasks (Eccleston et al., 1999). This suggests that, in order to modulate or even attenuate cognitively, controlled and top-down cognitive strategies might have the potential to fulfill the down-regulation purpose. It is necessary, therefore, to understand how the brain down modulates acute or chronic pain in a top-down manner among healthy people and those with chronic pain.

STUDY RATIONALE & SIGNIFICANCE

People with chronic pain might find it difficult to apply a distraction strategy to modulate pain perception due to hypervigilance to pain Few behavioral studies have suggested the potential of focused attention in pain modulation among those with chronic pain (Moseley et al., 2008; Nouwen et al., 2006). Yet this strategy might have the advantage over distraction as it requires orienting attention on a nociceptive stimulus instead of distracting attention away. Studies on focused attention are mainly behavioral in nature, and the underlying processes of how a nociceptive stimulus is attended to, perceived and then modulated have not been explored. This study was conducted to gain a better understanding of the neural processes and effects of modulation of perception of nociceptive sensation among patients with chronic pain when compared to pain-free counterparts.

The results of this study will further enrich the theoretical basis of focused attention using somatosensory imagery modulating pain perception in people with and without chronic pain. The findings can shed light on the benefit of using somatosensory imagery as one of the cognitive strategies to tackle pain perception among people with chronic pain.

STUDY OBJECTIVES

The study consisted of pilot study and main study and the latter was further divided into two parts. Since pain perception was given to each subject using electrical stimuli, the pilot study aimed to examine the reliability of the level of electrical intensity emitted from the electrical stimulator (Model: S88K Dual Output

Square Pulse Stimulator (Grass Technologies, 2009)). The results provided information on the consistency the level of electrical intensities and how various levels of intensity were related to tactile and nociceptive perception.

The two parts of the main study consisted of experiments with an event-related Perception-Imagery design using electroencephalogram (EEG) recording. The first part of the main study aimed at:

(1) Comparing the neural processes of focusing attention to a nociceptive sensation and then orienting attention to generate sub-nociceptive image (imagery trials) and those of focusing attention to a nociceptive sensation followed by generating and maintaining the same nociceptive sensation (perception trials) after a short nociceptive stimulus was presented to the pain-free subjects;

(2) Comparing the pain ratings on the recalled nociceptive image of the external nociceptive sensation, which was given at the end of imagery and perception trials in the pain-free group; and

(3) Examining the inter-relationships among the electrophysiological data of identified ERP components (P2 and N400) and pain perception ratings in the pain-free group.

In the second part of the main study, the same experimental design was repeated on a group of patients with chronic pain. This part of the main study aimed at:

(1) Comparing the differences in neural processes during the imagery trials and the persepction trials for the subjects in both the chronic pain group and the pain free group;

(2) Comparing the pain ratings between the chronic pain group and pain-free group given at the end of imagery and perception trials on a recalled

nociceptive image of the external nociceptive sensation; and

(3) Examining the inter-relationships among the electrophysiological data of identified ERP components (P2 and N400) and pain perception ratings in the chronic pain group.

HYPOTHESES OF THE MAIN STUDY

Study One - Effect and Neural Process of Somatosensory Imagery on Pain Modulation

For pain-free group, it was hypothesized that the amplitude of the fronto-central P2 component, signifying reorienting attention from nociceptive stimulus to sub-nociceptive image, in imagery trials would be significantly increased compared to perception trials. It was also hypothesized that the amplitude of the frontal N400 component, signifying mental rehearsal of sub-nociceptive image, in imagery trials would be significantly increased compared to perception trials. The pain ratings were hypothesized to be lower in imagery trials, in which focused attention and generation of the sub-nociceptive imagery were conducted, when compared with perception trials across different levels of nociceptive intensity. The amplitudes of key ERP components P2 and N400 components were hypothesized to be correlated with pain modulation effect (pain $\text{rating}_{\text{Imagery}}$ − pain $\text{rating}_{\text{Perception}}$).

Study Two – Somatosensory Imagery Pain Modulation among People with Chronic Pain

For subjects with chronic pain, when compared to the healthy counterparts, the differences in the amplitudes of P2 and N400 components between imagery and perceptual trials were hypothesized to be diminished. In terms of pain rating, the differences in NRS between imagery and perceptual trials across different levels of nociceptive intensity were hypothesized to be diminished. In terms of associations, the correlations between the amplitudes of key ERP components P2 and N400 components and pain modulation effect (pain $\text{rating}_{\text{Imagery}}$ − pain $\text{rating}_{\text{Perception}}$) were hypothesized to be weakened.

CHAPTER THREE

PILOT STUDY: RELIABILITY OF PAIN SENSATION RATING

In both parts of the study subjects were presented with electrical stimulations and were then required to rate the sensation felt. The purpose of the pilot study was to gather evidence on the test-retest reliability of the numerical rating scale for measuring the subjects' rating of the nociceptive and sub-nociceptive stimuli. The stimuli were the different levels of electrical intensity produced by an electrical stimulator, whilst the ratings represented the pain intensity perceived by the subjects. The chapter begins with a description of methods. The findings of the reliability of the pain sensation ratings are then reported and discussed.

METHODS

Subjects

Eighteen healthy individuals between 21 and 55 years of age were recruited via convenience sampling. They were free of neurological or psychotic conditions that could affect their somatosensory functions. Ethics approval was obtained from the Ethics Committee of the Department of Rehabilitation Sciences, The Hong Kong Polytechnic University (Appendix I). The purpose of the study was explained to each recruited subject and he/she was informed that all personal information and data obtained from the study were to be kept strictly confidential.

Stimuli

Electrical Stimulus

The electrical stimulations were generated by the *S88K Dual Output Square Pulse Stimulator* (Grass Technologies, Grass-telefactor, West Warwick, RI). The apparatus is a dual-channel, general purpose stimulator for nerve and muscle stimulation. The stimulator emits electrical impulses in varied intensity and patterns which can elicit responses from a single nerve cell to an entire muscle. The two output channels can be operated in an independent or synchronized manner to meet requirements in complex paradigms. The equipment consists of four-parameter control of two different outputs. In addition to single, repetitive, twin pulses, pairs of unlike pulse, train of pulses and mid- and post-train pulses, continuous or trains of pulses are available at one output with continuous and discontinuous operation at the other output. The Constant Current Unit (CCU) connected in series with the pulse stimulator controls a constant current emission. The meter panel gives a reading in milliamperes (mA) (Dowman, 2007a) (Figure 3.1).

Sensory Threshold Determination

The procedure of determining sub-painful and painful thresholds was referenced to the methods described by De Pascalis et al. (2001 & 2008). One electrical output of the S*88K Dual Output Square Pulse Stimulator* (Grass Technologies, 2009) was used in the procedure. The positive and negative Ag/AgCl electrodes (8 mm in diameter) were filled with electro-conductive hypocollagen gel to minimize the skin impedance. The positive electrode was securely positioned at the volar side of the index finger tip of the dominant hand (the C6 dermatome) of the

subject. Current specification was referred to specifications reported by Katayama et al.'s study (1985), in which 25-pulse train of stimuli (0.5-millisecond pulse duration and 500 Hz frequency) was used. A 25-pulse train pulse with train duration of 50 ms was set (pulse duration: 0.5 ms; rate = 500 pulses per second (pps) (500 Hz)). The outputs emitted from the stimulator are non-isolated constant voltage positive pulses. The operation of the equipment has been referred to in the Spare S88 Manual (Grass Technologies, 2009).

Figure 3.1 The S88K Dual Output Square Pulse Stimulator (Grass Technologies, West Warwick, RI) (left) and the Constant Current Unit (CCU) (right) (Adapted from http://www.grasstechnologies.com/products/stimulators/stimulators.html, 2010)

The sub-painful threshold was first obtained by ascending and descending procedures. The sub-painful threshold is defined as the minimum level of electrical intensity that could be felt by an individual. Each subject was given a series of single pulse train with 50 ms-duration. The intensity of the electrical stimulus started from 0.0 mA and increased with increments of 1.0 mA until the subject detected a minimal detectible sensation which was reported to the investigator (called first minimal

detectible sensation). The procedure was then repeated in a descending manner. It started from 1.0 mA above the electrical intensity corresponding to the first minimal detectible sensation and decreasing with steps of 1.0 mA. The two thresholds obtained from the ascending and descending procedures were then averaged to determine the subject's average sub-painful threshold. Subsequently, the intensity of the electrical stimulus for producing sub-nociceptive sensation was increased with steps of 1.0 mA. Each time a sub-nociceptive stimulus was presented to the subject, s/he was required to perceive the sub-nociceptive sensation and rate its intensity based on the 11-point numerical rating scale (NRS) (Williamson et al., 2005) (Appendix II). The maximum sub-nociceptive level was 1mA below the painful threshold, which was determined in the next step.

The next step was to determine the painful threshold of the subject. The painful threshold is defined as the minimum level of electrical intensity when the subject started to perceive a pinprick sensation. The minimal painful threshold was determined by increasing the intensity of the electrical stimulation which generated sub-nociceptive sensation to a point where the subject reported starting to feel a minimal pin-prick sensation. The intensity of the stimulation was recorded and the NRS rating on this nociceptive sensation was set as "1" for the subject (Jensen, 1986; Williamson et al., 2005) (Appendix III). Similar to the procedure used for establishing the sub-painful threshold, the painful threshold was determined in a descending manner. Starting from the 1.0 mA above the electrical intensity corresponding to the minimum painful threshold, the electrical intensity was decreased with steps of 1.0 mA until the subject did not feel any nociceptive sensation but sub-nociceptive sensation by detecting the disappearance of pinprick sensation. The ascending and descending painful thresholds were then averaged to obtain the average painful

threshold. The electrical intensity was then increased with steps of 1.0 mA, and the subject was required to perceive the nociceptive stimulus and assign an intensity rating which represented the pain perceived. The procedure continued until the subject gave a pain NRS of "7", which is labeled as "very painful". With the subject's agreement, the electrical intensity was further increased until the subject gave a pain NRS of "9", labeled as "intolerable pain". In the test-retest reliability experiment, the maximal stimulus intensity to be given to the subject was 2mA below this intolerability level. In case subjects felt apprehensive about experiencing stimulus intensity beyond the very painful pin-prick level, i.e. equivalent to pain NRS of "7", the maximal electrical intensity given to the subject was set at "very painful" level (i.e. pain NRS = 7)

The electrical intensity between the average sub-painful threshold (equivalent to sub-pain NRS of "1") and the average painful threshold (equivalent to pain NRS of "1") formed the sub-painful range. The electrical intensity between the average painful threshold and the "very painful" intensity (i.e. pain NRS "7") formed the painful range. Table 3.1 provides the definition of five sub-painful and painful levels determined by the calibration procedure.

The testing of repeatability of the sub-pain and pain NRS involved presentations of self-calibrated sub-nociceptive (N=5) and nociceptive (N=5) stimuli and subjects' NRS ratings on the sensations elicited by each of these stimuli. The five sub-nociceptive stimuli were the two electrical intensities of the average sub-pain threshold and average pain threshold, and three evenly distributed intensities between these two thresholds. The five nociceptive stimuli were the electrical intensities of the average pain threshold and the "very painful" intensity, and the three evenly distributed intensities between these two extremes.

Table 3.1 Definition of ten levels of electrical stimulations in relation to sub-painful and painful sensations

Range	Level	Definition of Level of Stimulus
Sub-painful Range	1	Sub-painful threshold / Minimal detectible sensation: averaged minimum level of electrical intensity that could be felt after ascending and descending procedures (with increment of 1.0 mA)
	2 3 4	Three evenly distributed electrical intensities between sub-painful and maximum sub-painful thresholds
	5	Maximum sub-painful level was set at 1.0 mA below the painful threshold
Painful Range	1	Pain threshold: averaged minimum level of electrical intensity that the subject started to perceive a pinprick sensation through ascending and descending procedures, equivalent to NRS = 1
	2 3 4	Three evenly distributed electrical intensities between pain threshold (NRS = 1) and "very painful" level (NRS = 7)
	5	"Very painful" level: level of electrical intensity that was repeatedly rated as "7" on NRS by the subject

Instrument

Eleven-point Numeric Rating Scale (NRS)

Subjects were trained to rate the intensity of the perceived sub-nociceptive and nociceptive sensations based on an eleven-point Numeric Rating Scale (NRS) (Jensen, 1986; Williamson et al., 2005) (Appendix II & III). The NRS has been commonly used in a number of pain-related studies for representing subjects' perception of painful sensation (De Pascalis et al., 2005 & 2008; Jensen, 1986; Williamson et al., 2005). It is an ordinal measure with "0" as the left anchor denoting "no pain sensation" to "10" as the right anchor denoting "the most intense pain sensation imaginable". The NRS for pain has been shown to have high repeatability and be sensitive to changes (Ferraz et al., 1990; Joos et al., 1991). In this study, the lowest anchor of the scale refers to "no sensation perceived" while the highest anchor refers to "the highest tactile intensity perceived".

Procedure of Test of Repeatability of NRS

The test of repeatability was conducted separately on the sub-painful and painful NRS. For each NRS, the subject was calibrated for the sub-painful and painful thresholds. These enabled the investigator to obtain 10 levels of electrical intensities, five for each of the sub-nociceptive and nociceptive sensation (see above for details), for the testing. The subject was randomly presented with one of the five electrical stimulations and then asked to assign a rating on the sub-pain or pain NRS to reflecting the amount of the sub-nociceptive sensation felt. The positive electrode was securely taped at the subject's volar side of the index finger tip of the dominant hand

under the cutaneous median nerve supply (the C6 dermatome). The electrode was placed at the targeted site as gently as possible in order to avoid unnecessary mechanical pressure. The five intensities of electrical stimulations elicited sub-nociceptive sensation were used. The subject was presented with the five stimulations arranged in ascending and then descending orders for familiarization. The order was made known to the subject and whilst perceiving the stimulation the subject was to assign a sub-pain NRS rating. The testing began with the subject being pseudo-randomly presented with one of the sub-nociceptive stimulations for a total of 50 trials (5 intensities × 10 times) (Appendix IV). The same procedure was repeated for the five intensities of electrical stimulations producing nociceptive sensations. The subject was asked to assign a rating on the perceived sensations using the pain NRS. Similarly, there were 50 trials which were pseudo-randomly presented to the subject.

The next part of the testing of reliability focused on the consistency of subjects classifying the intensities of the sub-nociceptive or nociceptive sensation produced by the different levels of electrical stimulation. There were Levels 1 to 5 for the five sub-nociceptive stimuli and Levels 1 to 5 for the nociceptive stimuli. The weakest stimulus was classified as "1" whilst the strongest stimulus was classified as "5". Different from the previous repeatability test, the subject was asked to memorize the intensity of the stimulus together with the pre-defined level label. The subject was to perceive the intensity of the sub-nociceptive or nociceptive stimulus and then name the level label which best described the intensity. The responses of the subject were recorded. There were 25 sub-nociceptive and 25 nociceptive trials. The subject completed the sub-nociceptive block in which the trials were pseudo-randomized. The same process was repeated for the nociceptive block.

Statistical Analysis

Descriptive statistics for the voltage intensity of the electrical stimulations of the pain and sub-pain thresholds, and the "very painful" level were computed. The pain and sub-pain NRS ratings of the subjects were also calculated. Pearson product-moment correlation coefficient (r) was used to examine the relationships between voltage intensity and NRS ratings for the sub-nociceptive and nociceptive stimuli. Intraclass coefficient (ICC) was used for expressing the extent of repeatability of the NRS rating whilst Kappa statistics was used for expressing the consistency of labeling the perception of the intensity of the stimuli. In addition, qualitative information about mental processes that occurred during the experiment was obtained from each subject in order to refine the overall procedures of the main study. All statistical analyses were conducted using SPSS™ version 16.0 (SPSS Inc., Chicago, IL).

RESULTS

Subjects

Eighteen subjects were recruited to the pilot study via convenience sampling. Eleven (61.11%) were male, and 17 of them were right-handed. The mean age was 39.91 years (standard deviation (SD) = 15.96 years). The mean current intensity elicited the minimal detectable stimulus, minimal nociceptive sensation and very nociceptive sensation were found to be 1.63mA (SD=0.52mA; minimum=0.60mA; maximum=3.00mA), 3.26mA (SD=2.44mA; minimum=1.32mA; maximum=9.60mA) and 9.29mA (SD=5.78mA; minimum=2.60mA; maximum=14.40mA), respectively.

Strong to moderate correlations were revealed between age and all these critical thresholds (ranged from 0.576 to 0.775 ($p<0.050$)).

Test-retest Reliability of NRS

The mean score for the 11-point NRS ranged from 1.96 (SD=1.51) for Level 1 (the weakest) stimulus to 4.84 (SD=2.10) out of 10 for the Level 5 (the strongest) stimulus to 4.84 (SD=2.10) out of 10. The Pearson product-moment correlation coefficients (r) for electrical stimulus intensity and NRS on sub-nociceptive sensation were calculated separately for each subject. The correlation coefficients ranged from 0.29 ($p<0.05$) to 0.87 ($p<0.01$). For the rating consistency of sub-nociceptive stimuli, the ICC (random effect and consistency) was revealed to range from 0.85 (95%CI = 0.75-0.96) for Level 3 to 0.93 (95%CI = 0.85-0.98) for Level 1. The figures reflected a high level of rating consistency. Furthermore, the kappa statistics of exact matching agreement (which is defined as the percentage of correct identification of sub-nociceptive sensation given based on the original sensory stimulus) of sub-nociceptive sensation was found to range from 0.21 for Level 5 intensity to 0.67 for Level 1 intensity. A calculation was also made of approximated agreement. Approximated agreement is defined as the percentage identifying the original stimulus intensity as at least the neighboring intensity. For instance, a rating was considered to be in agreement when a Level 3 sub-nociceptive stimulus was identified to be Level 2 (one level down) and Level 4 (one level up). As expected, a higher level of agreement was revealed, with kappa values ranging between 0.58 and 0.92 as the method of analysis became less stringent. In both methods of agreement computation, the lowest agreement was found to be at the Level 5 intensity and the highest one was revealed

to be at the Level 1 intensity. When ICC statistics was used to analyze the data, the lowest and highest ICCs were revealed for identifying Level 5 sub-nociceptive intensity (ICC = 0.32; 95%CI = -0.50-0.78) and for identifying Level 1 sub-nociceptive intensity (ICC = 0.72; 95%CI = 0.34-0.91), respectively (Table 3.2). In general, the ICCs appeared to be higher for the method of NRS rating of sub-nociceptive stimuli.

The same analyses revealed different patterns for the consistency of the NRS rating of the pain felt from perceiving the nociceptive stimuli. The mean 11-point NRS scores of the nociceptive stimulus ranged from 3.20 (SD=1.85) for Level 1 (the weakest) stimulus to 4.84 (SD=2.10) for the Level 5 (the strongest) stimulus to 7.45 (SD=1.78). The Pearson product-moment correlation coefficients (r) for electrical stimulus intensity and NRS rating on nociceptive sensation were also calculated separately for each subject. Correlation coefficients ranging from 0.52 ($p<0.01$) to 0.92 ($p<0.01$) were obtained. The ICCs (random effect and consistency) were found to be even higher across five intensities selected for the experiment, ranging from 0.90 (95%=0.77-0.97) for the Level 3 electrical intensity to 0.92 (95%CI=0.83-0.98) for the Level 2. Similar to NRS rating of sub-nociceptive stimuli, the range of ICCs also fell within the high consistency level. As for the exact identification agreement of pain sensation, the exact agreement ranged from 0.34 for Level 5 intensity to the 0.56 for Level 1 intensity. The approximated agreement reflected by kappa statistics, on the other hand, ranged from 0.72 for Intensity 5 to 0.90 for Level 3 intensity. The ICCs of identifying 5 levels of electrical intensity ranged from 0.66 (95%CI=0.26-0.89) (for Level 3 intensity) to 0.84 (95%CI=0.63-0.95) (for Level 1 intensity). Similarly, the ICCs appeared to be higher in case of NRS rating of nociceptive stimuli (Table 3.2).

Table 3.2 Test-retest reliability of sub-nociceptive and nociceptive sensation rating

	Sensation Rating (11-point NRS)				Sensation Matching					
	Mean scores (SD)	ICC	95% CI	SE	Mean scores (SD)	ICC	95% CI	SE	Kappa	Approximated Agreement (%)
Sub-nociceptive Stimulus										
1	1.96 (1.51)	0.93	(0.85-0.98)	0.30	1.42 (0.67)	0.72	(0.40-0.91)	0.36	0.67	91.82
2	2.69 (1.69)	0.91	(0.79-0.97)	0.37	1.87 (0.79)	0.52	(-0.06-0.85)	0.53	0.50	87.50
3	3.24 (1.83)	0.85	(0.67-0.95)	0.54	2.48 (0.93)	0.35	(-0.43-0.80)	0.75	0.29	78.33
4	4.21 (1.92)	0.92	(0.83-0.98)	0.39	3.13 (0.91)	0.54	(0.00-0.80)	0.62	0.29	75.45
5	4.84 (2.10)	0.89	(0.75-0.96)	0.41	3.71 (0.91)	0.32	(-0.50-0.78)	0.73	0.21	58.18
Nociceptive Stimulus										
1	3.20 (1.85)	0.91	(0.80-0.97)	0.57	1.54 (0.74)	0.84	(0.63-0.95)	0.41	0.56	85.45
2	4.64 (2.01)	0.92	(0.83-0.98)	0.56	2.24 (0.85)	0.81	(0.58-0.94)	0.52	0.39	82.73
3	5.74 (1.80)	0.907	(0.77-0.97)	0.58	2.92 (0.93)	0.66	(0.26-0.89)	0.72	0.45	90.00
4	7.28 (1.73)	0.91	(0.80-0.97)	0.51	3.71 (1.01)	0.86	(0.69-0.96)	0.56	0.46	84.55
5	7.45 (1.78)	0.91	(0.91-0.99)	0.54	4.15 (0.89)	0.79	(0.53-0.93)	0.71	0.34	72.73

SD: standard deviation; NRS: numeric rating scale, 95%CI: 95% confidence interval; SEM: standard error of mean

DISCUSSION

The aims of the reliability study were three-fold. First, the results obtained will shed light on the relationship between the nociceptive stimuli generated by the electrical stimulator and the perception experienced by the subjects. Second, it establishes the evidence on test-retest reliability of the 11-point NRS for both sub-pain and pain perception induced by nociceptive and sub-nociceptive stimuli emitted from the electrical stimulator. Third, the reliability of recognizing different levels of sub-painful and painful perception will inform the somatosensory imagery processes occurring among the subjects. The results can help to refine the design of the experimental paradigm and the procedures of selecting appropriate levels of sensory stimuli from the stimulator in the main study.

The relationship between different levels of electrical intensity and the sub-nociceptive and nociceptive perception is first discussed. Despite the fact that there is a wide variability in terms of the level of electrical intensities corresponding to the three critical sensory thresholds, i.e. the minimal detectable stimulus, minimal painful sensation and very painful sensation, the objectivity of these thresholds could be observed across different groups in other studies. In this study, the values of the minimal detectable stimulus and minimal painful sensation thresholds obtained were 1.63 mA (SD=0.52 mA; min.=0.60 mA; max.=3.00 mA) and 3.26 mA (SD=2.44 mA; min.=1.32 mA; max.=9.60 mA). The standard deviations of each of these mean values were large. These reflect the subjective nature of perceiving sub-nociceptive and nociceptive sensation. In other words, the same intensity of electrical stimulus generated from the pain simulator can be perceived differently across individual subjects. This concurs with the findings of studies by De Pascalis et al. (1999, 2001 &

2008). In De Pascalis and other colleagues (2001), the minimal detectable stimulus and minimal painful sensation thresholds were obtained to be 1.20 mA (SD=0.093mA) and 4.22 mA (SD=0.61mA), respectively. Although the means of the thresholds are comparable, the variances obtained from the pilot study appeared to be wider than those reported by De Pascalis et al. (2001). This could be due to the lower sensitivity at the posterior malleolus region (dermatome L5-S1) in this study whereas the more sensitive site was at the ventral part of the right wrist (dermatome C7) in De Pascalis et al.'s study. This suggests that a less precise pain rating was expected during the experiment in the main studies.

As suggested in Melzeck's neuromatrix theory (2001), an individuals's pain neurosignature, i.e. pain perception and tolerance, varies across individuals as it is influenced by one's personal past experience with pain. One possible reason for relatively large variation of the minimal pain threshold (i.e. mean=1.63 mA; SD=0.52 mA) could be due to the fact that the tingling or pinprick sensation elicited by the pain stimulator might not be familiar to the subjects as mechanical pain and which they were less likely to have experiences prior to the study. The unfamiliarity might contribute to subjects' finding it difficult to determine the level of electrical intensity that corresponded to the the minimal pain threshold. The comparison of the variances, that are reflected by the standard error of mean (SE) between the minimal detectable (tactile) sensation and the minimal painful sensation further substantiates this point. With the subject number of 18, the standard error of mean (SE) = SD / $n^{½}$) for the two critical sensory thresholds were 0.12 and 0.58, respectively. The relatively small variance for the threshold of the minimal detectable (tactile) sensation suggests that it might be consistent for the subjects to detect the level that demarcated the presence and absence of sensation. In contrast, determining the difference between sub-painful

sensation and painful sensation would be more arbitrary. Subjects would need to pay attention to the different characteristics of sub-painful and painful sensation as the electrical intensity increased. This could be an explanation for the less precise level of minimal painful sensation. Perhaps additional training is needed in order to decrease the variability.

Furthermore, the wider variation for moderate painful level, i.e. 7.2 mA (SD=2.8 mA) is noteworthy. The experiment procedure allowed subjects to determine the maximal electrical intensity they would experience during the test-retest reliability experience. This could lead to wide variability in the "very painful" threshold. This is because it would very much depend on a subject's pain tolerability, previous painful experiences (such as physical injuries), and fear toward electrical stimulation. Although it would lead to some inconsistency on so-called very painful sensation to be applied among subjects, this procedure would allow subjects to determine their own level of maximally tolerable electrical threshold. This not only allowed the subject to determine the higher anchor point for the sensation corresponding to NRS of 7, but also attenuated the anxiety due to unpleasant sensation since they knew that they were only given intensity lower than the maximal threshold. As a whole, this procedure could ensure their compliance during the experiment that involved pain modulation.

The 11-point NRS for measuring the pain perception has been reported to have less than satisfactory reproducibility (Jensen et al., 1986; Williamson et al., 2005). The results of this study suggest that the pain NRS used for subjects' report of pain perception of the nociceptive stimulations has a rather satisfactory reproducibility. This is based on the Pearson's correlation coefficients between the electrical voltage intensity used for generating the nociceptive stimulation and the pain NRS rated on

the stimuli were moderate (0.52 ($p<0.01$)) to high (0.92 ($p<0.01$)). The intraclass correlation coefficient (ICC), a measure of reliability, for all five levels of electrical intensity fell within high correlation range ($0.66 < r < 0.86$). When an electrical stimulus was generated and a nociceptive sensation was felt by a subject, the subject might have referred to prior experience and assigned a number on the 11-point NRS which best described the perception of the stimulus. It is plausible that the relatively satisfactory reliability revealed in the pilot study resulted from the subjects' being given adequate time to enable them be exposed repeatably to the whole range of nociceptive stimuli and hence to "learn" the associated pain experience. In this study, each subject was at least given 50 trials for them to get familiarized with different levels of intensity for 30 minutes. Fewer than 5 subjects required extra trials to reach the required level of accuracy. The processes of training required 30 to 45 minutes.

Nevertheless, there is one drawback as reflected from the results. The satisfactory reliability was found in the pain NRS on the nociceptive but not on the sub-nociceptive stimuli. The ICCs obtained for the nociceptive stimuli were between 0.85 and 0.93 when compared with those for the sub-nociceptive stimuli which were between 0.29 and 0.87. There are a number of reasons to explain this phenomenon. First, the range of the electrical intensity used for generating the sub-sub-nociceptive stimuli was much narrower than that of the nociceptive stimuli. The narrower range would make the judgment on the perception of the stimuli less easy and hence would undermine the repeatability of the pain NRS on the sub-nociceptive stimuli. Second, unlike the painful sensation, the highest sub-painful sensation could be more arbitrary compared to the painful sensation. It might be more difficult for the subjects to relate the highest sub-painful intensity to the highest anchor of the 11-point NRS. The relatively lower repeatability and skewed mean scores for the pain NRS on the

nociceptive stimuli suggest longer training time in the main study so that subjects can get familiarized more with the different levels of sub-nociceptive stimulations.

CHAPTER FOUR

METHODS OF STUDY ONE AND TWO: FOCUSED ATTENTION PROCESSES IN CHRONIC PAIN PATIENTS AND PAIN-FREE SUBJECTS

This chapter covers the methods of Study One and Study Two. It first describes the experimental design, measures, procedure and statistical analysis used in Study One. The aim of this study was to investigate the neural processes of focused attention through generating pre-learned sub-nociceptive images for modulating perception of acute nociceptive sensations in a group of pain-free subjects. This is followed by the description of methods used in Study Two for comparing the neural processes of focused attention in subjects with chronic low back pain and those of pain-free counterparts. The procedures and measures used in this part of the main study were similar to those used in the first part of the study. With a focus on pain experience, subjects with chronic low back pain were also assessed on their chronic pain condition and pain-related coping skills.

METHODS OF STUDY ONE: FOCUSED ATTENTION PROCESSES IN PAIN-FREE SUBJECTS

Subjects

Twenty-five healthy subjects without any chronic pain conditions who had not participated in the pilot study were recruited through convenience sampling on a voluntary basis. They were invited to attend the experimental session at the Applied

Cognitive Neuroscience Laboratory, Department of Rehabilitation Sciences, The Hong Kong Polytechnic University. Due to poor quality EEG data, seven subjects were excluded resulting in 18 valid cases for data analysis. All of them were right-handed. After the procedures and potentials risks arising from the study were explained by the principle investigator (Appendices V & VI), informed consent was obtained from each subject (Appendices VII & VIII). The procedure was approved by the Departmental Research Committee, Department of Rehabilitation Sciences, The Hong Kong Polytechnic University (Appendix I).

Stimulus

Electrical Stimulating Device

The same *S88K Dual Output Square Pulse Stimulator* (Grass Technologies, Grass-telefactor, West Warwick, RI) as in the pilot study was used to generate the electrical stimulations. The apparatus is a dual-channel, general purpose stimulator for nerve and muscle stimulation. The equipment consists of four-parameter control of two different outputs. In addition to single, repetitive, twin pulses, pairs of unlike pulse, train of pulses and mid- and post-train pulses, continuous or trains of pulses are available at one output with continuous and discontinuous operation at the other output. The meter panel gives a reading in milliamperes (mA).

Sensory Threshold Calibration

The procedure for calibration of the sub-pain and painful thresholds was described in the pilot study (Chapter 3). The only difference in the main study was that the location of the electrode was placed at the posterior aspect of the right lateral

malleolus. After a subject was comfortably seated in a sound-proof chamber, the positive and negative Ag/AgCl electrodes (8mm in diameter) were filled with electro-conductive hypocollagen gel. The positive electrodes were secured at the right lateral malleolus which was supplied by the sural nerve (L5-S1 dermatome). The stimulation site was selected because the subjects in the second main study (experimental group) all had low back pain condition. As the low back region is supplied by the spinal nerves at L4, L5 and S1 levels, it was assumed that the sural nerve (L5-S1 dermatome) would share similar regions at the cortical levels, and this would make pain modulation effect under investigation more relevant. Besides, the evoked potentials of the sural nerve have been well studied (Dowman, 1996, 2007a & b). Voltage and stimulation parameters were based on specifications reported by Katayama et al.'s study (1985), in which 25-pulse train of stimuli (0.5-millisecond pulse duration and 500 Hz frequency) was used. A 25-pulse train pulse with train duration of 50 ms was set (pulse duration: 0.5 ms; rate = 500 pulses per second (pps) (500 Hz)). The outputs emitted from the stimulator were non-isolated constant voltage positive pulses. The operation of the equipment was based on the Spare S88 manual (Grass Technologies, 2009). The calibration procedure for the sub-painful and painful thresholds and the maximal level of stimulation are similar to those described in the pilot study (Chapter 3). The calibration resulted in setting the intensities of electrical stimulation for the sub-pain threshold, pain threshold, and the "very painful" level. The voltage intensities of electrical stimulations were set for the three in-between levels between the sub-painful and maximum sub-painful threshold, which composed the five levels of sub-nociceptive stimuli. The voltage intensities of electrical stimulations were also set for the three in-between levels between the painful threshold and the "very-painful" level, which was composed of the five levels of nociceptive stimulus. Table

4.1 summarizes the definition of five sub-painful and painful levels determined by the calibration procedure. Each subject received training prior to the experiment to become familiarized with the sub-nociceptive and nociceptive sensations.

Table 4.1 Definition of ten levels of electrical stimulations in relation to sub-painful and painful sensations

Range	Level	Definition of Level of Stimulus
Sub-painful Range	1	Sub-painful threshold / Minimal detectible sensation: averaged minimum level of electrical intensity that could be felt after ascending and descending procedures (with increment of 1.0 mA)
	2	Three evenly distributed electrical intensities between sub-painful and maximum sub-painful thresholds
	3	
	4	
	5	Maximum sub-painful level was set at 1.0 mA below the painful threshold
Painful Range	1	Pain threshold: averaged minimum level of electrical intensity that the subject started to perceive a pinprick sensation through ascending and descending procedures, equivalent to NRS = 1
	2	Three evenly distributed electrical intensities between pain threshold (NRS = 1) and "very painful" level (NRS = 7)
	3	
	4	
	5	"Very painful" level: level of electrical intensity that was repeatedly rated as "7" on NRS by the subject

Experimental Design

The paradigm design was inspired by the Go/Nogo dual feature design described by Alexander et al. (2007) and the Stroop Test (Stuss et al., 2001). Analogous to using visual attributes: an alphabet (X or O) and its color (blue or red), the current study used electrical stimulations elicited sensation coupled with auditory cue. There were two types of trials: perceptual versus imagery. A perception trial required the subject to perceive calibrated nociceptive sensations delivered by the electrical stimulator. An imagery trial involved the subject after perceiving the nociceptive sensation generating and mentally rehearsing a pre-learnt sub-nociceptive image.

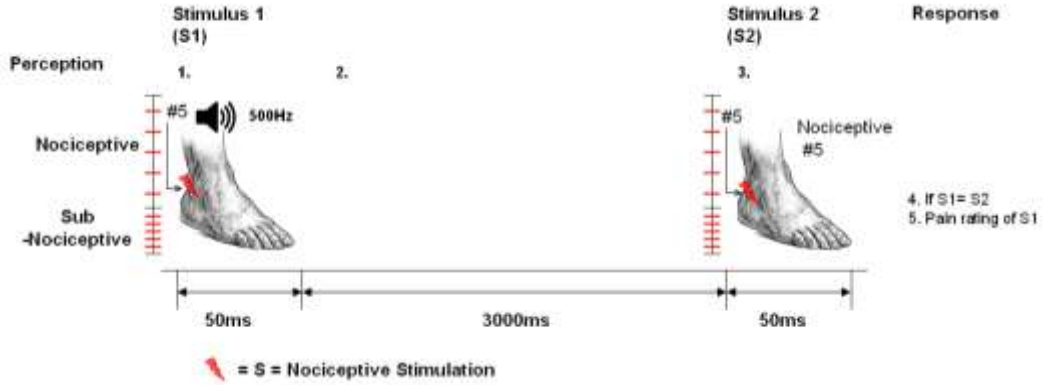
Figure 4.1 shows the diagrammatic presentation of the paradigm. Each subject was asked to perform two types of mental task. In a perception trial, the subject was given one calibrated nociceptive stimulus (one out of five) of 50 ms in duration coupled with a low-pitch sound (50 ms, 500 Hz, 80 db) (called S1). The subject was to perceive and maintain the nociceptive image (Pe1) for 3000 ms. A second calibrated nociceptive stimulus (one out of the five) of 50 ms in duration was then presented (called S2). The subject was to perceive S2 and decide whether its magnitude and that of the maintained nociceptive image (Pe1) were the same. At the end of a trial, the subject was required to recall the nociceptive image from the first stimulus (S1) and give a verbal pain perception rating on the recalled image sensation using 11-point NRS rating (Jensen, 1986; Williamson et al., 2005) (Figure 4.1 A).

In an imagery trial, the schedule was the same as that of the perceptual trial except that the first nociceptive stimulus (called S1) was coupled with a high-pitch tone (1500 Hz, 80 db). In the 3000 ms perception and maintenance period, the subject was instructed to generate an intrinsic sub-nociceptive image which was learnt in the

training session prior to the experiment (Im1) (e.g. generating Level 1 sub-nociceptive image once when a Level 1 nociceptive stimulus was perceived, and the same for Levels 2-5). By the end of the 3000 ms mental rehearsal, the subject was presented with a sub-nociceptive stimulus which also lasted for 50 ms (called S'2). After perceiving S'2, the subject was to decide whether its magnitude was the same as that of the self-generated sub-nociceptive image (Im1). As in the perception trial, the subject was required to recall the nociceptive image according to the first stimulus (S1) and assign a verbal 11-point NRS rating which described the pain perception (Figure 4.1 B). One block had 20 trials of which 10 were perception trials and 10 were imagery trials. All the trials were arranged in a pseudo-randomized order. There were 8 blocks giving a total of 160 trials (80 perception and 80 imagery trials) in the entire experiment. With an attrition rate of 10%, it gave 72 trials for further analysis. This would be sufficient for averaging cognition-related potentials. EEG signals were captured at the time when the subject performed in the tasks.

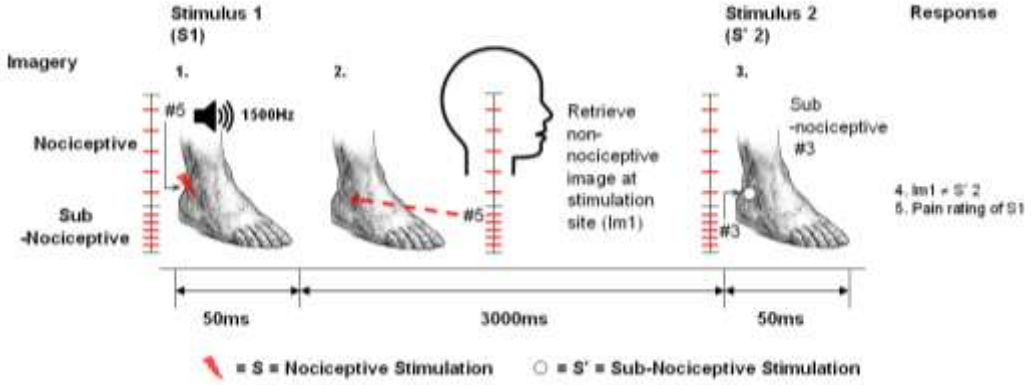
Figure 4.1 Diagrammatic representations of Perception (A) and Imagery (B) trials in Perception / Imagery Paradigm in the main study

(A)



1. The subject was given one calibrated nociceptive stimulus (one out of five) of 50 ms in duration coupled with a low-pitch sound (50 ms, 500 Hz, 80 db) (called S1).
2. The subject was to perceive and maintain the nociceptive image (Pe1) for 3000 ms.
3. A second calibrated nociceptive stimulus (one out of the five) of 50 ms in duration was then presented (called S2). The subject was to perceive S2 and decide whether its magnitude and that of the maintained nociceptive image (Pe1) were the same. This was followed by assigning a verbal NRS rating which best described the intensity of the pain had felt when recalling the nociceptive image from S1.

(B)



1. The subject was given one calibrated nociceptive stimulus (one out of five) of 50 ms in duration coupled with a high-pitch tone (1500 Hz, 80 db) (called S1).
2. In the 3000 ms perception and maintenance period, the subject was instructed to generate an intrinsic sub-nociceptive image (Im1) which was learnt in the training session prior to the experiment (e.g. generating Level 5 sub-nociceptive image once when a Level 5 nociceptive stimulus was perceive).
3. The subject was presented with a sub-nociceptive stimulus of 50 ms in duration (called S'2). After perceiving S'2, the subject was to decide whether its magnitude was the same as that of the self-generated sub-nociceptive image (Im1). This was followed by assigning a verbal NRS rating which best described the intensity of the pain had felt when recalling the nociceptive image from S1.

Subject Position and Equipment Setup

Subject Position

The experiment took place in an isolated chamber in the Applied Cognitive Neuroscience Laboratory, The Hong Kong Polytechnic University. Each subject was comfortably seated on an armchair in front of a computer monitor, on which visual instructions and stimuli were shown. The eye-to-monitor distance was set to be 60 cm (±1 cm). As the electrical stimuli were to be applied to the lateral malleolus of the right ankle where the cutaneous dermatome was supplied from the sural nerve (L5-S1 dermatome) (see the next section for details), both feet were placed comfortably on the floor with the thighs positioned horizontally to the floor. A footstool and a back cushion were used to provide stable support whenever needed. The forearms were also supported on the desk to avoid prolonged muscle tension during the experiment.

Equipment for Stimulus Presentation

Visual stimuli, including task instructions and central fixation crosshair, were presented via a computer monitor. Since auditory cues were given to the subjects during the experiment, a pair of speakers was placed on both sides of the computer monitor in such a way that each speaker was in the same distance away from each ear. The volume of the sound was set to be 80 db (±10 db). The electrical stimulations were emitted from the *88 Dual Output Square Pulse Stimulator*. The Ag/AgCl electrodes connected to the stimulator were filled with electro-conductive hypocollagen gel and were then placed securely on the posterior aspect of the right malleolus (under the cutaneuous supply of sural nerve (L5-S1 dermatome)). The placement of the electrodes was slightly displaced by 1 mm away from the original position after each block was completed but still within the same dermatome in order

to avoid overstimulation of one particular skin spot that could lead to desensitization. The timing and presentation of all the output stimuli were synchronized by the stimulus presentation software STIM2 (NeuroScan Labs, Sterling, VA). This software also sent real-time triggers representing the onset of the nociceptive or sub-nociceptive stimulations to the EEG recording.

Equipment Setup of Electroencephalogram (EEG) Acquisition

The EEG recording took place in the sound-proof chamber. The ERP signals are captured by NuAmps Digital DC EEG Amplifier with 128 channels using 90mm Ag/AgCl sintered electrodes (NeuroScan Inc., Sterling, VA). Vertical and horizontal electrooculograms (EOGs) were recorded by two pairs of electrodes to monitor eye movements. The EEG signals were amplified and digitized at a sampling rate of 1024Hz. The montage was referenced to the left and right mastoid processes, and the ground electrode was placed on the forehead. The band-pass filters were set to between 0.5 Hz and 40 Hz. The 128-channel Quikcap was connected to the two head-boxes of the SynAmps2 Digital DC EEG Amplifier. The configuration of the electrode positions was pre-defined according to the SynAmps2 Digital.

A specific procedure was followed when the EEG cap was fitted onto the subject's head. A measuring tap was used to obtain the nasion-to-inion distance and interauricular distance. The cap was then placed on the subject's scalp in such a way that the front rim lined up with the anterior 10% level of the nasion-to-inion distance. The vertex electrode (marked as "ref") was positioned at the interaction of midway of nasion-inion line and midway of periauricular line. Besides, two pairs of electrooculogram electrodes to placed around ocular area to electrical activities due to blinks and saccades. A pair of vertical electrooculogram (VEOG) was positioned

supra-orbitially (directly above the iris) and infra-orbitally (directly underneath the iris) at the left eye. The horizontal electrooculogram (HEOG) was placed at both the temples. Two reference electrodes were placed at the left and right mastoid processes. The subject was asked to have the scalp thoroughly lathered and rinsed before the capping fitting, and all skin sites for reference electrodes and electrooculogram electrode were prepared by Nuprep (a gel for skin scrubbing) with a cotton applicator. This cleaning procedure helps reduce the skin impedance. The Quikgel (NeuroScan, Inc., Herndon, VA, USA) was injected into each of the electrode sites from a syringe and a blunt-tipped hypodermic needle. The Quikgel is a conductive gel that bridges the gap between the scalp and each electrode. The electrode impedance menu of NeuroScan 4.3 software (NeuroScan, Inc., Herndon, VA, USA) was activated during the Quikgel application in order to guide to bring down the impedance of all electrodes set at or below 5kΩ. The NeuroScan 4.3 software was used for online EEG acquisition. The signals were in digitized mode and amplified by 10000 times, and were preceded with an on-line band-pass filter of DC-200 Hz. The sampling rate was set at 1000 Hz/channel.

Digitization of Locations of Electrodes and Headshape

A Polhemus electromagnetic device allowed the digitization of the three-dimensional coordinates of all the electrodes by means of a magnetic field measurement between a stylus receiver and a base with three extra receivers adhered to the subject's forehead (NeuroScan, Inc., Herndon, VA, USA). Each of the four receptors provided six data, including the x, y, z coordinates of the receiver's endpoint, and the angles for the its orientation in three-dimension (i.e. azimuth, elevation and roll angles). Before recording the 3-dimension coordinates, the base of the Polhemus

device was positioned close to the back of subject's head with the arrow pointing toward the subject. The three receivers were then adhered onto three landmarks: above the nasion, left and right temples, which were firstly recorded by pointing the tip of the stylus at the receivers and pressing the button on the stylus. All the other electrodes were registered into the software in the same manner to obtain all three-dimension distribution of the electrodes in relation to the head shape. The three-dimensional location of all electrodes was then used for dipole sourcing analysis at the later stage (NeuroScan, Inc., Herndon, VA, USA).

EEG Processing

The raw EEG data recorded from the experiment was further processed using the offline Analysis module of Software NeuroScan 4.3 (NeuroScan Inc., Sterling, VA). The procedure of processing the EEG in order were referencing, ocular artefact correction, epoching, noise artefact rejection, averaging of epochs, baseline correction and digital filtering.

The specifications of the pre-processing are discussed here. All channels of EEG data were first re-referenced to the average mastoid reference deviation from left and right mastoid reference electrodes. The ocular artifact reduction was applied to the re-referenced data using regression algorithm in the NeuroScan 4.3 software. Sections of EEG data ranging from the 100 ms pre-stimulus to 2000 ms post-stimulus were epoched, followed by baseline correction against the pre-stimulus interval. The epoches with amplitudes larger than 100mV were rejected. The remaining epochs were then averaged according to the task conditions, i.e. perception and imagery tasks.

The grand averaged was then digitally filtered with a "Zero Phase Shift" filter with low-pass of 30 Hz and 24db/oct.

Neuropsychological Instruments

There were four questionnaires to cover demographic data, imagery function and frontal lobe function that the subjects were required to complete before the commencement of the ERP experimental with the EEG recording. There were as follows:

a. Demographic data (Appendices IX and X)
b. Vividness of Visual Imagery (VVIQ) (Marks, 1973 & 1989) (Appendices XI and XII)
c. Stroop Test (Stroop, 1935; Stuss et al., 2001) (Appendix XIII)
d. Arrow Test (Lee et al., 2005 & 2006; Yuen et al., 2005) (Appendix XIV)
e. Numeric Rating Scale for Pain Perception (Jensen, 1986; Williamson et al., 2005) (Appendix III).

Demographic Data (Chinese: Appendix IX; English: Appendix X)

The subject was required to complete the questionnaire on demographic data that covered the subject's age, gender, marital status, education level, and employment status.

***Vividness of Visual Imagery Questionnaire (VVIQ)* (Marks, 1973 & 1989) (Chinese Appendix XI; English: Appendix XII)**

The VVIQ is an instrument measuring how clear an individual is able to generate visual images of different objects or scenery. This is designed to tap on frontal lobe function (Ganis et al., 2004; Kosslyn et al., 2001). It consists of 16 items that require the respondent to rate the vividness of visual imagery in four different scenarios, namely a friend's face, rising sun, familiar shop, and a country scene. The 5-point rating scale for vividness ranges from "1" indicating "Perfectly clear and as vivid as normal vision" to "5" indicating "No image at all, you only "know" that you are thinking of an object." The instrument was translated into Chinese for the Chinese speaking sample and validation processes were conducted. The administration time was about 15 minutes.

***Stroop Test* (Qiu et al., 2006; Stroop, 1935; Stuss et al., 2001) (Appendix XIII)**

The Stroop test measures the subject's ability of conflict monitoring and resolution, in which the subject is required to inhibit a more potent stimulus and simultaneously enhance a less potent one. This mental process is governed by frontal lobe functions. The test consists of three parts, and in each condition, the subject was shown with an 8 1/2 x 11 inches sheet of paper with 100 stimuli arranged in 10 rows and 10 columns. For each condition, the subject was required to read the words or name the colors row by row as fast and accurately possible. He or she was not supposed to skip any items but was allowed to self-correct his/her response immediately if s/he realized the first response was not correct. The three conditions are: (1) word reading (WR) in which the subject was presented with one of four color word in Chinese printed in black ink (e.g. red "紅", yellow "黃", blue "藍" and green

"綠") and the subject was asked to read the word; (2) color naming (CN) in which the stimuli were 6 x 13 red, yellow, blue and green rectangular blocks and the subject was asked to name the color of each block; amd (3) incongruent color naming of color words (INC) in which the stimuli were the Chinese color words red, yellow, blue and green printed in an incongruent color and the subject was asked to name the color of the ink in which the word was printed. In all conditions, the stimuli were arranged in pseudorandom order with same number of word or color stimuli, and no identical stimuli appeared consecutively. For each condition, the test administrator recorded the time a subject needed to read all stimuli, the number of incorrect responses made and the total number of self-corrected responses. There were two types of independent outcomes from the test: speed and accuracy. There were three measures of speed. The first measure was the total time (in second) the respondent needed to complete each conditions. The second measure was the difference scores calculated from subtracting the time score of the earlier condition from that of the later one. There were three scores: INC – WR, INC – CN, and CN – WR. The difference scores reflect the standard measure by which to determine the extent of interference the later test induced (Stuss et al., 2001). The third type of speed measure was a proportional score. This was computed by dividing the difference score by the time score of the earlier condition, i.e. (INC – WR)/WR, (INC – CN)/CN, and (CN – WR)/WR. The proportional scores were to overcome the baseline differences in response speed between conditions (Stuss et al., 2001). Those difference proportional scores that were computed from INC time scores would reflect the so-called Stroop effects as it reflected the respondent "suppressing" the color name and "energizing" the actual color of the ink in which the word was printed. There were two types of accuracy: (1) number of error made and (2) the self-corrections made for each stimulus. Lesions

studies have shown that the bilateral superior medial frontal lesion appeared to be linked with increased error and reaction time in INC condition (Alexander et al., 2007; Stuss et al., 2001 & 2007). It is suggested that it was to do with the failure of maintenance of consistent activation of the intended response (i.e. reading the ink color but not the word) in the INC condition. The reason the Stroop test is included is that the paradigm in the main study involves the maintenance of a certain set task to manipulate pain perception. In this study, the Chinese version of the Stroop Test was used. It was shown to be a valid tool among Chinese speaking subjects (Qiu et al., 2006). The administration was about 15 minutes.

Arrow Test **(Lee et al., 2005 & 2006; Yuen et al., 2005) (Appendix XIV)**

Developed by Lee et al. (2005), the Arrow Test is a computer-interfaced test which was designed to assess the ability of response regulation. The computer program was written via stimulus presentation software E-Prime 1.1© (Psychology Software Tools, 1996-2001) to display all stimuli visually to the respondent. The respondent was required to perform two types of tasks: Compatible and Incompatible conditions. In the compatible condition, a black arrow in one of the four directions (upward, downward, leftward and rightward) was displayed on a crucifix shape. Within 1 second-time, the subject is required to use the right hand to press one of the four pre-assigned direction keys that represented the same direction as the stimulus shown as fast and accurately as possible. The upward, downward, leftward and rightward keys were represented by the number keys “5”, “2”, “1” and “3” at the number pad (right-hand side of the keyboard), respectively. In incompatible condition with the exact timing, a grey arrow with one of the four directions is shown. The respondent is required to respond to press the direction key that was opposite the

arrow direction displayed on the monitor. A practice session preceded the actual experiment to ensure the subject's full understanding of the tasks. There were a total of 144 trials with all trials fully randomized. The reaction time and accuracy rate were recorded by the E-Prime software for analysis. The interference scores were obtained by subtracting the total time of compatible trials from that of the incompatible trials. The examples of the stimuli shown on the monitor are illustrated in Appendix XIV. The test validity and mental processes underlying the test were studied previously. It was shown that the incompatible trials were mediated by the right medial frontal gyrus, left superior frontal gyrus and left frontal gyrus (Lee et al., 2005 & 2006; Yuen et al., 2005). The test took 20 minutes to complete.

Numeric Rating Scale (NRS) for Pain Perception **(Appendix III)**

The NRS for pain perception was used during the ERP experiment. The subjects were required to rate subjective pain perception at the end of each trial based on an eleven-point Numeric Rating Scale (NRS) (Jensen, 1986; Williamson et al., 2005) (Appendix III). They were trained to use the scale during threshold determination. An 11-point NRS has been commonly used as a clinical tool to capture one's subjective pain rating (De Pascalis et al., 2005 & 2008; Jensen, 1986; Williamson et al., 2005). It has an 11-point ordinal scale in which "0" as the left anchor denotes "no pain sensation" to "10" as the right anchor denotes "the most intense pain sensation imaginable". The NRS for pain has been shown to give reproducible and consistent measurements and be sensitive to changes (Ferraz, et al., 1990; Joos, et al., 1991).

Data Collection Procedure

The overall procedure of the experiment was explained to each subject, and signed consent was obtained from them. Each subject was asked to complete the questionnaires of demographic data and three neuropsychological tests, including VVIQ, Stroop Test and Arrow Test. Afterwards, the subject was seated in the isolated chamber to go through the procedure of the sub-painful and painful threshold calibration. The five voltage intensity levels of sub-nociceptive stimulations evenly distributed within the sub-painful range and 5 voltage intensity levels of nociceptive stimulations evenly distributed across the painful range were set.

Each subject participated in a two-hour training session before the experiment. The training was to familiarize the subject with the 10 voltage intensities which produced sub-nociceptive or nociceptive sensations. The subject was required to first memorize the intensity of the 5 sub-nociceptive stimulations and hence the sensations. Familiarization included identifying the level of stimulus by telling the researcher one of the five specific levels (e.g. saying “first level”, and same for other level magnitudes). Each level of the sub-nociceptive stimulations was presented 20 times, i.e. 20 trials. This gave a total of 100 trials which were pseudo-randomized and organized into 10 blocks. The training ended if the subject reached 80% accuracy of identifying the level of the sub-nociceptive stimulations. Otherwise, additional blocks were conducted until an accuracy of 80% was fulfilled. The same procedure was repeated for familiarization of the nociceptive stimuli.

After the familiarization training, the subject was involved in completing the second stage training. The aim was to enable the subject to learn the skills of generating sub-nociceptive images which was critical for completing the trials in an

imagery block. The subject first learned differentiating the low- versus high-pitch auditory cues. The former prompted perceiving the incoming nociceptive stimulus in the perception block whilst the latter prompted the time when perceiving the incoming nociceptive stimulus generating and rehearsing the previously learnt sub-nociceptive images in the imagery block. The subject was given the opportunity of practising on both for at least ten trials (5 perception and 5 imagery trials) so as to be familiarized with the processes.

After completing the training, the subject began the experimental tasks as previously described (Figure 4.1) with concurrent EEG recording. The subject could take a break whenever he/she felt fatigue and discomfort. The experimental tasks took about two-and-a-half hours to complete.

Data Analysis

Behavioral Data

Descriptive statistics were computed for the demographic characteristics of the subjects which included gender, age, marital status, educational level and employment status. Means and standard deviations of scores on the neurophysioloical tests were collated and presented. For VVIQ, the four subtest scores, i.e. face, sunshine, shop and scenery, the total scores, were computed. For Stroop Test, means and standard deviations of total time scores, error and self-correction for all three conditions, i.e. wording reading (WR), color naming (CN) and incongruent color naming (INC). The difference tiem scores, i.e. (IN – WR) and (IN – CN), and proportional time scores, i.e. (IN – WR)/WR and (IN – CN)/CN, and total time between conditions were also calculated. Furthermore, for Arrow Test, mean and standard deviation of the reaction

time and accuracy of the compatible and incompatible were obtained. The composite scores, which were computed by dividing the accuracy scores by the reaction time, were also calculated. Moreover, the man interference score (reaction time of incompatible condition minus reaction time of compatible condition) were obtained.

Pain NRS was collected at the end of each trial in the perception and imagery conditions, and the mean ratings on the pain sensation perceived from the recalled nociceptive image in the perception and imagery conditions were computed. Only those trials, in which the participants accurately matched S1 and S2 stimulus intensity in the perception condition and accurately matched S'2 and the rehearsed sub-nociceptive image (Im) in the imagery condition, were chosen for analysis in order to collect trials in which the participants more likely performed the maintenance of images as required. The percentages of accurately matched trials selected for further analysis ranged from 41.7 % for Level 1 electrical intensity to 67.6 % for Level 5 electrical intensity. Two-way ANOVA models with 2 (perception vs imagery) × 5 (pain levels) were used to examine the main and interaction effects of pain levels and 2 mental tasks on pain NRS rating, followed by post-hoc contrast test. Pearson's correlation was used to examine the association between the normalized NRS scores on the pain perception of the recalled nociceptive image [= (mean scores for the imagery trials) minus (mean scores for the perception trials) for minimizing within-group variations] and the scores on the neuropsychological tests. All statistical analyses were conducted using SPSS™ version 16.0 (SPSS Inc., Chicago, IL).

EEG Data

For the EEG data, in order to obtain more appropriate time windows of ERP components for componential analysis, independent component analysis (ICA) was applied to extract the ERP component that reflected top-down cognitive neural processes occurring in the perception / imagery experiment. The EEGLAB software with MATLAB platform was used for the analysis. The advantage of using ICA methods is that it can extract the ERP based on the raw EEG data from all the 128 Channels, instead of mainly relying on the conventional inspection of onset and offset of a certain component. This was particularly useful for components with close temporal proximity, such as P2 and N400 components, in which their onsets and offsets could be difficult to determine simply by inspection. The filtered EEG signals from 128 channels collected from imagery trials were decomposed into same number of independent component (IC). Each IC would have a distinct scalp distribution along with a specific activity course, which designated the onset and offset of that particular IC. Those ICs that had clear spatial topography, contributed most energy (in μV), and showed time course consistent to the hypothesized neural processes in the experiment, would be selected for subsequent conventional componential analysis (Makieg et al., 1997). It was hypothesized that earlier ERP components were related to the somatosensory evoked potential elicited from receiving the electrical stimulation (Dowman et al., 2007a & b) whereas the later ERP components were related to shifting the attention, inhibition processes of pain perception and generation of sub-painful images (Chow et al., 2007, Polich, 2007; Qiu, Li, Liu & Zhang, 2007).

For each identified ERP component from ICA, grand-averaged waves were obtained using NeuroScan software (NeuroScan Inc., 2009). Both mean amplitude

and latency of each component were analyzed using the differences in component latency between two conditions across selected electrodes.

Pearson's correlation between the scores of Stroop Test (reaction time, error and self-correction of word reading, color reading and incongruent color reading and difference and proportional scores between them) and Arrow Test (reaction time, accuracy and composite scores of compatible and incompatible condition), and the normalized NRS scores [= (mean of pain NRS in imagery trials) minus (mean of pain NRS in perception trials)] of five levels of pain intensity and were computed. Besides, the correlations between the mean amplitudes of the identified ERP components and the normalized NRS score of each pain level were also calculated. These would shed light on the plausible meanings of the pain NRS ratings on the recalled nociceptive image after focused attention through sub-nociceptive imagery. All statistical analyses were conducted using SPSS™ version 16.0 (SPSS Inc., Chicago, IL).

Curry 6.0.2 (Compumedics Neuroscan) is used for the dipole sourcing analysis, which is a mathematic method to use the EEG signals recorded at the surface of scalp to predict the source of EEG in the subcortical levels. The principle component analysis was applied on the later ERP components from P2 and N400 components with the same time windows as in mulitivariate repeated measures ANOVA. The number of components used for source localization was based on the results obtained in the principle component analysis and independent analysis, in which only components with signal-to-noise ratio larger than 1.0 were included for subsequent source localization. The Boundary Element Method (BEM) head model provided by the software was used as the template of localization, on which the location of sources were computed by the Curry 6.0.2 software. The rotating dipole type was adopted. The amount of fit was reflected by the percentage of variance explained and residual

deviation. The dipole location solutions of each identified component were then plotted onto neuroimage templates of the cortex in sagittal, horizontal and coronal views. The Talairach coordination system (http://www.talairach.org/) was subsequently applied in order to determine anatomical sites of the dipole sources.

METHODS OF STUDY TWO: FOCUSED ATTENTION PROCESSES IN CHRONIC PAIN PATIENTS

Subjects

There were 19 subjects with chronic low back pain of musculoskeletal origins. The subjects were recruited from the Pain Clinic of United Christian Hospital, Hospital Authority, Hong Kong. Two patients were excluded from the analysis since they were not able to complete the whole experiment. Thus, 17 subjects with chronic pain validly participated in the main study. The inclusion criteria were:

a. Age between 21 and 55;
b. Primary six or above education level;
c. Chronic pain condition between six months to three years;
d. Chronic pain condition with musculoskeletal origin;

The exclusion criteria were:

a. Presence of neurological deficits with demonstrable anatomic lesions (such as Herpes Zoster, clinical signs or imaging proven nerve or spinal cord impingement); this attempted to ensure that the chronic pain was cortical rather than peripheral originated;

b. Cancer as primary aetiology, history of cardiac diseases (especially arrhythmias), psychosis, currently on strong opioid medications (Ohara et al., 2005); and
c. Previous history of training on cognitive strategies for visualization replacement.

Subjects with chronic low back pain were all patients referred from other specialties, such as orthopedics, to the Pain Clinic of United Christian Hospital. At the clinic, the patients attended consultations with the senior anesthesiologist and one trainee medical officer along with a multidisciplinary team including a pain nurse, a physiotherapist, and a clinical psychologist. The researcher joined the weekly consultation sessions for screening for potential subjects joining the study between December, 2009 and July, 2010.

The members in the multidisciplinary team played specific roles in providing pain management services to the patients (i.e. potential subjects). The medical management included pharmaceutical intervention and peripheral nerve block. The nurse was responsible for delivering education on pain management such as self-pacing in daily living. The physiotherapist provided the patient with pain alleviation modality such as acupuncture and transcutaneous electrical stimulation. The clinical psychologist offered counseling and cognitive behavioral therapy to the patients.

The procedure and ethics were approved by the Ethics Committee of Kowloon East Cluster, Hospital Authority, Hong Kong and Department of Rehabilitation Sciences, The Hong Kong Polytechnic University (Appendix XV). Each subject received an amount of HK$200 for reimbursement for the expenses incurred from traveling and meals.

Stimulus

The electrical stimulating device and sensory and painful threshold determination procedure was the same as in the first part of the main study on pain-free subjects described in the previous section (pp. 65 – 66)).

Experimental Design

The experimental design in the second part of the main study was the same as the one adopted in the experiment on pain-free subjects (p. 68).

Subject Position and Equipment Setup

The procedures for subject positioning and equipment setup were the same as in the first part of the main study on pain-free subject described in the previous section (pp. 72 – 73).

EEG Processing

The procedure and specification of EEG processing were the same as in the the first part of the main study on pain-free subject described in the previous section (pp. 75 – 76).

Neuropsychological and Pain-related Instruments

Before the commencement of the ERP experiment, the subjects were required to complete the same set of questionnaires as in the first part of the main study on pain-free subjects. This included demographics (Appendices IX & X) and vividness of visual imagery (Marks, 1973 & 1989) (Appendices XI & XII), Stroop Test (Stroop, 1935; Stuss et al., 2001) (Appendix XIII), and Arrow Test (Lee et al., 2005 & 2006; Yuen et al., 2005) (Appendix XIV). They were also trained to use the Numeric Rating Scale for Pain Perception (Jensen, 1986; Williamson et al., 2005). The details of these instruments have been described in the previous sections. Besides, they were also asked to complete a number of measures that were related to pain. There were as follows:

a. Pain assessment, including Pain Body Chart and 11-point NRS (Jensen, 1986) (Appendix XX);
b. Pain History Questionnaire (Appendix XXI);
c. Coping Strategy Questionnaire (CSQ) (Hastie et al., 2004; Rosenstiel & Keefe, 1983) (Appendix XXII);
d. Numeric Rating Scale for Pain Perception (Jensen, 1986; Williamson et al., 2005) (Appendix III).

Pain Assessment

The purpose of this test was to identify the location of chronic pain and to obtain information about pain intensity at the beginning of the experiment period. The researcher used a body chart (Appendix XX) to gather information on the pain felt by the subject. This included the locations, nature and extents of the painful site(s). The

subject was also required to use the 11-point NRS to assign a number which best described the intensity of the pain felt (Jensen, 1986) (Appendix III). A brief history on the pain sensation was obtained: onset time and cause of injury that led to the painful conditions, the treatments (such as surgery and pharmaceutical injection) and rehabilitation interventions the subject had received.

Pain History Questionnaire

The purpose of the Pain History Questionnaire (Appendix XXI) was to obtain details on the subject's pain history and self-perception of chronic pain in the recent past. It covers duration of the pain history, medical treatment received, engagement of self-help groups, medication currently taken, the extent of chronic pain (frequency, duration and intensity), general healthy and physical tolerance, number of visits at different professionals (including psychiatrists, clinical psychologist, community nurse, physiotherapist, and occupational therapist), use of emergency services and hospital stays in the past six months.

Coping Strategy Questionnaire (CSQ) **(Hastie et al., 2004; Rosenstiel & Keefe, 1983) (Appendix XXII)**

The CSQ is a 42-item questionnaire which was designed to measure the ways that clients cope or deal with their pain. Each of the items represents one particular method of pain coping the respondent might use on a regular basis. The subjects are to report how often that they use each of the methods on a 0 to 6 scale with "0" referring to never do and "6" referring to always do that. The subjects' ratings are then collated to six cognitive coping strategies: diverting attention, reinterpreting the pain sensations, catastrophizing, ignoring sensations, praying or hoping, coping self-

statements. The Chinese version of this questionnaire was constructed by direct translation of its English version. Its psychometric properties have also been widely studied with reported satisfactory internal consistency (Cronbach's alpha = 0.72 – 0.91).

Data Collection Procedure

Before commencing the study, the subject was given an information sheet (Appendices XVI & XVII) and the objectives and procedures of the study were explained. The subject was then asked to complete an informed consent form (Appendices XVIII & XIX). This was followed by a testing session, a training session and then an experiment session held on the same day.

Before the training, the subject was interviewed to obtain the brief history on the chronic pain and record the current pain condition using the Pain Body Chart and 11-point NRS. The subject also completed questionnaires/tests on personal particulars, Pain History Questionnaire, vividness of visual imagery (Marks, 1973 & 1989)) (Appendices XI & XII), Stroop Test (Stroop, 1935; Stuss et al., 2001) (Appendix XIII), and Arrow Test (Lee et al., 2005 & 2006; Yuen et al., 2005) (Appendix XIV), and CSQ (Hastie et al., 2004; Rosenstiel & Keefe, 1983) (Appendix XXII).

They were then asked to go through the sensory threshold calibration procedure as previously described (pp. 65-66) to obtain five levels of sub-nociceptive and five nociceptive stimuli. Each subject then went through the two-hour sensation familiarization training same as for the control pain-free group (p. 81).

Data Analysis

Behavioral Data

Statistical analysis for behavioral data was the same as for the pain-free group, including demographic data and the scores of neurophysioloical tests, including VVIQ, Stroop Test and Arrow Test. Besides, the mean scores and standard deviations (SD) were also computed for the seven domain scores CSQ, i.e. diverting attention, reinterpreting the pain sensations, catastrophizing, ignoring sensations, praying or hoping, coping self-statements, increased Behavioral Activities. In order to compare the between-group differences, independent t-tests were conducted for all the neurophysiological measures.

Similar to the pain-free group, two-way ANOVA of 2 (perception vs imagery) × 5 (pain levels) model were used to examine the main and interaction effects on the pain NRS ratings on the recalled nociceptive image, followed by post-hoc contrast test. Three-way ANOVA repeated measures ANOVA with 2 (chronic pain vs control) × 2 (perception vs imagery) × 5 (pain levels) were then conducted to investigate the between-group difference in terms of NRS. Pearson's correlation was used to examine the association between the normalized NRS scores on recalled pain perception, and the scores on the neurophysioloical tests and CSQ subscores.

EEG Data

Same as the EEG data of the control group, the average baseline-to-peak amplitudes of each chosen component with same time window as for the control group were submitted to two-way repeated measures ANOVA with 2 Conditions (perception vs imagery) × 6 Midline Sites (Fz, FCz, Cz, CPz, Pz, and POz) testing the

differences in the midline electrodes. Additional three-way repeated measures ANOVA with 2 Conditions × 2 Laterality (left and right) × 7 Sites on either hemisphere (F3, FC3, C3, CP3, P3, PO3 and T7 on the left and F4, FC4, C4, CP3, P4, PO4 and T8 on the right) were conducted testing the lateralization effects. Same two-way repeated measures ANOVA for midline electrode sites and three-way measures ANOVA for lateral electrode sites were used to compare the differences in component latency between two conditions across selected electrodes. All statistical analyses were conducted using SPSS™ version 16.0 (SPSS Inc., Chicago, IL).

In order to compare the between-group differences, three-way repeated measures ANOVA with a model of 2 Groups (chronic pain vs control) × 2 Conditions (perception vs imagery) × 6 Midline Sites (Fz, FCz, Cz, CPz, Pz, and POz) was conducted on the amplitude and latency of the identified event-related potential components. Four-way repeated measures ANOVA was a model of 2 Groups (chronic pain vs control) × 2 Conditions × 2 Laterality (left and right) × 7 Sites on either hemisphere (F3, FC3, C3, CP3, P3, PO3 and T7 on the left and F4, FC4, C4, CP3, P4, PO4 and T8 on the right) were conducted to test the lateralization effects on the ERP components. Three-way repeated measures ANOVA for midline electrodes and four-way repeated measures ANOVA were also conducted for comparing the differences between the chronic pain and pain-free groups in terms of the peak latency of ERP component.

Pearson's correlations were used to explore the relationships between normalized recalled NRS scores of the five levels of nociceptive stimuli [= (mean of pain NRS in imagery trials) minus (mean of pain NRS in perception trials)] and the scores on Stroop Test (reaction time, error and self-correction of word reading, color reading and incongruent color reading and difference and proportional scores between

them) and Arrow Test (reaction time, accuracy and composite scores of compatible and incompatible condition) for the chronic pain and control groups. The patterns of significant correlation coefficients were compared qualitatively between the two groups. Furthermore, separate Pearson's correlation was also computed between the magnitudes of pain down-regulation of five level of pain intensity with the scores of CSQ, which were only completed by the subjects with chronic pain.

Curry 6.0.2 (Compumedics Neuroscan) was also used for the dipole sourcing analysis on the chronic pain group data. The principle component analysis was applied on the later ERP components from P2 and P600 with the same time windows as in mulitivariate repeated measures ANOVA. The principle component and independent analyses, included only components with signal-to-noise ratio larger than 1.0, were used for determining the number of components for the healthy group. The Boundary Element Method (BEM) head model and rotating dipole type were also adopted as for healthy group. The amount of fit was reflected by the percentage of variance explained and residual deviation. The Talairach coordination system (http://www.talairach.org/) was subsequently applied in order to determine anatomical sites of the dipole sources.

CHAPTER FIVE

RESULTS OF STUDY ONE AND TWO:

PAIN MODULATION IN PAIN-FREE SUBJECTS

AND CHRONIC PAIN PATIENTS

RESULTS OF STUDY ONE: MODULATION OF PAIN PERCEPTION IN PAIN-FREE SUBJECTS

Demographic Data

Table 5.1 summarizes the demographic characteristics of the pain-free subjects. Eighteen healthy subjects with age and gender matched with chronic pain patients (male = 7; were recruited via convenience sampling. Seven were male and mean age was 35.78 years (SD = 13.15). Half of the subjects were married. Twelve of them (12 out of 18) received undergraduate or above education level. In terms employment status, 12 of them had either full-time job or part-time job, and four (22.22%) were studying. subjects.

Numeric Rating Scale of Pain Perception

Among the pain-free subjects, three levels of mean voltage intensity were elicited: the minimal detectable stimulus, the minimal painful sensation and the very painful sensation. The respective results were 3.86 mA (SD=1.50 mA; minimum=0.50 mA; maximum=7.00 mA); 7.433 mA (SD=5.21 mA; minimum=3.50 mA; maximum=24.50 mA); and 14.92 mA (SD=9.92 mA; minimum=7.20 mA;

maximum=37.00 mA), respectively. The thresholds were quite different from those obtained in the pilot study. This implies variability across pain-free participants in terms of sensitivity to nociceptive stimulation intensity. The mean NRS scores on the perception of the 5 levels of recalled nociceptive image in the imagery trials ranged from 2.17 (SD=1.45) to 4.83 (SD=1.54) (out of 10). Those obtained in the perception trials ranged from 2.51 (SD=1.65) to 4.87 (SD=1.76) (Table 5.2). The normalized NRS scores for each of the five stimulus levels were computed by subtracting the scores obtained from the perception trials from those of the imagery trials for each level of nociceptive stimuli, i.e. mean $NRS_{Imagery}$ − mean $NRS_{Perception}$. The mean normalized NRS scores ranged from -0.34 to -0.04.

A two-way ANOVA model with 2 conditions × 5 pain levels revealed significant condition effect on the NRS rating on the recalled nociceptive image [$F(1,17)=10.666$, $p<0.010$] and pain level [$F(1.24, 17.37)=34.820$, $p<0.001$]. The Condition × Pain interaction effect was not significant ($p>0.050$). Post-hoc contrast tests revealed significant differences in the NRS ratings in levels 1 to 3 [$t(17)=-2.63$ to 3.52, $p<0.050$]. Marginal differences were found in the in level 4 [$t(17)=-1.99$, $p<0.06$] (Appendix XXIII (a)).

Table 5.1 Demographics of pain-free subjects (n = 18)

Male (%)	7 (38.89)
Age (SD) (years)	35.78 (13.15)
Marital Status (%)	
Single	9 (50.00)
Married	9 (50.00)
Divorce	0 (0.00)
Educational Level (%)	
Secondary	4 (22.22)
Matriculation	2 (11.11)
Undergraduate	3 (16.67)
Postgraduate	9 (50.00)
Employment Status	
Unemployed	0 (0.00)
Full-time	3 (16.67)
Part-time	9 (50.00)
Student	4 (22.22)
Housewife	1 (5.56)
Retired	1 (5.56)

Key: SD = standard deviation;

Table 5.2 Mean and normalized NRS of five levels of nociceptive stimulation in imagery and perception conditions among pain-free subjects

	Pain Levels				
	Level 1	Level 2	Level 3	Level 4	Level 5
Imagery	2.17	2.77	3.43	4.07	4.83
	(1.45)	(1.59)	(1.58)	(1.54)	(1.54)
Perception	2.51	3.10	3.79	4.41	4.87
	(1.65)	(1.60)	(1.70)	(1.73)	(1.76)
Normalized	-0.34	-0.34	-0.35	-0.34	-0.04
scores	(0.38)	(0.40)	(0.52)	(0.72)	(0.45)

Key: Standard deviation is in parenthesis ( ); Normalized NRS = Mean $NRS_{Imagery}$ − Mean $NRS_{Perception}$

Results of Neuropsychological Tests on Pain-free Subjects

The mean scores of four subtests of VVIQ ranged from 3.31 (SD=1.24) to 3.69 (SD=1.24). For the Stroop Test, the total time of Word Reading (WR) was 49.28 s (SD=12.81 s), and mean error and self-correction error were 0.06 (SD=0.24) and 0.47 (SD=0.72), respectively. For the Color Naming (CN) Test, the mean total time was 70.33 s (SD=15.38 s). The mean error was 0.35 (SD=0.75) and self-correction error was 1.29 (SD=1.79). The mean complete time of the Incongruent Color Naming Test (INC) was 121.65 s (SD=29.31 s). The mean error was 1.88 (SD=2.00) and the self-correction error was 2.47 (SD=2.78). The difference scores of INC – WR, IN – CN and CN – WR were 72.36 s (SD=21.16 s), 51.32 s (SD=17.00 s) and 21.05 s

(SD=9.35 s), respectively. Finally, the proportional scores of (IN – WR) / WR, (IN – CN) / CN, (CN – WR) / WR were 0.51 (SD=0.43), 0.73 (SD=0.20) and 0.46 (SD=0.24), respectively. For the compatible condition of the Arrow Test, the pain-free subjects had a mean reaction time of 729.20 ms (SD=87.83 ms) with a mean accuracy rate of 0.63 (SD=0.28). This yielded a composite quotient (accuracy / reaction time) of 0.09 (SD=0.050). For the incompatible condition, the mean reaction time was 730.44 ms (SD=109.78 ms) with a mean accuracy rate of 0.61 (SD=0.29). This yielded a composite score of 0.09 (SD=0.050). The average inference score (= $Time_{incompatible}$ minus $Time_{compatible}$) of the pain-free subjects was 12.70 (SD=14.10). Tables 5.3 – 5.5 summarize the mean (and SD) of these three neuropsychological tests.

Table 5.3 Mean scores (and standard deviations) of vividness of Visual Imagery Questionnaire of the pain-free subjects

Construct	Test	Mean (SD)
Imagery	Face	3.69 (1.24)
	Sunrise	3.54 (1.08)
	Shop	3.50 (1.12)
	Scenery	3.31 (1.24)
	Total	3.51 (1.07)

Table 5.4 Mean scores (and Standard Deviations) of Stroop Test of pain-free subjects

Construct	Subtest	Mean Scores (SD)
Attention	Word Reading	
	Total Time (second)	49.28 (12.81)
	Error	0.06 (0.24)
	Self-correction	0.47 (0.72)
	Color Naming	
	Total Time (second)	70.33 (15.38)
	Error	0.35 (0.79)
	Self-correction	1.29 (1.79)
	Incongruent Color Naming	
	Total Time (second)	121.65 (29.31)
	Error	1.88 (2.00)
	Self-correction	2.47 (2.78)
	Difference Score	
	IN – WR (second)	72.36 (21.16)
	IN – CN (second)	51.32 (17.00)
	CN – WR (second)	21.05 (9.35)
	Proportional Score	
	(IN – WR) / WR	1.51 (0.43)
	(IN – CN) / CN	0.73 (0.20)
	(CN – WR) / WR	0.46 (0.24)

Key: WR = Wording Reading; CN = Coloring Naming; IN = Incongruent Color Naming; RT = Reaction Time

Table 5.5 Mean scores (and Standard Deviations) of Arrow Test of the pain-free subjects

Construct	Subtest	Mean Scores (SD)
Response	Compatible condition	
Regulation	Reaction Time (ms)	729.20 (87.83)
	Accuracy	0.63 (0.28)
	Composite	0.09 (0.05)
	Incompatible condition	
	Reaction Time (ms)	730.44 (109.78)
	Accuracy	0.61 (0.29)
	Composite	0.09 (0.05)
	Interference score	12.70 (14.10)

Key: Composite score = Accuracy / Reaction Time; Inference score = Incompatible RT – Compatible RT

Results of ERP Component Analysis

Results from ICA identified five components: P1 (177-265ms), P2 (273-341ms), P3 (349-409ms) and two late components: N400 (411-475ms) and P600 or called later positive component (LPC) (507-650ms).

Two-way repeated measures ANOVA with a 2 Condition (Perception vs imagery condition) × 6 Midline Site (midline electrode sites) design were used to test the amplitudes of the eight identified components. The six midline electrodes were Fz, FCz, Cz, PCz, PZ and POz. A three-way repeated measures ANOVA with a 2 Condition (Perception vs imagery conditions) × 2 Laterality (left vs right) × 7 Site (electrode sites) design was also conducted on the same mean amplitudes. The sites for the left hemisphere were: F3, FC3, C3, PC3, P3, PO3 and T7; those on the right hemisphere were Fz, FCz, Cz, PC4, P4, PO4 and T8. The same models were used for testing the peak latency of each identified component.

Figure 5.1 shows the grand average of ERP of eleven selected channels of perception and imagery conditions in the pain-free subjects. Figure 5.2 shows topographical distribution of five components between perception and imagery conditions of the pain-free subjects.

Figure 5.1 Grand average of ERP waveforms of 11 selected electrode sites of the pain-free subjects. The five ERP components were labeled at their prominent electrode sites.

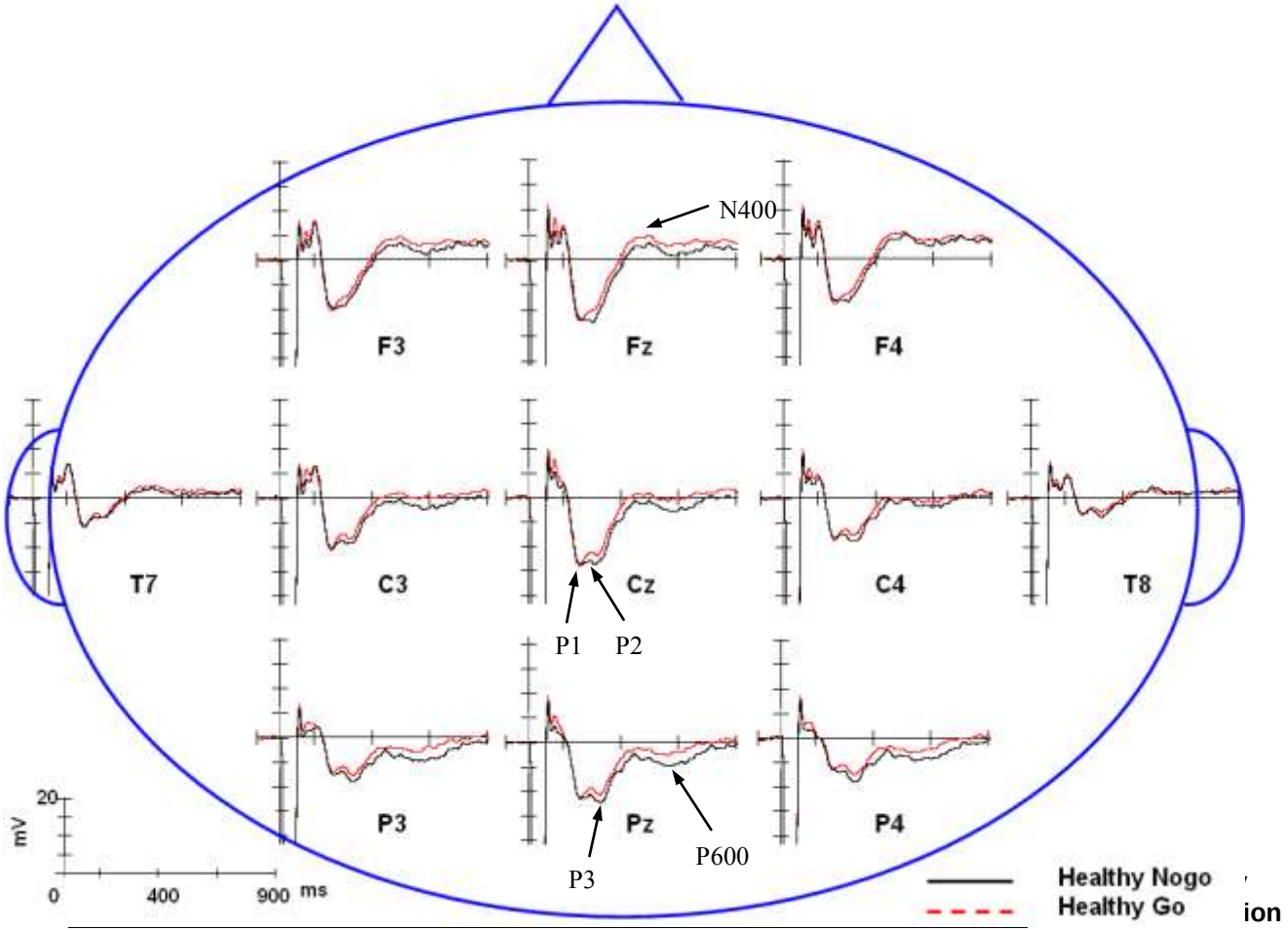
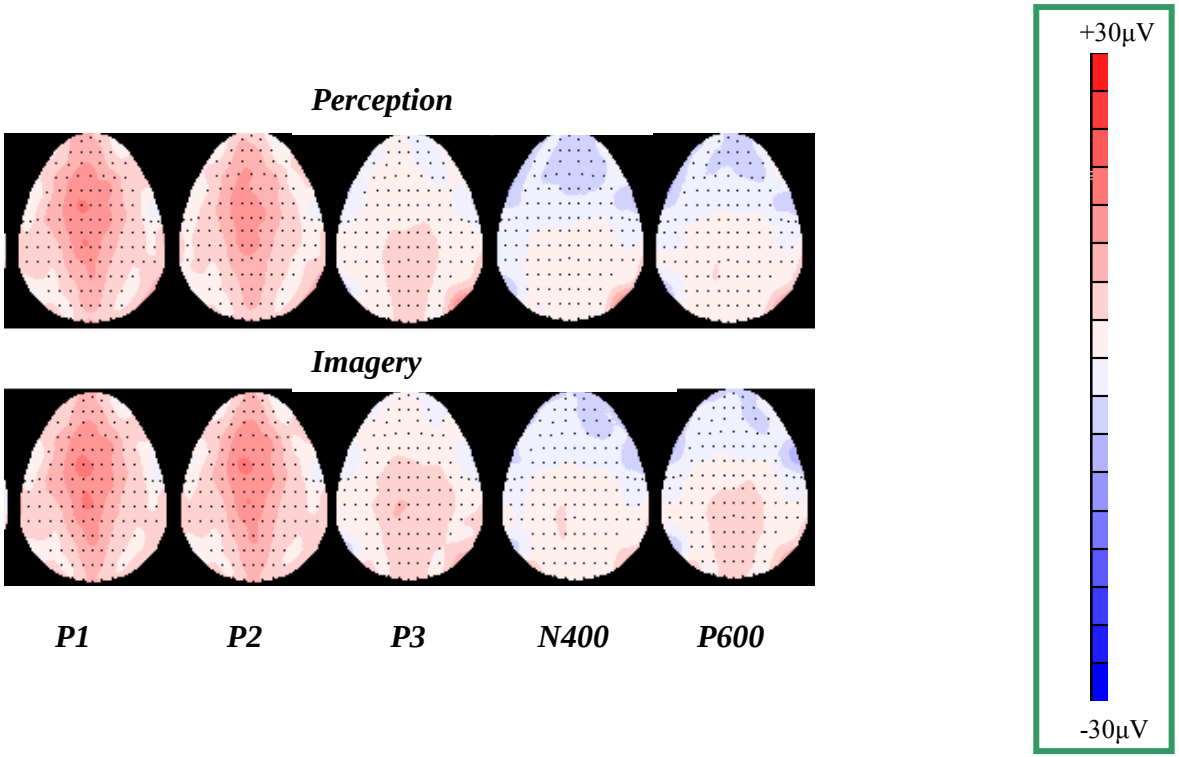


Figure 5.2 Topographical distributions of five EPR components in Perception and Imagery conditions of pain-free subjects.



P1 Component

The mean amplitudes of P1 peaked at CPz among the midline electrode sites in pain-free subjects for both perception (16.42 ± 7.97 μV) and imagery conditions (16.88 ± 7.05 μV (Figure 5.3). Among the left lateral sites, P1 peaked at FC3 for the perception (14.81 ± 7.21 μV) and imagery (14.41 ± 6.16 μV) condition. Among the right lateral sites, P1 peaked at FC4 for the perception and imagery trials (12.61 ± 6.35 μV & 12.55 ± 6.02μV, respectively) (Table 5.6).

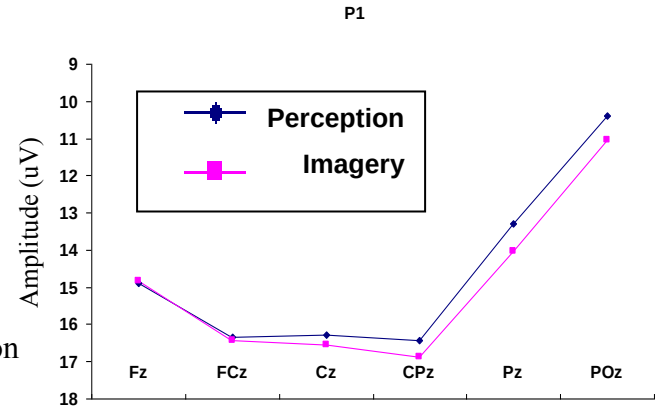


Figure 5.3 Mean amplitudes of six midline electrode sites (i.e. Fz, FCz, Cz, PCz, Pz and POz) of P1 component in Imagery and Perception conditions

The 2 (conditions) × 6 (midline sites) repeated measures ANOVA revealed a significant Site effect [$F(2.58,43.89)=13.81$, $p<0.005$]. Post-hoc tests did not reveal significant between-condition differences in any electrode sites (at corrected $p<0.001$). The Condition effect and Condition × Midline Site interaction effects were statistically not significant ($p>0.050$). The 2 (conditions) × 2 (laterality) × 7 (sites) repeated measures ANOVA revealed that only the Site effect was statistically significant [$F(2.48,42.23)=15.03$, $p<0.0005$]. Post-hoc tests only showed significant between-condition difference with imagery condition eliciting more positive-going amplitude at left PO3 ($p<0.005$) (Appendix XXIII (b)).

The P1 peak latency at midline sites ranged from 227.11 ms (SD=21.24 ms) at CPz to 233.00 ms (SD=21.57ms) at Fz in the perception condition and ranged from 235.00 ms (SD=20.90 ms) at POz to 244.39 ms (SD=20.49 ms) at Fz. The 2

(conditions) × 6 (midline sites) repeated measures ANOVA revealed significant Condition effect on peak latency [$F(1,17)=6.82$, $p<0.050$]. Post-hoc tests revealed that P1 peak latencies in imagery condition at Fz and CPz were significantly larger than those in perception condition (corrected p value < 0.005). The Midline Site effect and Condition × Midline Site interaction were not statistically significant ($p>0.050$). The 2 (conditions) × 2 (laterality) × 7 (sites) comparisons showed significant Condition effect [$F(1,17)=6.08$, $p<0.050$]. Post-hoc tests showed that P1 peak latency was significantly larger in the imagery than perception condition at FC3 and C3 (corrected $p < 0.050$). Other main and interaction effects were not statistically significant ($p>0.050$) (Appendix XXIII (c)).

P2 Component

For P2 component, the peaks appeared around the central regions. The mean amplitudes peaked at the CPz for perception trials (14.80 ± 7.63 μV) and for imagery conditions (17.17 ± 6.97 μV) in the pain-free subjects (Figures 5.4 & 5.5). For the lateral sites, the peaks appeared to be more frontally distributed. The mean amplitudes peaked at FC3 for perception condition (11.06 ± 6.15 μV) and for imagery condition (13.48 ± 5.73 μV) on the left hemisphere whilst those peaked at the C4 for perception condition (9.48 ± 6.39 μV) and at FC4 for imagery condition (11.95 ± 5.65 μV) on the right hemisphere (Table 5.7).

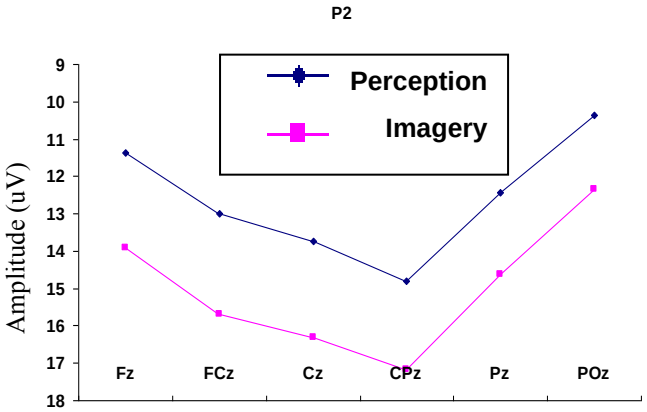
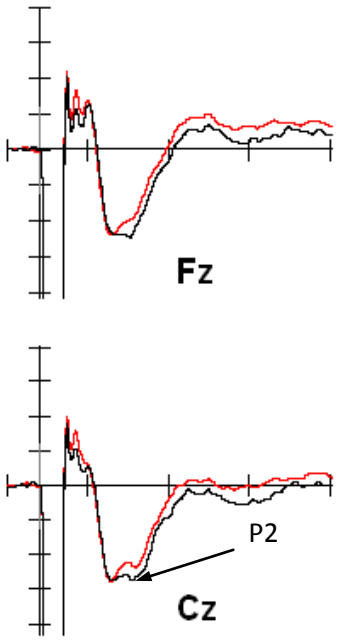


Figure 5.4 Mean amplitudes of six midline electrode sites (i.e. Fz, FCz, Cz, PCz, Pz and POz) of P2 component in Imagery and Perception conditions



Healthy Imagery

Healthy Perception

Figure 5.5 Grand average of ERP waveforms at of Fz and Cz sites of the pain-free subjects with P2 component labeled

The 2 (conditions) × 6 (midline sites) repeated measures ANOVA revealed significant Conditions and Sites effects [$F(1,17)=12.241$, $p=0.003$ & $F(2.147,36.592)=7.706$, $p=0.001$]. Yet the Conditions × Sites interaction effect was not significant ($p>0.050$). A post-hoc test showed that the main amplitudes of the imagery condition were significantly more positive than those in the perception condition ($p<0.050$), and mean amplitudes were significant more positive going in the imagery condition than perception condition at FCz, Cz, CPz and Pz sites (corrected $p<0.0005$). Three-way models with a 2 (conditions) × 2 (laterality) × 7 (sites) design for lateral sites of the pain-free subjects were built. The main effects of both conditions and sites were shown to be significant [$F(1,17)=12.24$, $p=0.003$ & $F(2.15,36.59)=7.71$, $p=0.001$, respectively]. The Conditions × Sites interaction effect was also found to be significant [$F(2.31,39.23)=4.10$, $p<0.020$]. Post-hoc tests showed that the imagery condition had more positive going mean amplitudes of P1 component than the perception counterpart ($p<0.005$). The post-hoc tests also revealed significant differences in F3, FC3, P3, PO3 and FC4 sites between two conditions (corrected p level <0.0005) (Appendix XXIII (d)).

In the pain-free subjects, the peak latencies of the perception condition ranged from 291.28ms (SD=22.53 ms) at Fz site to 304.89 ms (SD=22.02 ms) at POz site and those of the imagery conditions ranged from 296.89ms (SD=19.09 ms) at Fz site to 304.61ms (SD=20.80 ms) at POz site (Table 5.7). A two-way repeated measures ANOVA with 2 (conditions) × 6 (electrode sites) did not indicate significant results in the main effect of condition or electrode sites ($p>0.050$) or the conditions × electrode sites interaction effect ($p>0.050$). On the other hand, a three-way repeated measures ANOVA with a 2 (conditions) × 2 (laterality) × 7 (sites) design only revealed significant findings in the Site main effect [$F(2.64,44.93)=12.80$, $p<0.0005$]. A post-

hoc test found a significant difference between the two conditions at F4 site (corrected p level <0.050 only) (Appendix XXIII (e)).

P3 Component

For the pain-free subjects, P3 component peaked more posteriorly. The peaks of the midline electrode sites also occurred at the PCz site for the perception trials (8.74 ± 5.94 μV) and imagery trials (10.83 ± 4.93 μV) (Figures 5.6 & 5.7). A similar pattern was found for lateral sites in the pain-free subjects. The mean amplitudes peaked at P3 site for perception (6.58 ± 4.15 μV) and imagery trials (8.22 ± 4.56 μV) on the left hemisphere. On the other hand, they peaked at P4 for perception (6.72 ± 5.15 μV) and imagery conditions (8.27 ± 4.72 μV) on the right hemisphere (Table 5.8).

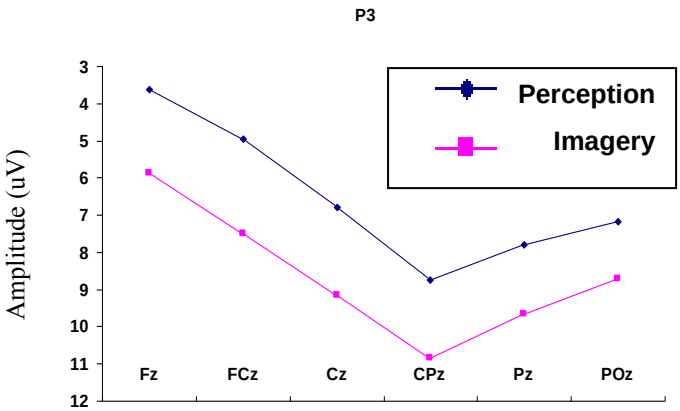


Figure 5.6 Mean amplitudes of six midline electrode sites (i.e. Fz, FCz, Cz, PCz, Pz and POz) of P3 component in Imagery and Perception conditions

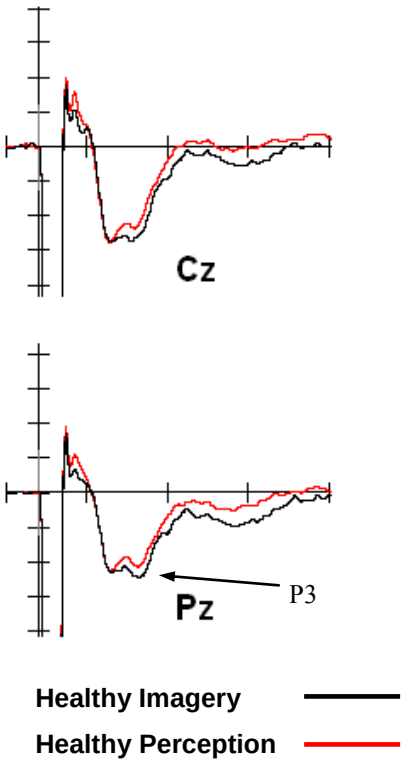


Figure 5.7 Grand average of ERP waveforms at of Cz and Pz sites of the pain-free subjects with P3 component labeled

A two-way repeated measures ANOVA with a design of 2 (conditions) × 6 (sites) was built for midline electrodes of the pain-free subjects. It was found that the main Condition and Site effects were revealed significant [$F(1,17)=9.02$, $p=0.008$ & $F(1.70,28.90)=10.85$, $p=0.001$]. A post-hoc test showed that mean amplitudes of the imagery condition was more positively going than the perception conditions at Fz, FCz and Cz sites (corrected $p<0.005$ level). The Condition × Sites interaction was not found to be significant ($p>0.050$). A Three-way repeated measures ANOVA with a 2 (conditions) × 2 (laterality) × 7 (sites) design was built. The main effect of the conditions and electrode sites were found to be significant [$F(1,17)=9.27$, $p=0.007$ & $F(1.99,33.98)=10.57$, $p<0.0005$]. As revealed by the post-hoc test, the mean amplitude was more positive going than the perception condition ($p<0.010$) at F4, FC4, C4 and CP4 sites on the right hemisphere (corrected $p<0.010$ only) (Appendix XXIII (f)).

The peak latencies of the pain-free subjects, ranged from 355.44ms (SD=10.62ms) to 358.61ms (SD=12.45 ms) for perception condition and from 355.39ms (SD=12.63 ms) to 358.83ms (SD=15.14ms) (Table 5.8). A two-way repeated measures ANOVA did not reveal any significant findings in peak latencies in terms of the main Condition and Site main effects and their interaction effect ($p>0.050$). A three-way repeated measures ANOVA revealed significant findings in the Site effect [$F(2.72,46.29)=3.92$, $p=0.017$]. Yet, post-hoc tests did not reveal significant differences at any sites between two conditions (corrected p level of 0.005). Three-way repeated measures ANOVA was constructed from lateral sites. Only the Site effect was found to be significant [$F(2.72,46.29)=3.92$, $p=0.017$]. Post-hoc tests did not reveal any significant condition differences at any electrode sites (corrected p level = 0.005) (Appendix XXIII (g)).

N400 Component

The topography of the N400 component has more frontal distribution in the pain-free subjects. The amplitude of midline electrode sites also peaked at Fz sites in the pain-free subjects (-5.30 ± 6.39 μV for perception trials and -3.84 ± 6.70 μV for imagery trials) (Figures 5.8 & 5.9). For lateral electrode sites, the peaks were also found to be at F3 (-4.95 ± 5.44 μV for the perception condition & -3.97 ± 5.68 μV for the imagery condition) and F4 (-3.84 ± 6.70 μV for the perception condition & -4.90 ± 6.89) μV for the imagery condition) (Table 5.9).

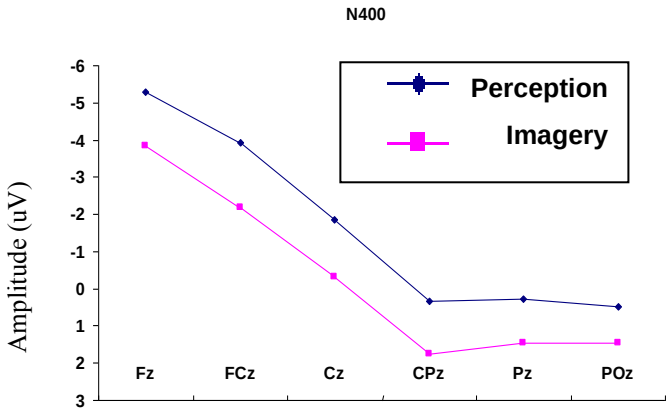


Figure 5.8 Mean amplitudes of six midline electrode sites (i.e. Fz, FCz, Cz, PCz, Pz and POz) of N400 component in Imagery and Perception conditions

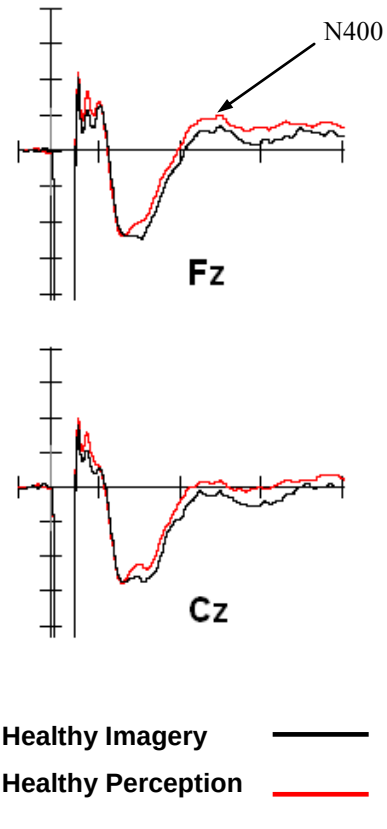


Figure 5.9 Grand average of ERP waveforms at of Fz and Cz sites of the pain-free subjects with N400 component labelled

A two-way repeated measures ANOVA with a design of 2 (conditions) × 6 (sites) was built for midline electrode sites of the pain-free subjects. A significant finding was obtained in the main effects of condition [$F(1,17)=9.21$, $p=0.007$] and electrode sites [$F(1.40,23.82)=13.86$, $p<0.0005$]. There was no significant interaction between conditions and sites ($p>0.050$). Post-hoc tests showed that the mean

amplitudes of the imagery condition was less negative going than the perception condition ($p<0.010$) at the FCz, Cz and CPz (corrected p level <0.050 only). The three-way 2 (conditions) × 2 (laterality) × 7 (sites) repeated measures ANOVA revealed significant differences in the main Condition effect [$F(1,17)=9.58$, $p=0.007$] and Lateral effect [$F(1.42,24.16=15.04$, $p<0.0005$). The Laterality × Site interaction effect was found to be significant [$F(2.95,50.12)=3.27$, $p=0.029$]. Post-hoc tests showed that the imagery condition was less negative going than the perception condition at PO3 (corrected $p<0.010$) (Appendix XXIII (h)).

The peak latencies of the midline electrodes of the pain-free subjects ranged from 455.72 ms (SD=21.04 ms) for perception condition and from 452.82 ms (SD=15.95 ms) for the imagery conditions (Table 5.15). The 2 (conditions) × 6 (midline sites) repeated measures ANOVA for the N400 peak latencies of midline electrode sites did not reveal any significant findings ($p>0.050$). The 2 (conditions) × 2 (laterality) × 7 (sites) repeated measures ANOVA for those on the lateral electrode sites only showed significant main effect for electrode sites [$F(2.68.45.56)=3.50$, $p=0.027$]. Post-hoc tests, however, did not show significant between-condition differences at any electrode sites that reach the corrected p level of 0.005 (Appendix XXIII (i)).

P600 Component

The P600 component peaked around parietal regions. The midline sites of the pain-free subjects also peaked at CPz for the two conditions (3.92 ± 4.23 μV for perception condition & 6.71 ± 4.25 μV imagery condition) (Figure 5.14). The peaks also occurred at P3 site (3.94 ± 3.96 μV for perception condition & 6.25 ± 5.16 μV for imagery condition) and P4 site (4.25 ± 4.50 μV for perception condition & 6.11 ± 4.81 μV for imagery condition) (Table 5.10).

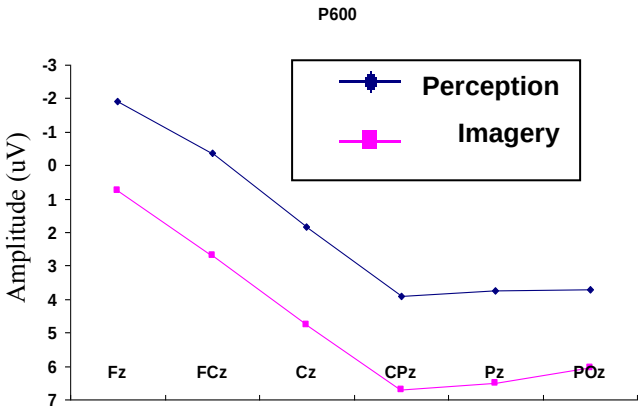


Figure 5.10 Mean amplitudes of six midline electrode sites (i.e. Fz, FCz, Cz, PCz, Pz and POz) of P600 component in Imagery and Perception conditions

The 2 (conditions) × 6 (sites) repeated measures ANOVA Showed significant main Condition and Site effects [F(1,17)=10.37, p=0.005] and sites [F(1.28,21.77)=14.10, p=0.002], but the interaction effect was not significant (p>0.050). Post-hoc tests showed that all sites were significantly different between two conditions (corrected p level <0.0005). The 2 (conditions) × 2 (laterality) × 7 (sites) repeated measures ANOVA showed significant findings in main Conditions and Sites effects [F(1,17)=9.69, p=0.006 & F(1.24,21.12)=16.43, p<0.0005, respectively]. The Condition × Sites and Laterality × Sites interaction effect were also found significant [F(2.24,38.01)=4.02, p=0.022 & F(3.32,56.48)=4.07, p=0.009]. Post-hoc tests showed that the mean amplitudes of imagery condition were significantly larger than those of perception condition at all the electrode sites on the

left hemisphere (except PO3 site), FC4 and C4 sites on the right hemisphere (corrected p level <0.005) (Appendix XXIII (j)).

The peak latencies of the midline electrode sites in the P600 component of the pain-free subjects ranged from 577.39 ms (SD=44.64 ms) at the POz site to 601.72 ms (SD=36.37 ms) at FCz site for perception condition and ranged from 596.28 ms (SD=35.43 ms) at POz site to 614 ms (SD=28.11 ms) at FCz site (Table 5.16). The 2 (conditions) × 6 (sites) repeated measures ANOVA showed a significant main effect of midline electrode sites [F(2.23,37.94)=4.43, p=0.016], but the post-hoc tests did not show between-group differences at corrected p level of 0.005 at any electrode sites. For lateral electrode sites, the three-way repeated ANOVA was built and did not indicate any significant findings (p>0.050) (Appendix XXIII (k)).

Summary of Electrophysiological Findings of Pain-free Subjects

While no between-condition effects were observed in P1 component, later components from P2 to P600 were shown to elicit more positive voltages in imagery trials compared to perception trials. The differences mainly existed in midline electrodes. No significant peak latency differences were revealed between imagery and perception conditions.

Table 5.6 The P1 mean amplitude (in μV) and peak latency (in ms) of the six midline electrodes and seven pairs of lateral (left and right) electrodes for Perception and Imagery trials of pain-free subjects

	Mean Amplitude		Peak Latency	
	Perception	Imagery	Perception	Imagery
Electrodes				
Midline				
Fz	14.90 (6.80)	14.84 (6.13)	**233.00 (21.57)**	**244.39 (20.49)**
FCz	16.36 (7.09)	16.42 (6.22)	230.83 (21.54)	237.22 (23.22)
Cz	16.28 (7.16)	16.54 (6.12)	230.89 (21.38)	235.56 (22.26)
CPz	**16.42 (7.97)**	**16.88 (7.05)**	**227.11 (21.24)**	235.11 (22.01)
Pz	13.29 (6.84)	14.02 (6.26)	229.83 (22.92)	**235.00 (20.90)**
POz	10.38 (6.08)	11.04 (5.63)	230.67 (22.95)	237.11 (19.86)
Left				
F3	12.45 (5.88)	12.08 (5.34)	235.17 (19.57)	**241.83 (20.68)**
FC3	**14.81 (7.21)**	**14.41 (6.16)**	229.50 (19.93)	239.94 (22.69)
C3	12.24 (6.60)	11.96 (5.65)	**229.33 (18.91)**	236.06 (19.67)
CP3	10.83 (6.50)	10.77 (5.77)	230.00 (18.31)	**234.72 (18.32)**
P3	8.52 (5.61)	9.27 (5.22)	**235.78 (21.64)**	238.50 (18.97)
PO3	5.46 (4.57)	5.89 (4.36)	233.94 (21.66)	235.06 (18.58)
T7	7.11 (4.54)	7.12 (4.00)	231.39 (17.80)	235.33 (17.85)
Right				
F4	11.52 (5.74)	11.17 (5.58)	**234.06 (22.21)**	**243.72 (20.61)**
FC4	**12.61 (6.35)**	**12.55 (6.02)**	232.11 (21.56)	240.33 (21.44)
C4	9.93 (7.14)	10.24 (6.29)	232.94 (19.74)	236.28 (23.37)
CP4	8.70 (5.95)	9.19 (5.26)	**231.67 (19.97)**	233.00 (26.24)
P4	8.11 (5.59)	9.19 (5.07)	231.78 (24.71)	232.61 (24.40)
PO4	6.23 (5.40)	7.02 (5.08)	223.33 (28.07)	**228.17 (29.50)**
T8	4.47 (5.13)	4.75 (5.00)	232.00 (17.60)	236.50 (19.75)

Key: Standard deviations are in parenthesis; bold figure indicates the site with the peak amplitude(s)

Table 5.7 The P2 mean amplitude (in μV) and peak latency (in ms) of the six midline electrodes and seven pairs of lateral (left and right) electrodes for Perception and Imagery trials of pain-free subjects

	Mean Amplitude		Peak Latency	
	Perception	Imagery	Perception	Imagery
Electrodes				
Midline				
Fz	11.35 (6.90)	13.92 (6.32)	**289.83 (21.90)**	**290.39 (16.65)**
FCz	13.01 (7.31)	15.69 (6.59)	291.28 (22.53)	296.89 (19.09)
Cz	13.75 (6.76)	16.31 (6.05)	296.67 (21.97)	297.89 (19.79)
CPz	**14.80 (7.63)**	**17.17 (6.97)**	299.50 (21.72)	300.44 (21.22)
Pz	12.43 (6.37)	14.63 (6.08)	304.28 (20.66)	304.00 (20.23)
POz	10.35 (5.89)	12.34 (5.75)	**304.89 (22.02)**	**304.61 (20.80)**
Left				
F3	9.06 (5.42)	11.23 (4.87)	**290.22 (21.81)**	291.94 (19.63)
FC3	**11.06 (6.15)**	**13.48 (5.73)**	291.00 (21.64)	**291.89 (19.73)**
C3	9.67 (4.78)	11.31 (5.05)	300.89 (19.77)	299.39 (22.10)
CP3	9.33 (5.46)	10.66 (6.00)	304.89 (17.54)	305.39 (20.81)
P3	9.13 (5.39)	11.09 (5.75)	311.56 (22.51)	309.67 (20.95)
PO3	6.47 (4.78)	7.93 (5.59)	**316.22 (21.63)**	**314.72 (20.94)**
T7	4.82 (3.88)	5.78 (3.85)	300.17 (22.44)	297.44 (24.24)
Right				
F4	8.48 (6.35)	10.45 (6.12)	**291.61 (24.64)**	296.72 (20.54)
FC4	**9.48 (6.39)**	**11.95 (5.65)**	292.56 (23.98)	**295.39 (18.29)**
C4	9.22 (6.13)	11.08 (5.11)	304.61 (21.85)	303.39 (22.23)
CP4	8.99 (5.42)	10.71 (4.29)	307.83 (22.96)	309.06 (19.80)
P4	8.89 (5.42)	10.97 (4.97)	312.11 (22.13)	312.17 (19.97)
PO4	6.80 (5.11)	8.38 (4.82)	**314.67 (21.71)**	**313.00 (21.38)**
T8	3.72 (4.40)	5.03 (4.63)	300.94 (23.16)	303.89 (20.38)

Key: Standard deviations are in parenthesis; bold figure indicates the site with the peak amplitude(s)

Table 5.8 The P300 mean amplitude (in μV) and peak latency (in ms) of the six midline electrodes and seven pairs of lateral (left and right) electrodes for Perception and Imagery trials of pain-free subjects

	Mean Amplitude		Peak Latency	
	Perception	Imagery	Perception	Imagery
Electrodes				
Midline				
Fz	3.62 (5.68)	5.86 (4.47)	356.11 (10.50)	356.72 (12.51)
FCz	4.97 (5.41)	7.50 (4.04)	**355.44 (10.62)**	356.28 (12.43)
Cz	6.80 (5.11)	9.17 (4.21)	355.67 (10.51)	**355.39 (12.63)**
CPz	**8.74 (5.94)**	**10.83 (4.93)**	357.00 (10.36)	355.94 (13.44)
Pz	7.79 (5.75)	9.67 (5.05)	357.06 (10.63)	357.11 (13.65)
POz	7.17 (5.26)	8.70 (4.74)	**358.61 (12.45)**	**358.83 (15.14)**
Left				
F3	3.19 (4.29)	4.79 (3.38)	357.22 (10.84)	359.61 (16.75)
FC3	4.16 (4.63)	6.21 (3.71)	**356.11 (10.64)**	357.89 (14.93)
C3	4.95 (3.53)	6.88 (3.64)	357.94 (11.75)	357.33 (14.86)
CP3	5.12 (3.73)	6.78 (4.34)	360.89 (15.12)	**356.89 (14.45)**
P3	**6.58 (4.15)**	**8.22 (4.56)**	358.89 (13.18)	360.78 (17.66)
PO3	4.78 (3.31)	5.84 (3.98)	**363.33 (15.99)**	361.78 (17.42)
T7	2.05 (2.78)	2.86 (2.33)	363.06 (19.35)	**363.39 (18.53)**
Right				
F4	2.53 (5.35)	4.37 (4.71)	357.33 (10.54)	358.33 (16.04)
FC4	3.05 (5.53)	5.48 (4.46)	**356.72 (10.78)**	**356.61 (12.78)**
C4	5.48 (5.13)	7.06 (4.22)	358.00 (10.44)	359.22 (15.02)
CP4	5.69 (4.79)	7.44 (4.32)	358.56 (12.20)	357.56 (15.79)
P4	**6.72 (5.15)**	**8.27 (4.72)**	358.72 (12.52)	362.06 (19.27)
PO4	5.45 (4.82)	6.43 (4.66)	360.06 (12.29)	363.56 (20.86)
T8	2.05 (3.89)	3.25 (3.85)	**361.28 (17.61)**	**370.17 (23.28)**

Key: Standard deviations are in parenthesis; bold figure indicates the site with the peak amplitude(s)

Table 5.9 The N400 mean amplitude (in μV) and peak latency (in ms) of the six midline electrodes and seven pairs of lateral (left and right) electrodes for Perception and Imagery trials of pain-free subjects

	Mean Amplitude		Peak Latency	
	Perception	Imagery	Perception	Imagery
Electrodes				
Midline				
Fz	**-5.30 (6.39)**	**-3.84 (6.70)**	**462.00 (15.58)**	**459.61 (15.95)**
FCz	-3.94 (5.64)	-2.19 (6.04)	456.72 (19.35)	458.50 (17.84)
Cz	-1.86 (4.57)	-0.32 (4.72)	456.78 (20.40)	458.78 (17.63)
CPz	0.33 (4.57)	1.76 (4.76)	457.89 (20.87)	456.61 (18.16)
Pz	0.27 (5.07)	1.45 (4.90)	456.06 (21.26)	**452.83 (19.48)**
POz	0.49 (4.79)	1.46 (4.70)	**455.72 (21.04)**	453.00 (19.29)
Left				
F3	**-4.95 (5.44)**	**-3.97 (5.68)**	**458.06 (17.38)**	**462.17 (17.57)**
FC3	-4.22 (5.25)	-2.78 (5.82)	454.17 (19.73)	459.89 (18.76)
C3	-1.69 (2.74)	-0.57 (3.28)	454.00 (21.13)	453.17 (21.56)
CP3	-1.14 (2.35)	-0.26 (3.31)	454.06 (21.34)	**448.33 (23.07)**
P3	0.97 (3.56)	1.89 (4.09)	448.28 (22.33)	455.94 (19.33)
PO3	0.21 (2.81)	0.82 (3.47)	**447.22 (21.67)**	449.11 (20.37)
T7	-3.13 (3.08)	-2.76 (2.96)	452.44 (20.44)	458.22 (19.63)
Right				
F4	**-3.84 (6.70)**	**-4.90 (6.89)**	459.72 (17.95)	**461.72 (13.44)**
FC4	-2.19 (6.04)	-3.75 (6.45)	**462.39 (15.35)**	457.11 (16.76)
C4	-0.32 (4.72)	-0.31 (4.54)	458.67 (18.14)	457.89 (19.46)
CP4	1.76 (4.76)	0.76 (4.21)	454.94 (20.26)	457.22 (18.16)
P4	1.45 (4.90)	2.00 (4.54)	451.17 (22.10)	453.78 (20.88)
PO4	1.46 (4.70)	1.11 (3.64)	**444.61 (20.70)**	**451.00 (19.79)**
T8	-3.84 (6.70)	-2.33 (3.74)	456.39 (18.46)	458.17 (20.32)

Key: Standard deviations are in parenthesis; bold figure indicates the site with the peak amplitude(s)

Table 5.10 The P600 mean amplitude (in μV) and peak latency (in ms) of the six midline electrodes and seven pairs of lateral (left and right) electrodes for Perception and Imagery trials of pain-free subjects

	Mean Amplitude		Peak Latency	
	Perception	Imagery	Perception	Imagery
Electrodes				
Midline				
Fz	-1.93 (5.77)	0.76 (5.76)	596.67 (34.58)	612.67 (30.08)
FCz	-0.38 (4.83)	2.70 (5.03)	**601.72 (36.37)**	**614.39 (28.11)**
Cz	1.82 (4.20)	4.78 (4.50)	587.00 (47.97)	609.06 (29.55)
CPz	**3.92 (4.23)**	**6.71 (4.25)**	580.50 (50.55)	602.33 (33.16)
Pz	3.74 (4.71)	6.49 (4.82)	582.83 (46.05)	597.94 (39.37)
POz	3.72 (4.41)	6.04 (4.37)	**577.39 (44.64)**	**596.28 (35.43)**
Left				
F3	-2.05 (4.55)	0.25 (4.99)	591.50 (38.48)	593.78 (45.63)
FC3	-1.07 (4.75)	1.80 (5.49)	**591.72 (38.67)**	**595.22 (40.21)**
C3	1.08 (2.79)	3.92 (3.97)	581.67 (46.21)	**588.50 (43.66)**
CP3	1.70 (3.03)	4.26 (4.91)	570.17 (40.50)	589.44 (43.54)
P3	**3.94 (3.96)**	**6.25 (5.16)**	**566.22 (42.52)**	590.89 (39.70)
PO3	3.04 (3.24)	4.70 (4.76)	568.72 (37.57)	588.78 (39.62)
T7	-0.62 (3.08)	0.80 (3.44)	586.89 (39.72)	**588.50 (50.52)**
Right				
F4	-2.68 (5.73)	-0.96 (5.81)	**603.33 (39.68)**	591.94 (50.80)
FC4	-2.03 (5.50)	0.67 (5.15)	602.28 (40.48)	**597.28 (48.36)**
C4	2.00 (4.23)	3.53 (3.78)	586.61 (50.51)	590.06 (43.50)
CP4	2.79 (3.77)	4.59 (3.89)	**580.28 (48.33)**	586.28 (40.09)
P4	**4.25 (4.50)**	**6.11 (4.81)**	580.78 (48.26)	**584.44 (41.88)**
PO4	3.68 (3.96)	4.98 (3.79)	583.56 (46.39)	574.67 (40.94)
T8	0.15 (4.04)	0.27 (3.97)	595.17 (48.07)	597.61 (46.04)

Key: Standard deviations are in parenthesis; bold figure indicates the site with the peak amplitude(s)

Dipole Sourcing Analysis of Cognition-related ERP Components

Source analysis on the results from the pain-free subjects was conducted using Curry 6.0.2 software. Since P2 component was hypothesized as the initiation of cognitive process of focused attention followed by image generation, ICA was applied on the time windows of 273 to 341 ms, 349-409 ms, 411-475 ms, and 507-650 ms, corresponding to the identified P2, P3, N400 and P600. The sources of P200 components were found to locate at the right cingulate gyrus (BA24) (x=3.5, y=-15.0, z=34.8), and the right culmen of cerebellum (x=2.0, y=-38.3, z=5.8). The variance explained by the solution was 90.14%, falling within the satisfactory level (residual deviation = 31.4%). Maximal dipole strength was 341.0 ms within the chosen time window. Three dipole sources were obtained for P300: left culmen of cerebellum (x=-3.0, y=-69.6, z=-7.8), left fusiform gyrus, (BA19) (x=-21.7, y=-65.3, z=-4.8), right parahippocampal gyrus (BA37) (x=24.7, y=-44.0, z=-5.9). The variance explained by these 3 dipoles was 96.73% (residual deviation=18.1%). The peak strength appeared to be at 378.0 ms post-stimulus. There were also three dipoles revealed for N400: left posterior cingulate gyrus (BA30) (x=-5.4, y=-59.7, z=4.5), left lingual gyrus (BA19) (x=-24.7, y=-58.6, z=5.9) and right caudate tail (x=19.3, y=-35.7, z=15.8). The variance explained by these dipoles were 97.59% (residual deviation = 15.5%). The strength peaked at 462.0 ms after the onset of the stimulus. Finally, the dipoles identified for P600were: left culmen (x=-5.3, y=-61.6, z=-2.2), left lingual (BA19) (x=-24.1, y=-63.6, z=1.7), right pulvinar of the thalamus (x=21.0, y=-33.5, z=8.8). The dipole strength's maximum was found to occur at 519.0 ms post-stimulus. The variance explained by them was 98.02% (residual deviation = 14.1%). Figures 5.11

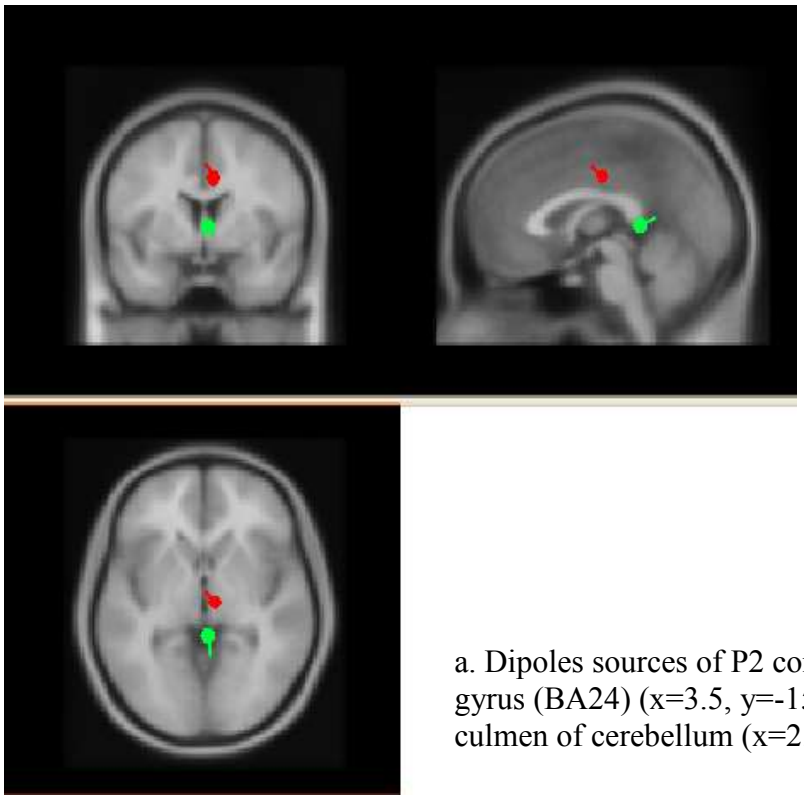
(a – d) show the locations of the dipoles identified or P2 to P600 components for the pain-free subjects.

Relationship between Normalized Pain NRS Ratings and Electrophysiological Data

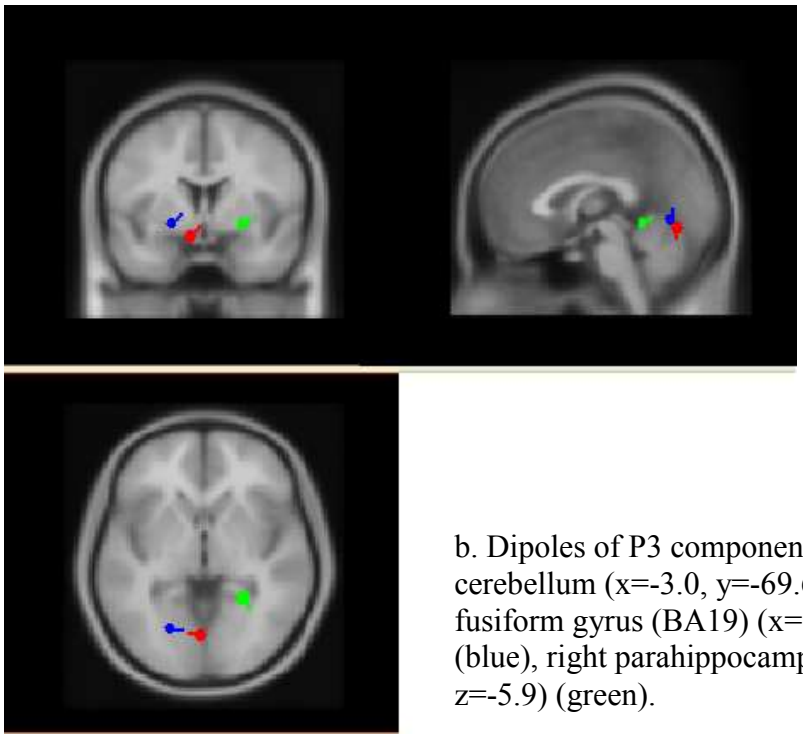
Pearson's correlation analysis was used to test the relationships between mean amplitudes of four later ERP components, i.e. P2, P3, N400 and P600 and the normalized NRS ratings for the pain-free subjects. This purpose was to shed light on the possible contribution of specific components to pain attenuation.

For P2, the normalized NRS ratings of the recalled level 3 nociceptive image was significantly correlated with amplitudes of CP3 ($r = -0.534$, $p<0.050$) and P3 ($r = -0.441$, $p<0.050$), whereas those of levels 1, 3 and 5 were moderately correlated with F4 and FC4 ($-0.469 > r > -0.549$, $p<0.050$). For P3, the normalized NRS ratings of level 1 was significantly correlated with amplitudes of FCz and Cz ($-0.497 > r > -0.582$, $p<0.050$). The normalized NRS rating of level 5 was also moderately correlated with the Cz electrode voltage ($r=-0.514$). Furthermore, the N400 amplitudes were found to be correlated with voltages elicited at a wider range of sites. The level 5 normalized NRS rating were associated with CP3, P3, FCz, F4 and FC4 voltages ($-0.417 > r > -0.549$, $p<0.050$) whilst that of level 1 was associated with Cz, F4 and FCz voltages ($-0.457 > r > -0.570$, $p<0.050$). For P600, only level 1 normalized NRS ratings were correlated with the average voltage of Cz ($r = -0.489$, $p<0.050$).

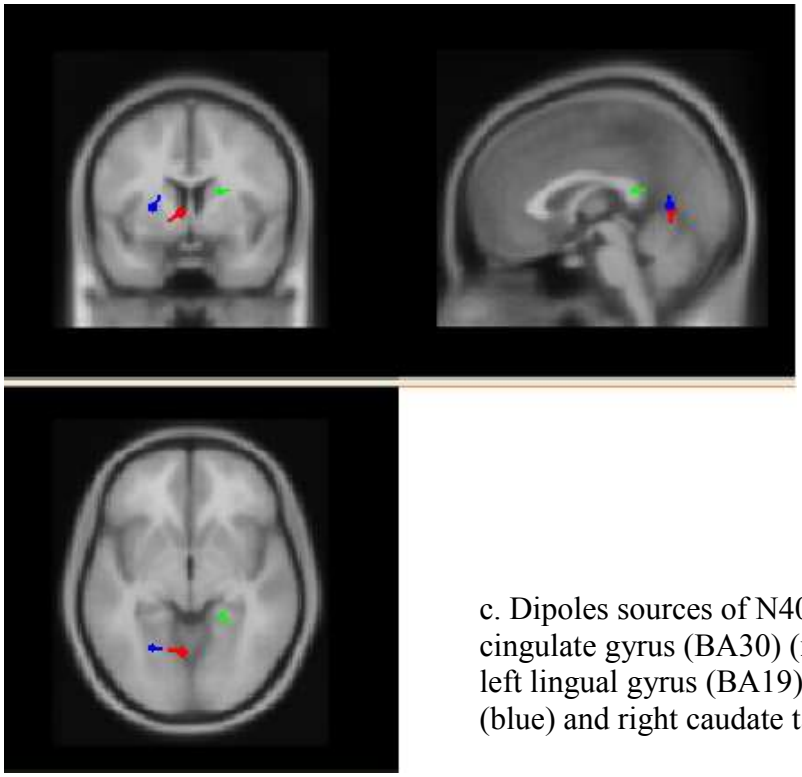
Figures 5.11 (a – d) The dipole sources of P2, P3, N400 and P600 of participants in pain-free subjects (n =18)



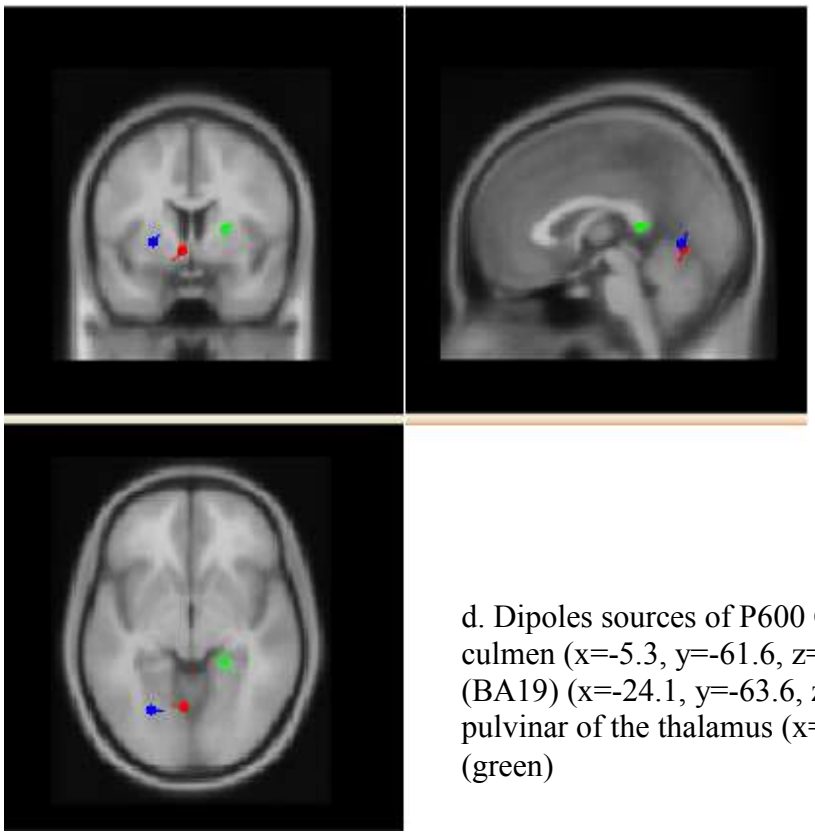
a. Dipoles sources of P2 components: right cingulate gyrus (BA24) (x=3.5, y=-15.0, z=34.8) (red), and right culmen of cerebellum (x=2.0, y=-38.3, z=5.8) (green).



b. Dipoles of P3 components: left culmen of cerebellum (x=-3.0, y=-69.6, z=-7.8) (red), left fusiform gyrus (BA19) (x=-21.7, y=-65.3, z=-4.8) (blue), right parahippocampus gyrus (x=24.7, y=-44.0, z=-5.9) (green).



c. Dipoles sources of N400 components: left posterior cingulate gyrus (BA30) (x=-5.4, y=-59.7, z=4.5) (red), left lingual gyrus (BA19) (x=-24.7, y=-58.6, z=5.9) (blue) and right caudate tail (x=19.3, y=-35.7, z=15.8)



d. Dipoles sources of P600 Components: left culmen (x=-5.3, y=-61.6, z=-2.2) (red), left lingual (BA19) (x=-24.1, y=-63.6, z=1.7) (blue), right pulvinar of the thalamus (x=21.0, y=-33.5, z=8.8) (green)

RESULTS OF STUDY TWO: MODULATION OF PAIN PERCEPTION IN CHRONIC PAIN SUBJECTS

Demographic Data

Seventeen people with chronic low back pain (mean pain duration = 4.1 years; range = 4 months and 10 years) (male = 7; mean age = 41.5 years; SD = 7.9 years) were recruited from the Kowloon East Pain Clinic located in the United Christian Hospital, Hospital Authority. They were invited to the main study when they were attending the consultation appointment or follow-up session. The researcher attended the medical consultation for screening patient subjects who fulfilled the inclusion criteria. The self-reported average pain level on their LBP condition based on an 11-point scale during the experiment was 5.0 (SD=2.5) (out of 10). Eight subjects (47.1%) were married, 8 (47.1%) were single and one (5.9%) was divorced. Twelve of them had secondary or matriculation education. Fourteen of them had full-time or part-time jobs. The difference in mean age or education level was not significant between the patient subject and pain-free groups [$t(28.11)=-1.71$, $p>0.050$; $\chi(3)=5.02$, $p>0.050$, respectively]. Table 5.11 summarizes demographic data of both groups of subjects. Appendix XXIV summarizes medical history of each subject with chronic LPB. The study protocol was approved by Ethics Committee of Hong Kong Hospital Authority.

Results of Pain History Questionnaire in Chronic Pain Group

The mean number of years for the pain history of patient subjects was 4.1 years (range = 3 – 168 months). The average pain intensity reported was 5.0 (SD=2.5)

(out of 11) and the worst pain intensity reported was 6.0. (SD=2.2). The modal response for pain occurrence was “very often” on a six-point Likert scale. In the past one month, the majority (52.2%) of the patient subjects rated that the pain “lasts for several hours” when it came. The modal rating for general healthy was “average” (“4” in the 5-point Likert scale). These subjects received professional attention for their conditions. In the questionnaire they indicated that over the last six week period that the most common service was physiotherapy and occupational therapy (mean hours=6.1 (SD=10.9)). The next most common service was clinical psychology (mean hours=1.4 hours (SD=2.00)). Table 5.12 summarizes the results obtained from the Pain History Questionnaire.

Results of pain history showed that the self-reported average and worst pain levels on patient subjects’ own LBP condition was 5.0 (out of 11) and 6.0 (SD=2.2) respectively. This suggested that the patient subjects were experiencing moderate pain during the experiment. Both scores fell within the midrange of the scale. In terms of the pain ordinal scale, the majority 52.9% (n=9) rated that the pain condition occurred “quite often” (3) to very often (4) (median=3.7) and 70.6% (n=12) the severity “moderate” (3) to “severe” (4) (median=3.4). The pain duration would last for “several hours” (3) to “one or two days” (4) (median=3.6). For their engagement in activities, the mean score for “physical fatigue” was 2.2 (SD=1.4), falling between “sometimes” (2) and “quite often” (3), the mean score for “full of energy” was 1.2 (SD=0.6), falling between “rarely” (1) and “sometimes” (2), mean scores of “tiredness” was found to be 3.2 (SD=0.7) between “quite often” (3) and “very often” (4). Furthermore, the mean scores of “having energy to perform daily activities” was 2.1 (SD=0.78), falling between “sometimes” (2) and “quite often” (3) and the mean scores of “full of stamina” was 1.4 (SD=0.7) falling between “rarely” (1) and

"sometimes" (2). The general health was 3.9 (SD=0.6) between the good and moderate anchors on the Likert scale. In terms of medical services receiving, the most visits was for tackling the orthopedic or pain problems (mean=6.5 visits (SD=12.3 visits) in 6 months) followed by receiving physiotherapy and occupational therapy (6.4 visits (SD=10.9 visits) in 6 months).

Table 5.11 Demographics of subjects in chronic pain and pain-free groups

	Patient Group (n = 17)	Pain-Free Group (n = 18)
Male (%)	7 (41.2)	7 (38.9)
Age (SD) (years)	41.5 (7.9)	35.3 (13.2)
Marital Status (%)		
Single	8 (47.1)	9 (50.0)
Married	8 (47.1)	9 (50.0)
Divorce	1 (5.9)	0 (0.0)
Educational Level (%)		
Secondary	9 (52.9)	4 (22.2)
Matriculation	3 (17.6)	2 (11.1)
Undergraduate	1 (5.9)	3 (16.7)
Postgraduate	4 (23.5)	9 (50.0)
Employment Status (%)		
Unemployed	1 (5.9)	0 (0.0)
Full-time	4 (23.5)	3 (16.7)
Part-time	10 (58.8)	9 (50.0)
Student	0 (0.0)	4 (22.2)
Housewife	2 (5.9)	1 (5.6)
Retired	0 (0.0)	1 (5.6)

Key: SD = standard deviation

Table 5.12 Summary of results of Pain History Questionnaire of patient subjects

Item	Possible Range	Mean (SD) / Median
Pain Duration (year)	–	4.05 (3.2)
Average Pain	1 – 11	5.03 (2.5)
Worst Pain	1 – 11	5.96 (2.2)
Pain Frequency #	0 – 5	3.7
Pain Intensity #	0 – 5	3.4
Pain Duration #	0 – 5	3.6
Physical Fatigue	1 – 5	2.0 (1.4)
Full of Energy	1 – 5	1.2 (0.6)
Tiredness	1 – 5	3.2 (0.7)
Having Energy to Perform Daily Activities	1 – 5	2.1 (0.8)
Full of Stamina	1 – 5	1.4 (0.7)
General Health	1 – 5	3.9 (0.6)
Professional Visits		
Medical Doctors	–	6.5 (12.3)
Psychatrist	–	1.2 (2.0)
Clinical Psychologist	–	1.4 (2.0)
Community Nurses	–	0.4 (1.5)
Physiotherapy / Occupational Therapy	–	6.4 (10.9)
Visit at Accident / Emergency Department	–	0.5 (1.7)
Length of Stay at Hospital (days)	–	1.6 (4.2)

Key: # Median score; SD = Standard deviation

NRS of Perception of the Recalled Nociceptive Image

For the chronic pain group, the minimal detectable stimulus, minimal painful sensation and very painful sensation were found to be 4.42 mA (SD=3.44 mA; minimum=0.60 mA; maximum=13.00 mA), 10.21 mA (SD=5.32 mA; minimum=3.50 mA; maximum=25.00 mA) and 20.79 mA (SD=7.17 mA; minimum=8.00 mA; maximum=31.00 mA), respectively. An independent t-test indicated a statistically significant difference between the patient and pain-free subjects in terms of the current corresponding to the very painful sensation level [$t(33) = -2.00$, $p<0.050$]. The patient subjects were shown to have higher sensory thresholds than the pain-free subjects. The mean NRS ratings on the recalled five-level nociceptive image of the chronic pain group ranged from 3.28 (SD=1.64) to 5.14 (SD=1.29) whereas those in perception trials ranged from 3.20 (SD=1.65) to 5.28 (SD=1.52). The normalized NRS ratings were between 0.08 (SD =0.58) and -0.15 (SD=0.66) from Level 1 to Level 5 nociceptive stimulus (Figure 5.12 and Table 5.13). The Condition (imagery versus perception) × Nociceptive levels (1 to 5) repeated measures ANOVA model revealed a significant Level effect in the chronic pain group [$F(1,30, 16.70)=52.01$, $p<0.001$]. The Condition main effect or Condition × Level interaction effects were statistically not significant ($p>0.050$). The Condition [$F(1,33)=6.98$, $p<0.050$] and Level effects [$F(1.29,34.85) = 75.58$, $p<0.01$] were statistically significant. No significant Condition × Level × Group interaction effects were found ($p>0.050$) (Appendices XXV (a) & (b)). Post-hoc contrast tests showed significant differences between the normalized NRS ratings of the pain intensity of the recalled levels 1 and 2 nociceptive images in chronic pain group [$F(1,16)=8.46$, $p<0.01$]. Similar to that in the pain-free group, the chronic pain subjects had a tendency of giving lower NRS

ratings in imagery than perception trials except for level 1 despite the non-significant findings (Figure 5.12). Significant difference in the normalized NRS ratings between imagery and perception trials was only found in the level 2 nociceptive stimulation in the chronic pain group ($t(16)=-2.21$, $p<0.050$). Another ΔNRS (levels 1 to 5) × Group (chronic pain versus pain-free) repeated measures ANOVA showed no significant main and interaction effects. The mean difference in the level 2 nociceptive stimulation is less than one point in an 11-point scale (NRS of 3.67 for imagery trials and NRS of 3.98 for perception, suggesting that the observed difference would likely be clinically non-significant.

Figure 5.12 Mean normalized NRS ratings of Imagery and Perception conditions of chronic pain and pain-free groups (error bars indicate standard errors of mean)

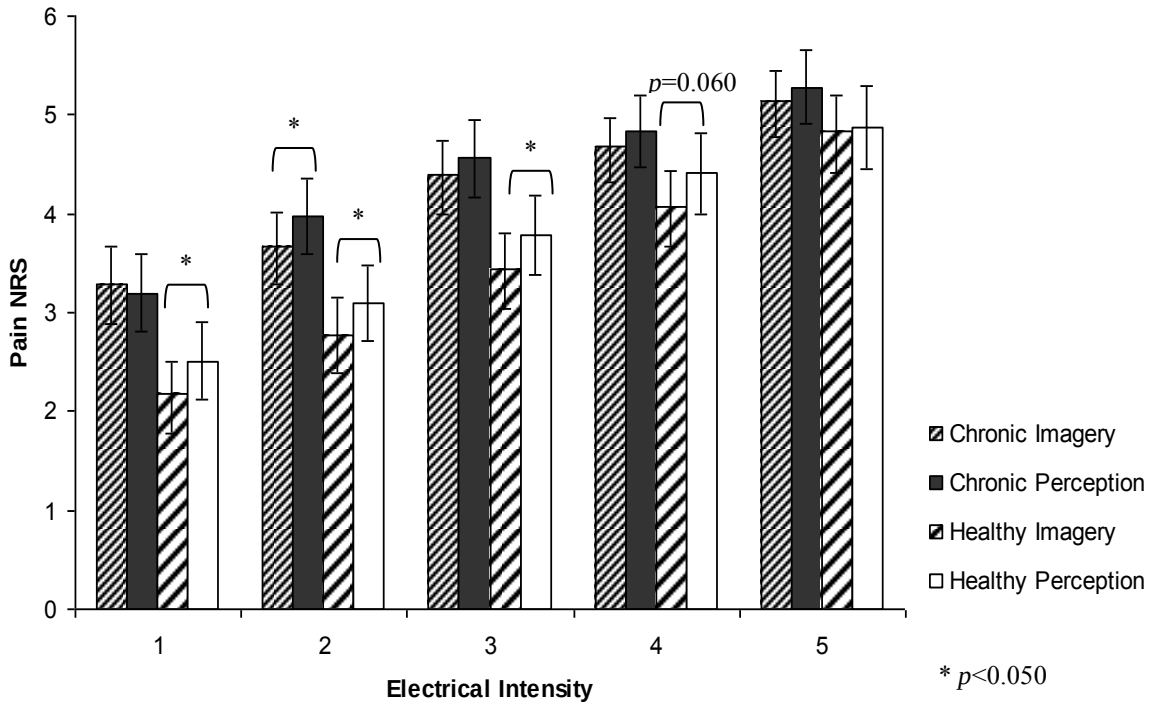


Table 5.13 Mean NRS score on pain intensity for Imagery and Perception conditions and normalized NRS scores (mean $NRS_{Imagery}$ – mean $NRS_{Perception}$) in patient and pair-free groups

	Nociceptive Stimuli				
	Level 1	Level 2	Level 3	Level 4	Level 5
Patient Group					
Imagery	3.28 (1.64)	3.67 (1.45)	4.40 (1.39)	4.68 (1.21)	5.14 (1.29)
Perception	3.20 (1.65)	3.98 (1.58)	4.56 (1.64)	4.83 (1.49)	5.28 (1.52)
Pain-free Group					
Imagery	2.17 (1.45)	2.77 (1.59)	3.43 (1.58)	4.07 (1.54)	4.83 (1.54)
Perception	2.51 (1.65)	3.10 (1.60)	3.79 (1.70)	4.41 (1.73)	4.87 (1.76)
Normalized NRS Ratings					
Patient Group	0.08	-0.31	-0.16	-0.15	-0.15
	(0.58)	(0.53)	(0.69)	(0.68)	(0.66)
Pain-free Group	-0.34	-0.34	-0.35	-0.34	-0.04
	(0.38)	(0.40)	(0.52)	(0.72)	(0.45)

Key: Standard deviation is in parenthesis ( ); Normalized NRS ratings = mean $NRS_{Imagery}$ – mean $NRS_{Perception}$

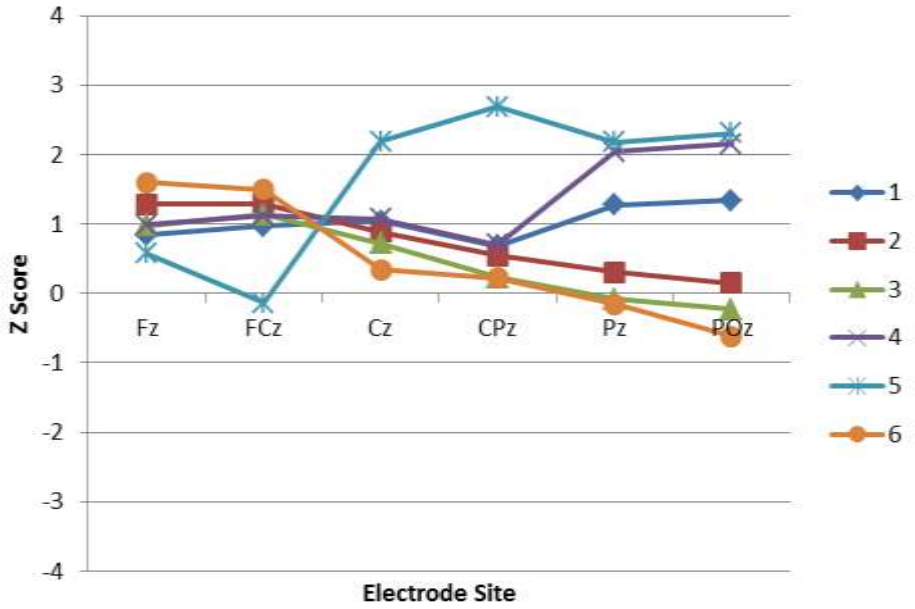
A review of the behavioral results indicated that not all patient subjects had obtained lower NRS ratings in the imagery condition (relative to perception condition). To reduce the heterogeneity of the patient subjects and hence obtaining meaningful interpretation of the results, patient subjects were further divided into two groups based on two criteria: (1) the relative amplitudes of the neurophysiological maker of focused attention, fronto-central P2 and (2) their behavioral responses in the focused attention and imagery process. For the first criterion, it was set in such a way that at least one of the mean amplitudes differences, imagery minus perception, chosen the frontal and central midline sites, i.e. Fz, FCz and Cz, needed to have the Z-score larger than +1.0 to be classified as undergone prominent focused attention. This

was under an assumption that larger amplitude of P2 component might be elicited in the imagery trials compared to the perception trials (Dowman, 2007a & b). For the second criterion, those who showed positive responses were classified into the respondent group whilst those who did not show positive responses were classified into the non-respondent group. The criteria set for identifying patient subjects with positive responses were a reduction in NRS ratings in the imagery condition (relative to the perception condition) in more than half of the trials in at least four levels of nociceptive stimuli. This four level condition was based on the fact that no patient subject showed NRS reduction in all five levels. Based on the two aforementioned classification criteria, 6 respondents and 11 non-respondents were identified. Figure 5.13 shows the z-scores of mean amplitude difference between imagery and perception of P2 component, i.e. the key marker of focused attention, across six midline sites of the respondents (A) and non-respondents (B).

The percentages of the imagery trials showing positive response in each level of nociceptive stimuli for the respondent and non-respondent patient subjects were computed (Table 5.14). They were found to be higher in the respondent than non-respondent patient subjects especially in the levels 1 to 3 nociceptive stimuli. Despite the small sample size, the between-group differences in the percentages of successful trials were statistically significant in the levels 2 and 3 nociceptive stimuli [Level 2: $t(15)=1.73$, $p=0.052$; Level 3 $t(15)=2.44$, $p=0.028$].

Figure 5.13 Z-scores of mean amplitude difference between imagery and perception (imagery minus perception) of P2 component across six midline sites of respondent (n=6) (A) and non-respondent patient subjects (n=11) (B)

(A)



(B)

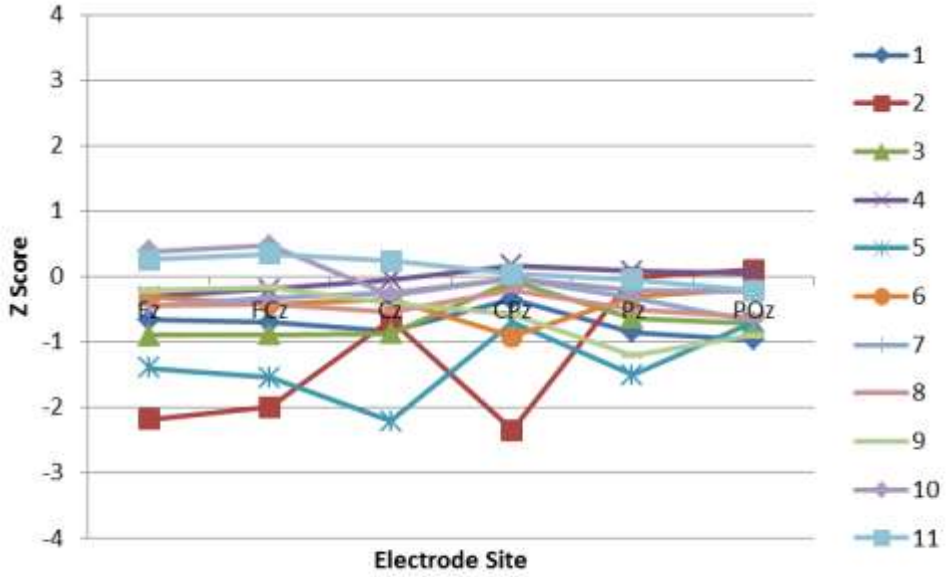


Table 5.14 Percentage of trials with positive responses in the five levels of nociceptive stimuli between respondent and non-respondent patient subjects (standard deviation in parenthesis)

	Nociceptive Stimuli				
	Level 1	Level 2	Level 3	Level 4	Level 5
Respondents	31.00	36.90	60.30	56.10	64.90
(%)	(7.70)	(40.50)	(47.50)	(48.30)	(39.90)
Non-respondents	6.60	9.60	20.60	45.20	63.80
(%)	(18.10)	(18.70)	(20.40)	(26.70)	(31.00)

The voltages of the sub-painful and painful thresholds for each of the respondent and non-respondent patient subgroups were computed. For the respondents, the minimal detectable stimulus, minimal painful sensation and very painful sensation were respectively 5.00 mA (SD = 4.52 mA; minimum = 1.00 mA; maximum = 13.00 mA), 10.58 mA (SD = 7.41 mA; minimum = 6.00 mA; maximum = 25.00 mA) and 16.50 mA (SD = 7.76 mA; minimum = 8.00 mA; maximum = 31.00 mA), respectively. The threshold values for the non-respondent patient subgroup were 4.100 mA (SD = 2.89 mA; minimum = 0.60 mA; maximum = 9.00 mA), 10.000 mA (SD = 4.41 mA; minimum = 3.50 mA; maximum = 19.00 mA) and 23.14 mA (SD = 4.32 mA; minimum = 22.00 mA; maximum = 33.00 mA), respectively. The non-respondent patient subgroup had marginally higher “very painful” threshold than the respondent counterparts [$t(15)=-2.02$, $p<0.050$].

The self-rated average and maximum pain ratings (in the past one month) for the respondent patient subgroup were 6.42 (SD=2.60) and 6.79 (SD=2.15), respectively. Those for the non-respondent patient subgroup were 4.20 (SD=1.83) and 5.50 (SD=2.54). The respondent patient subjects were found to have a marginally significant lower NRS ratings on the recalled nociceptive images than the non-

respondent patient subjects [t(14)=2.01, p<0.055]. The between-subgroup differences using a three-way repeated measures ANOVA: 2 conditions × 5 pain levels × 2 groups showed no significant differences [F(1,15)=1.90, p>0.05] ((Figure 5.14, Table 5.15, & Appendices XXV (c) & (d)). Repeated measures ANOVA: 2 conditions × 5 pain levels were constructed separately for each of the respondent and non-respondent patient subgroups. For the respondent patient subgroup, the level of nociceptive stimuli effect on the NRS ratings was statistically significant [F(1.32, 6.60) = 24.40, p<0.001]. Other main and interaction effects were not statistically significant (p>0.050). Similar results were revealed in the non-respondent patient subgroup where only the pain level effect was statistically significant [F(1.242,12.425)=49.143, p<0.001]. Among the respondent patient subjects, the only significant difference was found in the level 2 [t(5)=-3.31, p=0.021] in which the NRS ratings on the recalled nociceptive image in the imagery trials were lower than those in the perception trials. No between-condition differences in the NRS ratings were revealed among the non-respondent patient subjects (p>0.050). The comparisons based on the normalized NRS scores showed no significant between-subgroup differences [F(1,15)=0.014, p>0.050)]. Post-hoc tests also did not show any significant between-subgroup differences across the five intensity levels (p>0.050) (Appendix XXV (d)).

Figure 5.14 Mean and normalized NRS ratings of the five levels of recalled nociceptive images for Imagery and Perception conditions of respondents and non-respondent patient subjects (error bars indicate standard errors of mean)

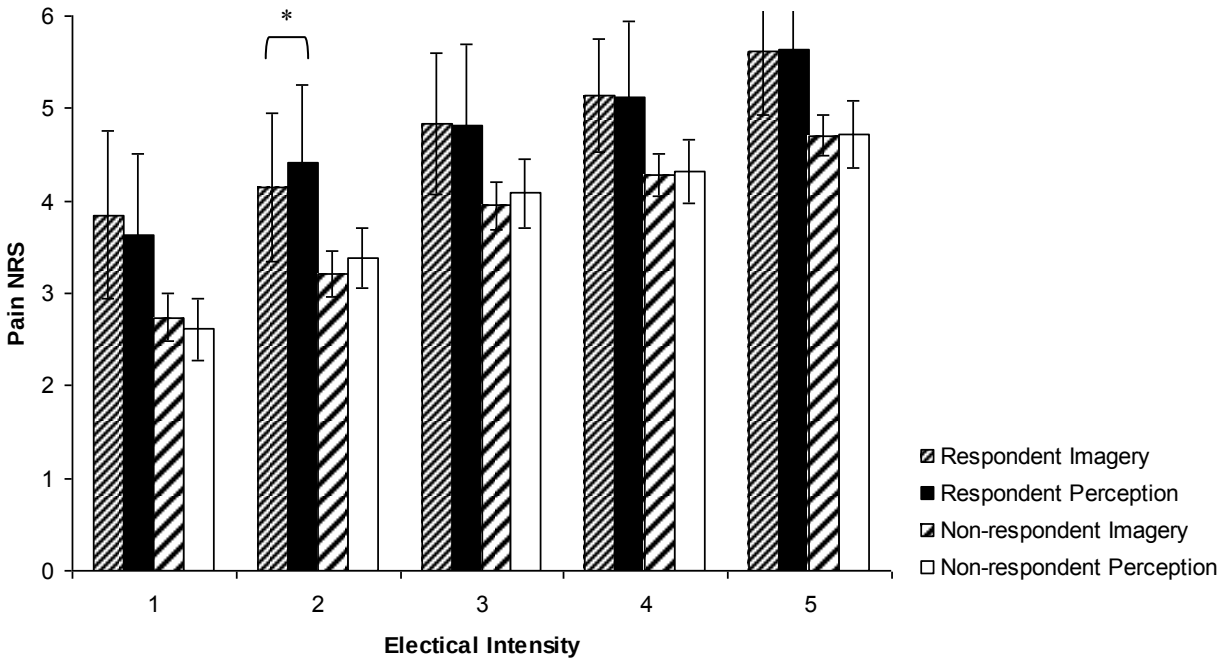


Table 5.15 Mean and normalized NRS ratings on the five levels recalled nociceptive images for Imagery and Perception conditions between the patient subjects (two subgroups) and pain-free subjects

	Intensity Levels				
	Level 1	Level 2	Level 3	Level 4	Level 5
Respondent Patient Subjects					
Imagery	3.85 (2.24)	4.15 (1.97)	4.83 (1.88)	5.14 (1.50)	5.62 (1.69)
Perception	3.64 (2.14)	4.41 (2.08)	4.81 (2.16)	5.13 (1.97)	5.64 (1.90)
Non-respondent Patient Subjects					
Imagery	2.74 (0.87)	3.21 (0.80)	3.95 (0.87)	4.28 (0.77)	4.71 (0.74)
Perception	2.61(1.12)	3.38 (1.07)	4.08 (1.21)	4.32 (1.13)	4.72 (1.21)
Pain-free Subjects					
Imagery	2.17 (1.45)	2.77 (1.59)	3.43 (1.58)	4.07 (1.54)	4.83 (1.54)
Perception	2.51 (1.65)	3.10 (1.60)	3.79 (1.70)	4.41 (1.73)	4.87 (1.76)
$NRS_{Imagery} - NRS_{Perception}$					
Chronic Respondent	0.21 (0.49)	-0.27 (0.20)	0.02 (0.55)	0.01 (0.96)	-0.03 (0.40)
Chronic Non-respondent	0.12 (0.63)	-0.17 (0.66)	-0.13 (0.73)	-0.004 (0.55)	0.01 (0.82)
Pain-free Group	-0.34 (0.38)	-0.34 (0.40)	-0.35 (0.52)	-0.34 (0.72)	-0.04 (0.45)

Key: Standard deviation is in parenthesis ( )

Pain-related Questionnaires of Chronic Pain Patient Subjects

The mean CSQ domain scores ranged from 14.82 (SD=5.60) for Reinterpreting the Pain Sensations to 22.76 (SD=5.80) for Coping Self-statements (Table 5.16).The non-respondent patient subjects had significantly lower scores than the respondent patient subjects on the Catastrophizing subscale of CSQ [$t(15)=3.00$, $p<0.050$]. No significant differences were revealed in the mean scores on the other six subscales of CSQ.

Results of Neuropsychological Tests of Patient and Pain-free Subjects

For the patient subjects, the mean scores on the four subtests of VVIQ ranged from 3.32 (SD=0.92) (Face) to 3.40 (SD=0.98) (Sunrise). No significant differences were found among the four subscale mean scores and the total scores on the VVIQ ($p>0.050$). For the Stroop Test, the total time of WR Test of the patient subjects was 50.39 s (SD=7.86 s) whilst the mean error and mean self-correction errors were 0.06 (SD=0.24) and 0.65 (SD=1.17) respectively (Table 5.17). For the CN Test, the average total time was 68.14 s (SD=12.28 s) with mean error and mean self-correction error as 0.18 (SD=0.39) and 1.88 (SD=1.17) respectively. For the IN Test, the average time for completion was 137.59 (SD=45.59) whilst the mean error and mean self-correction error were 1.06 (SD=1.56) and 3.41 (SD=2.35) respectively. For the secondary measures, the difference scores of IN – WR, IN – CN and CN – WR were 87.21 s (SD=46.80 s), 69.45 s (SD=43.43 s) and 17.75 s (SD=8.32 s), respectively. The proportion scores of (IN – WR) / WR, (IN – CN) / CN, and (CN – WR) / WR were 0.35 (SD=0.18), 1.05 (SD=0.64) and 0.36 (SD=0.18) respectively. Significant

differences between the respondent and non-respondent patient subgroups were only found in the proportional scores of (IN – CN) / CN [t(32)=2.02, p<0.050]. For the Arrow Test (compatible test), the mean reaction time scores for the patient subjects were 737.95 ms (SD=93.33 ms) and the mean accuracy rate was 0.70 (SD=0.26). The mean composite score was 0.10 (SD=0.05). The mean reaction time in the incompatible test were 790.48 ms (SD=89.23 ms) whilst the mean accuracy rate was 0.63 (SD=0.24). This resulted in a composite score of 0.08 (SD=0.04). Significant patient subject subgroup differences were revealed in the interferences scores [t(32)=2.308, p<0.050] with respondent patient subjects (mean = 42.32; SD=47.81) had higher scores than the non-respondent patient subjects (mean=56.61; SD=47.10). Other differences in the results of the Stroop Test and Arrow test between the respondent and non-respondent patient subjects were statistically not significant (p>0.050).

Table 5.16 Results of CSQ subscales of respondent and non-respondent patient subjects

Questionnaire Items	Max. Scores	Scores		
		All Subjects	Respondents	Non-respondents
Cognitive Strategies Questionnaire				
Diverting attention	36	17.29 (5.35)	19.33 (3.14)	16.18 (6.08)
Reinterpreting the pain sensations	36	14.82 (5.60)	15.17 (5.00)	14.64 (6.14)
Catastrophising	36	15.82 (5.60)	20.33 (6.28)	13.36 (3.41)
Ignoring sensations	36	19.06 (6.54)	19.00 (6.26)	19.09 (6.99)
Praying or hoping	36	16.82 (5.04)	19.83 (4.92)	15.18 (4.49)
Coping self-statements	36	22.76 (5.80)	22.83 (4.79)	22.73 (6.51)
Increased Behavioral Activities	36	18.71 (5.93)	21.00 (4.05)	17.45 (6.58)

Note: Standard deviation is in parenthesis ( ); Max. Scores = maximum scores

Table 5.17 Results of different neuropsychological tests for patient subjects (two subgroups) and pain-free subjects

Test	Patient Subject Group			Pain-free Group
	All	Respondent	Non-respondent	
VVIQ				
Face	3.32 (0.92)	3.04 (0.40)	3.48 (1.10)	3.69 (1.24)
Sunrise	3.40 (0.98)	3.13 (0.77)	3.55 (1.09)	3.54 (1.08)
Shop	3.35 (0.73)	3.46 (0.51)	3.30 (0.85)	3.50 (1.12)
Scenery	3.38 (1.08)	3.67 (1.07)	3.23 (1.10)	3.31 (1.24)
Total	3.36 (0.78)	3.32 (0.45)	3.39 (0.93)	3.51 (1.07)
Stroop Test				
Word Reading				
Total Time (sec.)	50.39 (7.86)	49.22 (8.65)	51.03 (7.76)	49.28 (12.81)
Error	0.06 (0.24)	0.17 (.41)	0.00 (0.00)	0.06 (0.24)
Self-correction	0.65 (1.17)	0.00 (0.00)	1.0000 (1.341)	0.47 (0.72)
Color Naming				
Total Time (sec.)	68.14 (12.28)	65.32 (15.33)	69.68 (10.78)	70.33 (15.38)
Error	0.18 (0.39)	0.00 (0.00)	0.27 (0.47)	0.35 (0.79)
Self-correction	1.88 (1.17)	2.00 (1.10)	1.82 (1.25)	1.29 (1.79)
Incongruent Color Naming				
Total Time (sec.)	137.59 (45.59)	126.78 (42.71)	143.49 (48.02)	121.65 (29.31)
Error	1.06 (1.56)	1.33 (1.75)	.91 (1.51)	1.88 (2.00)
Self-correction	3.41 (2.35)	2.00 (1.90)	4.18 (2.27)	2.47 (2.78)
Difference Score				
IN – WR (second)	87.21 (46.80)	77.57 (36.31)	92.46 (52.52)	72.36 (21.16)
IN – CN (second)	69.45 (43.43)	61.47 (34.60)	73.81 (48.58)	51.32 (17.00)
CN – WR (second)	17.75 (8.32)	16.10 (7.62)	18.65 (8.90)	21.05 (9.35)
Proportional Score				
(IN – WR) / WR	0.35 (0.18)	1.55 (0.56)	1.96 (1.46)	1.51 (0.43)
(IN – CN) / CN	1.05 (0.64)	0.95 (0.47)	1.10 (0.73)	0.73 (0.20)*
(CN – WR) / WR	0.36 (0.18)	0.32 (0.11)	0.38 (.21)	0.46 (0.24)
Arrow Test				
Compatible condition				
Reaction Time (ms)	737.95(93.33)	720.78 (35.73)	744.82	729.20 (87.83)
Accuracy	0.70 (0.26)	0.81 (0.10)	(109.42)	0.63 (0.28)
Composite	0.10 (0.05)	0.11 (0.02)	0.66 (0.30)	0.09 (0.05)
Incompatible condition			0.10 (0.05)	
Reaction Time (ms)				
Accuracy	790.48 (89.23)	763.10 (76.79)		730.44(109.78)
Composite	0.63 (0.24)	0.6354 .259	801.43 (95.22)	0.61 (0.29)
Interference score	0.08 (0.04)	0.09 (0.04)	0.63 (0.25)	0.09 (0.05)
	52.53 (45.91)	42.32 (47.81)	0.08 (0.04)	12.70 (14.10)*
			56.61 (47.10)	

WR = Wording Reading; CN = Coloring Naming; IN = Incongruent Color Naming; RT = Reaction Time; Composite score = accuracy / reaction time; Inference score = Incompatible RT – Compatible RT; * t-test: $p<0.050$

Results of ERP Componential Analysis

The five time windows identified for the patient subjects were P1 (177-265 ms), P2 (273-341 ms), P3 (349-409 ms), N400 (411-475 ms) and P600 or later positive component (LPC) (507-650 ms) (Figures 5.15 and 5.16). They were found to be similar to those revealed among the pain-free subjects (p. 103).

Summary of ERP Analysis between Patient and Pain-free Subjects

There were two types of models used in the analyses: midline and lateral sites. Two-way repeated measures ANOVA with 2 (conditions) × 6 (midline sites) and three-way repeated measures ANOVA with 2 (conditions) × 2 (laterality) × 7 (midline sites) were conducted on the mean peak amplitudes for all patient subjects. Besides, three-way repeated measures ANOVA with 2 (conditions) × 6 (midline sites) × 2 (groups) and four-way repeated measures ANOVA with 2 (conditions) × 2 (laterality) × 7 (midline sites) × 2 (groups) were built to test the significance of the main and interaction effects. As this chapter focuses on patient subjects, the report of the results on comparisons between patient and pain-free subjects will be brief.

Figure 5.15 Grand averages of ERP waveforms of 11 selected electrode sites between the patient and pain-free subjects. The five ERP components were labeled at their prominent electrode sites.

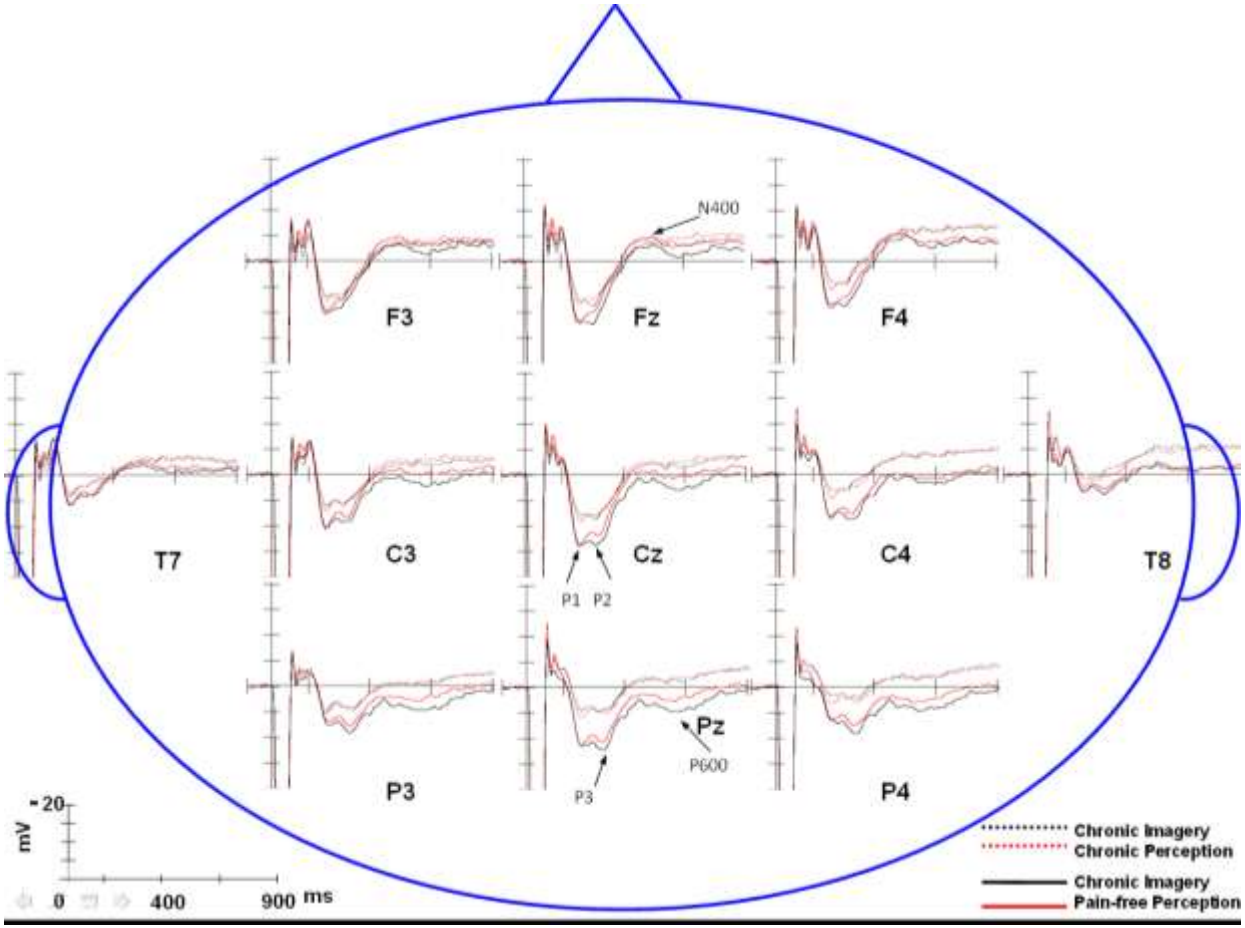
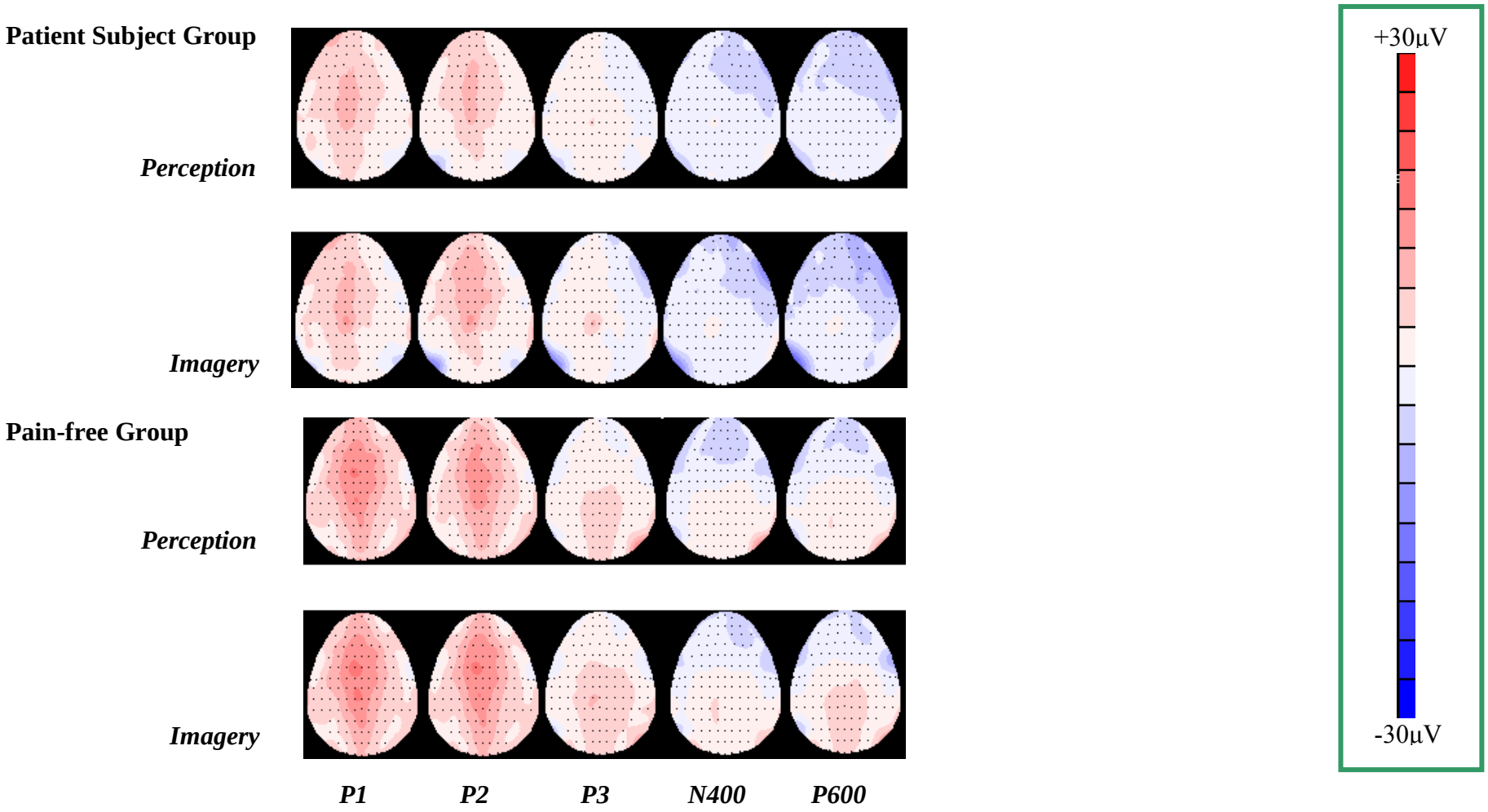


Figure 5.16 The topographical distribution of the five EPR components in Perception and Imagery conditions between the patient and pain-free subjects



For P1, both the midline and lateral site models did not reveal significant results (Table 5.18). For P2, the Condition × Group and Midline Site × Group effects were significant in the midline site model; whilst the Laterality, Condition × Group and Laterality × Group effects were significant in the lateral site model. For P3, the Condition × Group and Midline Site × Group effects were significant in the midline site model whilst the Laterality, and Site main effects and Condition × Group, Laterality × Group and Site × Group effects were significant in the lateral site model. For N400, only the Condition and Midline Site effects were reveal statistically significant in the midline site model; whilst the Laterality and Laterality × Group effects were significant in the lateral site model. Finally, for P600, only Group effect was significant in the midline site model; whilst the Group, Laterality, Laterality × Group and Condition × Group effects were statistically significant in the lateral site model. No significant findings were obtained of component latency comparisons. The mean amplitude (in μA) and peak latency (in ms) of the six midline electrodes and seven pairs of lateral (left and right) electrodes for perception and imagery trial and the detailed results of repeated measures ANOVA can be found in Appendices XXV (e) – XXV (s).

Table 5.18 Summary of repeated measures ANOVAs for the midline and lateral sites models on testing main and interaction effects on P1, P2, P3, N400, and P600 components in patient (n=17) and pain-free subjects (n=18)

Component	Peak Amplitude (μV) [Site]					
P1	**Midline Sites**		**Lateral Sites**			
	Chronic Pain	**Pain-Free**	**Chronic Pain**		**Pain-Free**	
			Left	Right	Left	Right
Perception	P:11.43 (6.90) [Cz]	P: 16.42 (7.97) [CPz]	P: 10.05 (5.95) [FC3]	P: 8.53 (6.60) [FC4]	P: 14.81 (7.21) [PC3]	P: 12.61 (6.35) [FC4]
Imagery	I:11.40 (6.75) [Cz]	I:16.88 (7.05) [CPz]	I: 9.95 (5.96) [FC3]	I: 8.42 6.58 [FC4]	I: 14.41 (6.16) [PC3]	I: 12.55 (6.02) [FC4]

	Within-group Effects			**Between-group Effect**
	Chronic Pain Group	**Pain Free Group**		
C	N.S.	N.S.	CG	N.S.
CS	N.S.	N.S.	CSG	N.S.
			BG	[F(1,33)=5.57, p=0.02] with the mean amplitude of the pain-free group having a more positive voltages.
L	Main effect of laterality [F(1,16)=42.72, p<0.01] (amplitudes of the left side electrodes were more positive going than the right counterparts (p<0.01))	N.S.	LG	No between-group effect; No group interaction effect
CL	N.S.	N.S.	CLG	N.S.
LS	N.S.	N.S.	LSG	N.S.
CLS	N.S.	N.S.	CLSG	N.S.
			BG	N.S.

Component	Peak Amplitude (μV) [Site]					
P2	**Midline Sites**		**Lateral Sites**			
	Chronic Pain	**Pain-Free**	**Chronic Pain**		**Pain-Free**	
			Left	Right	Left	Right
Perception	P: 9.84	P: 14.80	P: 8.40	P: 6.37	P: 11.06	P: 9.48
	(4.18) [Cz]	(7.63) [CPz]	(4.03) [FC3]	(4.47) [FC4]	6.15 [FC3]	6.39 [C4]
Imagery	I: 10.81	I:17.17	I: 9.81	I: 7.12	I: 13.48	I: 11.95
	(5.02) [PCz]	(6.97) [CPz]	(4.09) [FC3]	(5.24) [FC4]	(5.73) [FC3]	(5.65) [FC4]

	Within-group Effects			**Between-group Effect**
	Chronic Pain Group	**Pain Free Group**		
C	N.S.	F(1,17)=12.24, p=0.01 (amplitudes were more positive in the imagery condition at FCz, Cz, CPz and Pz sites (p<0.01)	CG	F(1,33)=4.66, p=0.04 (mean amplitudes of the pain-free groups at midlines sites (p<0.01) and Pz and POz sites of the chronic pain group were found to be less positive going (p<0.005))
CS	N.S.	N.S.	CSG	F(2.24,73.74)=3.88, p=0.02
			BG	F(1,33)=10.18, p=0.01
L	F(1,16)=18.41, p=0.01] (left sites were more positive (p<0.01) and the imagery condition were more positive going condition at Fz site (p<0.01)	N.S.	LG	F(1,33)=5.24, p=0.03 (mean amplitude of the electrode sites on the right hemisphere were less positive going for the chronic pain group (p<0.01))
CL		N.S.	CLG	N.S.
LS		N.S.	LSG	N.S.
CLS		N.S.	CLSG	N.S.
			BG	F(1,33)=8.89, p=0.01

Component	Peak Amplitude (μV) [Site]					
P3	**Midline Sites**		**Lateral Sites**			
	Chronic Pain	**Pain-Free**	**Chronic Pain**		**Pain-Free**	
			Left	Right	Left	Right
Perception	P: 5.77 (2.64) [CPz]	P: 8.74 (5.94) [CPz]	P: 4.29 (3.16) [P3]	P: 2.66 (3.17) [P4]	P: 6.58 (4.15) [P3]	P: 6.72 (5.15) [P4]
Imagery	I: 7.61 (4.28) [CPz]	I: 10.83 (4.93) [CPz]	I: 4.22 (3.70) [P3]	I: 2.12 (4.18) [P4]	I: 8.22 4.56) [P3]	I: 8.27 (4.72) [P4]

	Within-group Effects			**Between-group Effect**
	Chronic Pain Group	**Pain Free Group**		
C	N.S.	F(1,17)=9.02, p=0.01 (Post-hoc tests showed that mean amplitudes of imagery condition was more positively going at Fz, FCz and Cz sites, corrected p<0.01 level)	CG	Marginal: F(1,33)=3.59, p<0.07 (the mean amplitudes of midline electrode pain-free group were more significantly more positive going (p<0.01). The mean amplitudes of Pz and POz of the chronic pain group were less positive going (p<0.01).
CS	N.S.	N.S.	CSG	N.S.
			BG	N.S.
L	F(1,16)=15.26, p<0.001]	N.S.	LG	F(1,33)=8.70, p=0.01 (mean amplitudes of the right sites were significantly less positive than those of left electrodes in the chronic pain group)
CL	N.S.	N.S.	CLG	N.S.
LS	N.S.	N.S.	LSG	N.S.
CLS	N.S.	N.S.	CLSG	N.S.
			BG	F(1,33)=4.85, p=0.04 (pain-free group having more positive voltages

	Peak Amplitude (μV) [Site]					
Component	**Midline Sites**		**Lateral Sites**			
N400	**Chronic Pain**	**Pain-Free**	**Chronic Pain**		**Pain-Free**	
			Left	Right	Left	Right
Perception	P: -4.84 (3.99) [Fz]	P: -5.30 (6.39) [Fz]	P: -3.97 (3.89) [FC3]	P: -6.08 (4.10) [F4]	P: -4.95 (5.44) [F3]	P: -3.84 (6.70) [F4]
Imagery	I: -3.63 (5.31) [Fz]	I: -3.84 (6.70) [Fz]	I: -3.14 (5.82) [FC3]	I: -5.70 (4.88) [F4]	I: -3.97 (5.68) [F3]	I: -4.90 (6.89) [F4]

	Within-group Effects			**Between-group Effect**
	Chronic Pain Group	**Pain Free Group**		
C	F(1,16)=7.61, p=0.01] (amplitudes of any sites were less negative in imagery trials, corrected p<0.01)	F(1,17)=9.21, p=0.01 (mean amplitudes of the imagery condition was less negative (p<0.01) at the FCz, Cz and CPz, p level <0.05 only)	CG	N.S.
CS	N.S.	N.S.	CSG	N.S.
			BG	N.S.
L	F(1,16)=10.27, p=0.01	N.S.	LG	F(1,33)=6.607, p=0.02
CL	N.S.	N.S.	CLG	N.S.
LS	N.S.	F(2.95,50.12)=3.27, p=0.03	LSG	N.S.
CLS	N.S.	N.S.	CLSG	N.S.
			BG	F(1,33)=3.66, p=0.06 (marginal)

Component	Peak Amplitude (μV) [Site]					
P600	**Midline Sites**		**Lateral Sites**			
	Chronic Pain	**Pain-Free**	**Chronic Pain**		**Pain-Free**	
			Left	Right	Left	Right
Perception	P: 0.27 (3.26) [CPz]	P: 3.92 ± (4.23) [CPz]	P: 0.57 (2.44)[PO3]	P: -0.68 (2.23) [P4]	P: 3.94 (3.96) [P3]	P: 4.25 (4.50) [P4]
Imagery	I: 2.47 (3.27) [CPz]	I: 6.71 (4.25) [CPz]	I: 1.14 (2.77) [P3]	I: -0.42 (2.98) [P4]	I: 6.25 (5.16) [P3]	I: 6.11 (4.81) [P4]

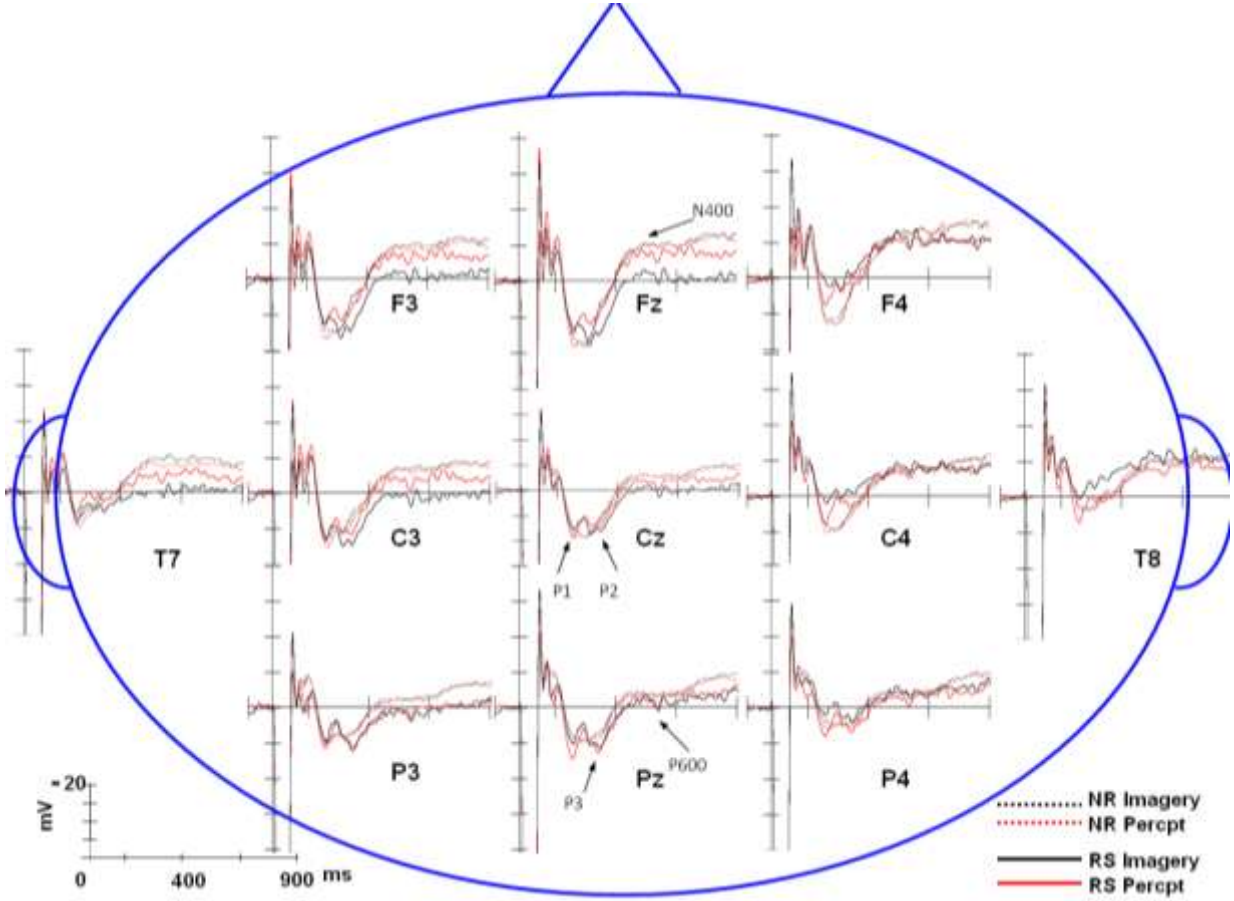
	Within-group Effects			**Between-group Effect**
	Chronic Pain Group	**Pain Free Group**		
C	F(1.44,23.03)=14.45, p<0.001 (amplitudes of imagery trials were more positive at FCz site, p<0.01)	F(1,17)=10.37, p=0.01 (amplitudes of imagery trials were more positive at FCz, p<0.01)	CG	N.S.
CS	N.S.	N.S.	CSG	N.S.
			BG	N.S.
L	F(1,16)=14.27, p=0.002 (left sites were more positive, p<0.01)	N.S.	LG	F(1,33)=5.87, p=0.02 (lateral sites were more positive going in pain-free group, p>0.01)
CL	N.S.		CLG	N.S.
LS	N.S.	F(3.32,56.48)=4.07, p=0.01 (mean amplitudes of imagery condition were larger at all left sites (except PO3 site), FC4 and C4 sites on the right, p<0.01)	LSG	N.S.
CLS	N.S.	N.S.	CLSG	
			BG	F(1,33)=9.83, p=0.004

Key: Two-way repeated measures ANOVA with 2 (conditions) × 6 (midline sites) design was used for analysis on midline sites; three-way repeated measures ANOVA with 2 (conditions) × 2 (laterality) × 7 (lateral sites) design was used for lateral sites; C = condition effect; S = site effect; L = lateral effect; G = group effect

ERP Analysis between Respondent and Non-respondent Patient Subjects

Similar repeated measures ANOVA models used in the comparisons between the patient and pain-free subjects were employed in the between-subgroup comparisons among the patient subjects. Since no significant results were revealed in comparing the peak latency between the patient and pain-free subject groups, such analyses will not be reported in this part of the results. Figure 5.17 shows grand average ERP waveforms for the respondent and non-respondent patient subgroups. The mean amplitudes and key repeated measures ANOVA findings of the five ERP components, i.e. P1, P2, P3, N400 and P600 are summarized in Table 5.19, respectively. The mean amplitudes of the six midline electrodes and seven pairs of lateral (left and right) electrode sites for perception and imagery trials and the details of the ANOVA analyses can be found in Appendices XXVI (a – j).

Figure 5.17 Grand average ERP waveforms of 11 electrode sites for respondent (RS) and non-respondent (NS) patient subjects. The five ERP components were labeled at their prominent electrode sites.



P1 Component

A three-way repeated measures with 2 (groups) × 2 (conditions) × 6 (sites) design was used to investigate between-group differences. No significant main or interaction effects were shown apart from an electrode main effect [$F(1.813,27,191)=17.752$, $p<0.001$]. A four-way repeated measures with 2 (groups) × 2 (conditions) × 2 (laterality) × 7 (sites) showed significant Condition × Laterality × Group interaction [$F(1,15)=8.374$, $p=0.011$] and marginally significant Condition × Laterality × Electrode × Group interaction [$F(1.874, 28.111)=3.246$, $p=0.057$].

For the respondent group, a two-way repeated measures ANOVA with 2 (conditions) × 6 (sites) design did not reveal significant main or interaction effects among the mean amplitudes of midline electrode sites ($p>0.050$). A three-way repeated measures ANOVA with 2 (conditions) × 2 (laterality) × 7 (sites) only revealed significant laterality main effect [$F(1,5)=10.733$, $p=0.022$] but no other main or interaction effects.

For the non-respondent group, only a main effect for the electrode sites was found to be significant in midline electrodes [$F(1.801,18.013)=24.649$, $p<0.005$], but the condition × electrode site interaction effect was not significant ($p>0.050$). The main effects of the electrode sites [$F(2.327,23.266)=8.487$, $p=0.001$] and the interaction effect of condition × laterality [$F(1,10)=7.398$, $p=0.022$] were found to be significant. Post-hoc tests revealed that the mean amplitudes of the imagery trials on the right hemisphere were less positive-going ($p<0.05$) (Appendices XXVI (a) & (b)).

P2 Component

For between-group difference, a three-way repeated measures ANOVA with 2 (groups) × 2 (conditions) × 6 (sites) design was used for midline electrodes. Although the between-group difference was not significant ($p>0.050$), there was a marginally significant Condition × Group, and significant Electrode × Group [$F(1,15)=4.145$, $p=0.06$] and Electrodes × Group interaction effects [$F(2.16,32.35)=5.25$, $p<0.001$]. But the interaction effect of Condition × Site × Group was not significant ($p>0.050$). A four-way repeated measures ANOVA with 2 (groups) × 2 (conditions) × 2 (laterality) × 7 (sites) showed significant laterality and sites main effect [$F(1,15)=24.336$, $p<0.001$; $F(2.885, 43.272)=13.296$, $p<0.001$, respectively]. The Condition × Laterality × Groups interaction and Condition × Laterality × Electrode sites × Group interaction effect were found to be significant [$F(1,15)=22.95$, $p<0.001$ & $F(2.51, 37.60)=5.00$, $p=0.008$, respectively]. The post-hoc tests showed that the mean amplitudes of the left-side electrode sites were more positive-going for the imagery condition ($p<0.01$). It was also showed that the two electrodes at the left frontal region, i.e. Fz and FC sites, were more positive-going in the imagery trials in the respondent group [$t(5)=-5.35$, $p=0.003$ & $t(5)$ $p=0.021$].

For the respondent group, a two-way repeated measures ANOVA with 2 (conditions) × 6 (sites) design for midline electrode sites showed significant main effect of the electrode sites [$F(1.110,5.549)=7.530$, $p=0.013$]. A three-way repeated measures ANOVA with 2 (conditions) × 2 (laterality) × 7 (sites) revealed significant main effects for laterality [$F(1,5)=16.870$, $p<0.009$] and electrode [$F(1.69,8.43)=6.26$, $p=0.03$]. The Condition × Laterality interaction effect was significant [$F(1,5)=14.584$, $p=0.012$]. A post-hoc tests showed revealed that P2 amplitude was more positive-

going at F3 and FC3 on the left hemisphere in the imagery trials compared with the perception trials [$t(5)$=-5.35, p=0.003 and $t(5)$=-2.71, p=0.021].

For the non-respondent group, a two-way repeated measures ANOVA with 2 (conditions) × 6 (sites) design showed a significant main effect of the electrode sites [F(1.764, 28.750)=28.750, p<0.001]. A three-way repeated measures ANOVA with 2 (conditions) × 2 (laterality) × 7 (sites) revealed significant main effect for laterality [F(1,10)=6.485, p=0.029] but no condition interaction effect (p>0.050). No laterality interaction effects were shown (Appendices XXVI (c) & (d)).

P3 Component

A three-way repeated measures ANOVA with 2 (groups) × 2 (conditions) × 6 (sites) was used to examine the between-group differences between the respondents and non-respondents. The between-group effect was not found to be significant (p>0.050). Group × Condition interaction was found to be significant in midline electrode sites (F(15)=12.13, p=0.01).A four-way repeated measures ANOVA with 2 (groups) × 2 (conditions) × (laterality) × 6 (sites) design showed a significant Condition × Laterality × Group interaction effect [F(1,15)=5.38, p=0.04].

For the respondent group, a two-way repeated measures ANOVA with 2 (conditions) × 6 (sites) design showed that there was a significant condition [F(1,5)=7.86, p=0.04] and electrode sites main effect [F(2.01,10.03)=6.03, p=0.02]. The mean amplitudes of the imagery trials were more positive-going than the perception counterparts at CPz (t(5)=3.37, p<0.01). But the Condition × Electrode interaction effect (p>0.050) was not significant (p>0.050). For laterality sites, three-way repeated measures ANOVA with 2 (conditions) × 2 (laterality) × 7 (sites) was used to examine between-group differences. Apart from the main effect of Laterality

[F(1,5)=12.24, p=0.02], other main and interaction effects were found to be not significant (p>0.050).

For the non-respondent group, a two-way repeated measures ANOVA with 2 (conditions) × 6 (sites) design was used for midline electrode sites. No significant main or interaction effect was shown (p>0.050). For lateral sites, the main effect of laterality was found to be significant [F(1,10)=8.77, p=0.014]. A Condition × Laterality interaction effect was found to be marginally significant [F(1,10)=4.18, p=0.07] and a Condition × Laterality × Electrode were found to be significant [F(2.31,23.07)=3.45, p=0.043]. The post-hoc tests showed that the mean amplitudes of the left hemisphere were more positive-going. Post-hoc tests revealed significant differences in mean amplitudes between F3 and F4 electrodes (p<0.001) and FC3 and FC4 electrodes (p<0.001) in the perception condition, with the mean amplitudes of the left electrode sites more positive-going. In the imagery condition, the mean voltage amplitudes of these electrodes were also significant with larger p values (p=0.011 for F3 and F4 & p=0.004 for FC3 and FC4), with the mean amplitudes of the left electrode sites more positive-going (Appendices XXVI (e) & (f)).

N400 Component

A three-way repeated measures ANOVA with 2 (groups) × 2 (conditions) × 6 (midline sites) design showed a significant mean effect for condition [F(1,15)=9.45, p=0.01]. A four-way repeated measures ANOVA design with 2 (groups) × 2 (conditions) × 2 (laterality) × 7 (sites) was used to examine the differences for the lateral electrodes. Only the interaction effect of the Condition × Laterality × Group was found to be significant [F(1,15)=5.40, p=0.04].

For the respondent group, a two-way repeated measures ANOVA with 2 (conditions) × 6 (sites) design showed a main effect for the condition [F(1,15)=14.48, p=0.01] and electrode [F(1.50,7.49)=7.80, p=0.02] at the midline electrode sites. The imagery trials were less negative-going than the perception trials at Fz (t(5)=3.39, p<0.01) and FCz (t(5)=3.38, p<0.01). A three-way repeated measures ANOVA with 2 (conditions) × 2 (laterality) × 7 (sites) a at the lateral electrode sites showed that only the mean effect of electrodes sites were significant [F(1.88,9.39)=4.23, p=0.05].

For the non-respondent group, a two-way repeated measures ANOVA with 2 (conditions) × 6 (sites) design showed a significant main effect of the electrode sites [F(1.41,14.11)=5.80, p=0.02]. A three-way repeated measures ANOVA with 2 (conditions) × 2 (laterality) × 7 (sites) showed only significant main effect at the electrode sites [F(1.56,15.59)=5.77, p=0.02]. There was a significant Condition × Laterality effect [F(1,10)=3.22, p=0.047], with electrodes on the left hemisphere less-negative in the imagery than perception trials (t(1,10)=3.13, p<0.05) (Appendices XXVI (g) & (h)).

P600 Component

A three-way repeated measures ANOVA with 2 (groups) × 2 (conditions) × 6 (Electrode sites) design indicated there were no between-group differences (p>0.050) but a significant main effect of the condition and group [F(1,15)=7.26, p=0.02]. ,A four-way repeated measures ANOVA with 2 (groups) × 2 (conditions) × 2 (laterality) × 7 (sites) revealed significant interaction effects of Condition × Laterality × Group and Condition × Laterality × Electrode [F(1,15)=5.00, p=0.041 & F(1.71,25.68)=4.53, p=0.025].

For the respondent group, a two-way repeated measures ANOVA with 2 (conditions) × 6 (sites) design showed that there was a significant main effect of conditions [$F(1,15)=14.81$, $p=0.012$] and electrode sites [$F(1.16,5.81)=7.46$, $p=0.033$]. There was no significant Condition × Site interaction effect ($p>0.050$). , A three-way repeated measures ANOVA with 2 (conditions) × 2 (laterality) × 7 (sites) showed that there were only significant main effects of laterality and electrode sites [$F(1,5)=12.44$, $p=0.02$ & $F(1.94,9.71)=4.27$, $p=0.048$. There were no condition interaction effect ($p>0.050$).

For the non-respondent group, a two-way repeated measures ANOVA with 2 (conditions) × 6 (sites) design showed a significant main effect of the midline electrode site [$F(1.58,15.79)=8.56$, $p=0.005$]. A three-way repeated measures ANOVA with 2 (conditions) × 2 (laterality) × 7 (sites) showed that there was a significant main effect of laterality [$F(1,10)=5.73$, $p=0.038$] and electrode sites [$F(1.49, 14.90)=9.25$, $p=0.004$]. The interaction effect of the Condition × Laterality × Electrode site was also found to be significant [$F(3.48,34.77)=3.85$, $p=0.014$]. A post-hoc test showed that significant differences between mean amplitude of F3 site were more positive-going than that of the F4 site ($p<0.001$) and the FC3 site was more positive-going that FC4 site in perception conditions ($p<0.001$). The mean amplitude of the F3 site was more positive-going than that of the F4 ($p<0.01$) with a smaller amplitude under imagery conditions (Appendices XXVI (i) & (j)).

Table 5.19 Summary of repeated measures ANOVAs of the midline and lateral site model on P1, P2, P3, N400 and P600 between respondent (n=6) and non-respondent (n=11) patient subjects

Component	Peak Amplitude (μV) [Site]					
P1	**Midline Sites**		**Lateral Sites**			
	Respondent	**Non-respondent**	**Respondent**		**Non-respondent**	
			Left	Right	Left	Right
Perception	11.22	11.71	8.44	7.75	10.94	8.96
	(3.88) [Cz]	(8.58) [Fz]	(2.65) [FC3]	(4.24) [FC4]	(7.12) [FC3]	(7.75) [FC4]
Imagery	12.02	11.78	9.50	7.17	10.32	9.19
	(3.06) [CPz]	(8.76) [Fz]	(3.03) [F3]	(3.38) [FC4]	(7.15) [FC3]	(8.11) [F4]

	Within-group Effects			**Between-group Effect**
	Respondent	**Non-respondent**		
C	N.S.	N.S.	CG	N.S.
CS	N.S.	N.S.	CSG	N.S.
			BG	N.S.
L	F(1,5)=10.73, p=0.02 (mean amplitudes of the left sites were less negative-going in imagery trials, p<0.05)	F(1,10)=11.31, p=0.01	LG	
CL	N.S.	F(1,10)=7.40, p=0.02 (mean amplitudes of imagery trials on the right hemisphere were less positive-going (p<0.05)	CLG	[F(1,15)=8.37, p=0.01]
LS	N.S.	N.S.	LSG	N.S.
CLS	N.S.	N.S.	CLSG	F(1.87, 28.11)=3.25, p=0.06
			BG	N.S.

Component	Peak Amplitude (μV) [Site]					
P2	**Midline Sites**		**Lateral Sites**			
	Respondent	**Non-respondent**	**Respondent**		**Non-respondent**	
			Left	Right	Left	Right
Perception	8.57	10.67	6.39	4.24	9.59	7.53
	(2.18) [CPz]	(4.94) [Cz]	(2.59) [P3]	(4.16) [FC4]	(4.11) [FC3]	(4.37) [FC4]
Imagery	12.85	10.70	10.92	5.63	9.53	7.93
	(3.02) [CPz]	(5.50) [FCz]	(3.24) [F3]	(5.75) [FC4]	(4.38) [FC3]	(5.04) [FC4]

	Within-group Effects			**Between-group Effect**
	Respondent	**Non-respondent**		
C	N.S.	N.S.	CG	F(1,15)=4.15, p=0.06 (marginal)
CS	N.S.	N.S.	CSG	N.S.
			BG	N.S.
L	F(1,5)=16.87, p<0.01	F(1,10)=6.49, p=0.03	LG	F(1,15)=3.92, p=0.07 (marginal)
CL	F(1,5)=14.58, p=0.012 (left sites was more positive going in the imagery condition, p<0.01)	N.S.	CLG	F(1,15)=22.95, p<0.01 (Mean amplitudes of the left-side electrode sites were more positive-going in imagery trials (p<0.01).
LS	N.S.	N.S.	LSG	N.S.
CLS	N.S.	N.S.	CLSG	F(2.51,37.59)=5.01, p=0.01 (the two electrodes at the left frontal region, i.e. Fz and FC sites, were found to be more positive-going in imagery trials among respondents, p<0.05)
			BG	

Component	Peak Amplitude (μV) [Site]					
P3	**Midline Sites**		**Lateral Sites**			
	Respondent	**Non-respondent**	**Respondent**		**Non-respondent**	
			Left	Right	Left	Right
Perception	6.26	5.50	4.60	3.01	4.16	2.47
	(2.65) [CPz]	(2.72)[CPz]	(1.52) [C3]	(1.89) [P4]	(3.22) [FC3]	(3.77) [P4]
Imagery	11.08	5.72	6.32	2.00	3.39	2.19
	(4.27) [CPz]	(3.00) [CPz]	(4.66) [C3]	(5.66) [P4]	(3.37) [FC3]	(3.45) [P4]

	Within-group Effects			**Between-group Effect**
	Respondent	**Non-respondent**		
C	F(1,5)=7.86, p=0.04 (mean amplitudes of the imagery trials was found to be more positive, p<0.01)	N.S.	CG	F(15)=12.13, p=0.01
CS	N.S.	N.S.	CSG	N.S.
			BG	N.S.
L	N.S.	F(1,10)=8.77, p=0.014	LG	N.S.
CL	N.S.	F(1,10)=4.18, p=0.07	CLG	F(1,15)=5.39, p=0.04
LS	N.S.		LSG	N.S.
CLS	N.S.	F(2.31,23.07)=3.45, p=0.04 (In the imagery condition, the mean voltage amplitudes of these electrodes were also significant (p=0.011 for F3 and F4 & p=0.004 for FC3 and FC4), with the mean amplitudes of the left electrode sites more positive-going	CLSG	N.S.
			BG	N.S.

Component	Peak Amplitude (μV) [Site]					
N400	**Midline Sites**		**Lateral Sites**			
	Respondent	**Non-respondent**	**Respondent**		**Non-respondent**	
			Left	Right	Left	Right
Perception	-4.65	-4.95	-4.00	-6.13	-3.97	-6.05
	(4.17) [Fz]	(4.09) [Fz]	(3.71) [FC3]	(3.58) [F4]	(4.12) [F3]	(4.52) [F4]
Imagery	-1.41	-5.00	-1.58	-5.77	-4.24	-5.67
	(5.09) [FCz]	(5.20) [Fz]	(6.49) [FC3]	(4.17) [F4]	(5.12) [F3]	(5.42) [F4]

	Within-group Effects			**Between-group Effect**
	Respondent	**Non-respondent**		
C	F(1,15)=14.48, p=0.013 (amplitudes of the imagery trials were less negative, p<0.01).	N.S.	CG	F(1,15)=9.45, p=0.008
CS	N.S.	N.S.	CSG	N.S.
			BG	N.S.
L	N.S.		LG	N.S.
CL	N.S.	F(1,10)=3.21, p=0.047 (left sites less negative in the imagery condition, p<0.05)	CLG	F(1,15)=5.408, p=0.035
LS	N.S.	N.S.	LSG	N.S.
CLS	N.S.	N.S.	CLSG	N.S.
			BG	N.S.

Component	Peak Amplitude (μV) [Site]					
P600	**Midline Sites**		**Lateral Sites**			
	Respondent	**Non-respondent**	**Respondent**		**Non-respondent**	
			Left	Right	Left	Right
Perception	1.01	0.19	2.30	-0.06	-0.34	-1.00
	(1.97) [POz]	(2.90) [CPz]	(2.53) [PO3]	(0.51) [P3]	(2.06) [PO4]	(2.72) [P4]
Imagery	4.63	1.30	3.09	-0.22	0.26	-0.53
	[3.13] CPz	(2.81) [CPz]	(5.09) [CP3]	(4.00) [P3]	(1.82) [P4]	(2.49) [P4]

	Within-group Effects			**Between-group Effect**
	Respondent	**Non-respondent**		
C	F(1,5)=14.81, p=0.012 (amplitudes of the imagery trials were less negative, p<0.01)	N.S.	CG	F(1,15)=7.26, p=0.02
CS	N.S.	N.S.	CSG	N.S.
			BG	N.S.
L	N.S.	F(1,10)=5.73, p=0.038	LG	
CL	N.S.		CLG	F(1,15)=5.00, p=0.041
LS	N.S.		LSG	
CLS	N.S.	F(3.48,34.767)=3.85, p=0.014 (mean amplitude of F3 and FC3 were more positive than that of F4 and FC4 (p<0.01) and FC3 were more positive, respectively (p<0.01). Mean amplitude of the F3 were more positive than that of F4 (p<0.01) with smaller amplitude in imagery trials	CLSG	F(1.71,25.68)=4.53, p=0.025
			BG	

Summary of ERP Analyses for Respondent and Non-respondent Patient Subgroups

A main observation is that the Laterality effect was found to be more prominent among the respondent patient subjects whose waveforms were less negative-going in the imagery condition on the left when compared to right hemisphere. The between-subgroup Laterality effects were revealed in the attention orientation-related P2. Here, more centro-frontally distributed positive-going waveforms were elicited (left > right) by the respondent patient subjects in the imagery condition than by the non-respondent patient subjects. A post-hoc test found more positive-going at F3 and FC3 on the left hemisphere in imagery trials compared to the perception trials. In contrast, the respondent patient subjects elicited more centro-parietally distributed positive-going P3 in the imagery condition than their non-respondent counterparts. Similarly, the respondent patient subjects elicited middle frontal less-negative going N400 in the imagery condition than the non-respondent patient subjects. For the late P600, the respondent patient subjects elicited more centro-parietally distributed more positive-going waveform in the imagery condition (left > right) than the non-respondent patient subjects. The Condition × Laterality interaction effect was found in the non-respodent group. Post-hoc analysis suggested the amplitudes of the component in the imagery trials on the right hemisphere were less positive-going

Dipole Sources of Cognition-related ERP Components

Using Curry 6.0.2 software, dipole sources for later cognition-related ERP components (i.e. P2, P3, N400 and P600) were obtained for the respondent patient subgroup. The results shed light on the possible mental processes associated with shifting the attention and generation of nociceptive image when subjects engaged in the imagery trials. The BEM head template and rotating dipoles were adopted when the solutions were sought.

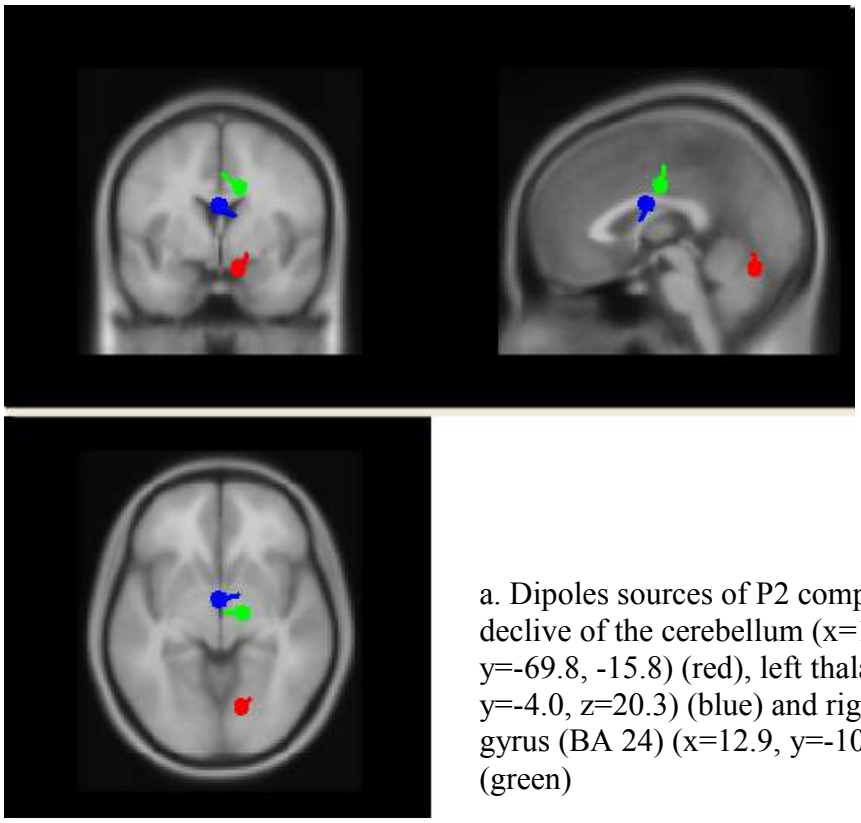
For the respondent patient subgroup, the dipole sources of P200 were located at the right declive of the cerebellum (x=11.8, y=-69.8, z=-15.8), the left thalamus (x=-1.6, y=-4.0, z=20.3) and the right cingulate gyrus (BA 24) (x=12.9, y=-10.6, z=29.8) (Figure 5.18a). The variance explained by the solution was 98.97% with residual deviation of 10.1%. The maximal dipole strength occurred at 281 ms. For P3, four dipoles were identified: the left medial frontal gyrus (BA6) (x=-3.8, y=16.4, z=46.8), the left middle temporal gyrus (BA39) (x=-44.7, y=-56.1, z=9.7), the right putamen (x=21.3, y=6.2, z=2.1) and the left declive of the cerebellum (x=-3.2, y=-68.4,-17.9) (Figure 5.18b). The variance explained by the solutions was 96.57% (residual deviation: 18.5%). The peak strength of the dipole occurred at 370 ms post-stimulus onset. For N400, four dipoles were shown: the frontal gyrus (BA6) (x=-6.2, y=11.0, z=49.3), the left caudate body (x=-15.5, y=-1.4, z=15.7) and the head (x=-3.3, y=15.5, z=3.6) and left lingual gyrus (BA 18) (x=-4.3, y=-83.1, z=-2.0) (Figure 5.18c). The variance explained by the solution was 93.69 % with residual deviation of 25.1%. The peak strength of these dipoles occurred at 475 ms post-stimulus onset. Finally, the dipoles of P600 were found at the right declive of the cerebellum (x=8.5, y=-68.1, z=-14.5), the medial frontal gyrus (BA8) (-3.8, 25.0, 43.1) and the right thalamus

(x=14.1, y=-12.0, z=2.2) (Figure 5.18d). The variance explained by the solution was 95.54% (residual deviation: 21.1%). The strength of the dipoles peaked at 500 ms.

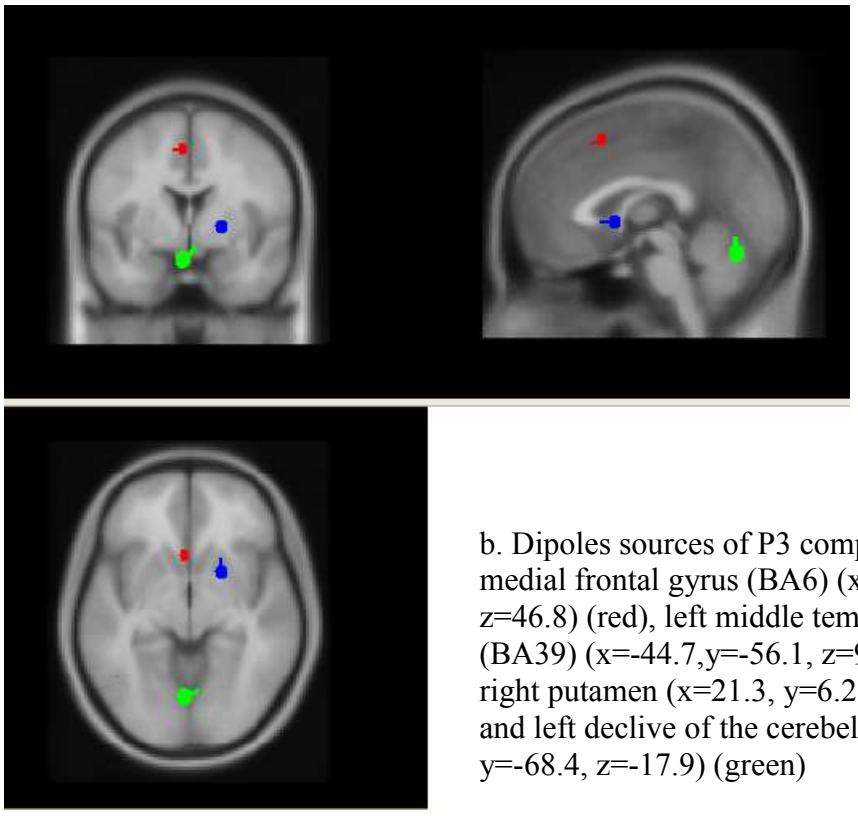
Relationship between Normalized NRS Scores and ERP Data in the Patient Group

Pearson's correlations were computed for the mean amplitudes of P2, P3, N400 and P600, and the normalized NRS ratings (Imagery minus perception conditions). For P2, the level 3 normalized NRS score was moderately correlated with the amplitudes elicited at CP3 ($r = -0.490$, $p<0.050$). For P3, the level 1 and 2 normalized NRS score was also weakly correlated with amplitudes at P3 and PO4 sites ($-0.466 > r > -0.463$, $p<0.050$), whilst the normalized NRS score on level 3 was moderately correlated with amplitude elicited at F4 ($r = -0.534$, $p<0.050$). For N400, the level 5 normalized NRS score was correlated moderately with the amplitudes elicited at C3, F3, and FC3 ($-0.455 > r > -0.486$, $p<0.050$). For P600, there were no significant correlations.

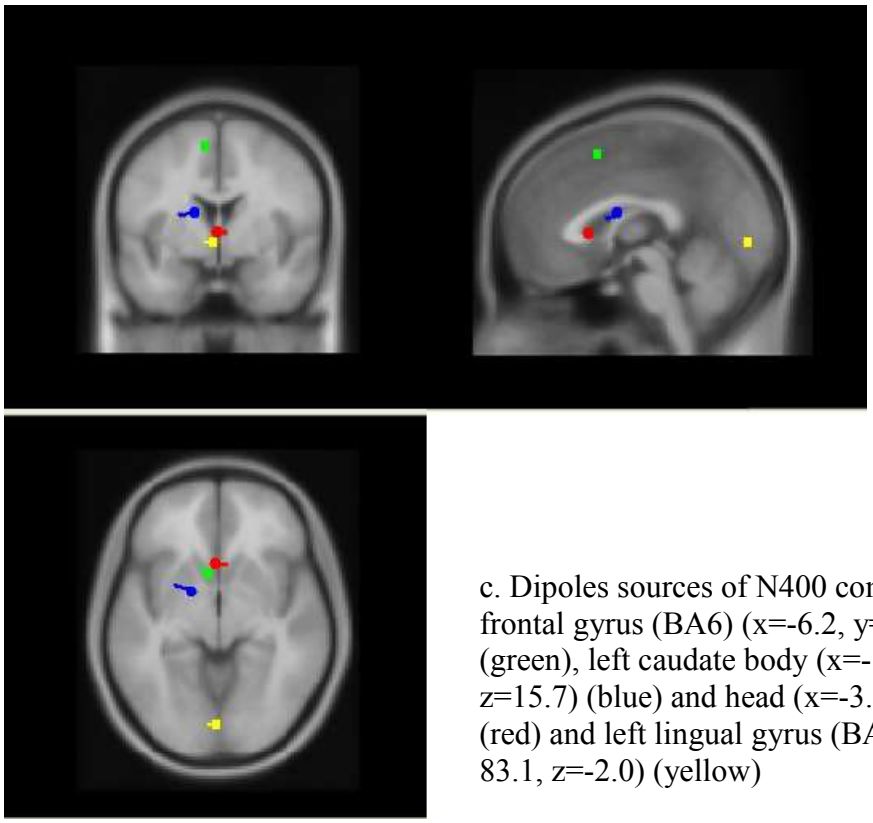
Figure 5.18a – d The dipole sources of P2, P3, N400 and P600 components of respondent patient subjects (n =6)



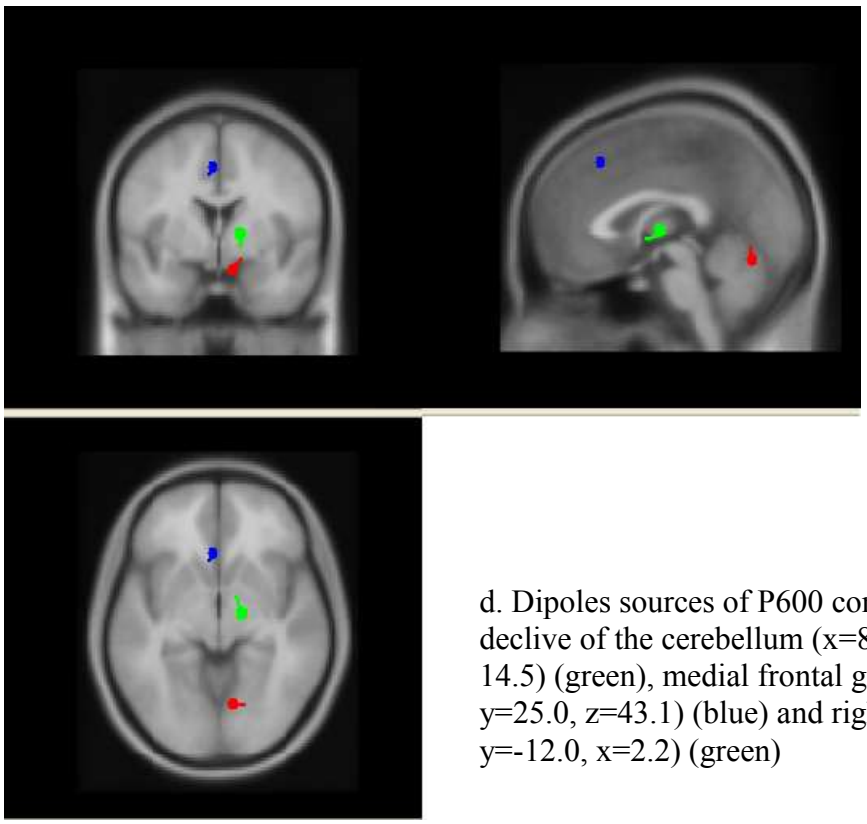
a. Dipoles sources of P2 components: right declive of the cerebellum (x=11.8, y=-69.8, -15.8) (red), left thalamus (x=-1.6, y=-4.0, z=20.3) (blue) and right cingulate gyrus (BA 24) (x=12.9, y=-10.6, z=29.8) (green)



b. Dipoles sources of P3 components: left medial frontal gyrus (BA6) (x=-3.8, y=16.4, z=46.8) (red), left middle temporal gyrus (BA39) (x=-44.7,y=-56.1, z=9.7) (purple), right putamen (x=21.3, y=6.2, z=2.1) (blue) and left declive of the cerebellum (x=-3.2, y=-68.4, z=-17.9) (green)



c. Dipoles sources of N400 components: superior frontal gyrus (BA6) (x=-6.2, y=11.0, z=49.3) (green), left caudate body (x=-15.5, y=-1.4, z=15.7) (blue) and head (x=-3.3, y=15.5, z=3.6) (red) and left lingual gyrus (BA 18) (x=-4.3, y=-83.1, z=-2.0) (yellow)



d. Dipoles sources of P600 components: right declive of the cerebellum (x=8.5, -y=68.1, z=-14.5) (green), medial frontal gyrus (BA8) (x=-3.8, y=25.0, z=43.1) (blue) and right thalamus (x=14.1, y=-12.0, x=2.2) (green)

Relationship between the Normalized NRS Scores and ERP Data among the Respondent and Non-respondent Patient Subjects

In the respondent patient subgroup, no significant correlations were revealed between the amplitudes of the four earlier ERP components: SP1-2, SP2-3, SP3/P1 and the normalized NRS scores except the mean amplitude of the P1 elicited at P3 was strongly correlated with the normalized NRS scores on the recalled levels 3 and 5 nociception images ($r=-0.924$, $p<0.01$; $r=-0.870$, $p<0.050$, respectively). More significant correlations were obtained for the P2 component. The mean amplitudes of all 20 except 5 sites, i.e. CPz, CP3, PO3, T7, PO4 sites, were strongly correlated with the level 2 normalized NRS score ($-0.957 < r < -0.857$, $p<0.01$). For P3, the level 1 normalized NRS score was strongly correlated with the amplitudes elicited at Pz, POz, FC4, C4, CP4, PO4 ($-0.935 < r < -0.813$, $p<0.050$). The mean amplitudes of N400 and P600 were found to correlate with the normalized NRS scores over extensive regions on the scalp. The mean amplitudes of N400 at CPz was correlated strongly with the level 1 normalized NRS score ($r=-0.886$, $p<0.050$); whilst those at F3, FC3, CPz, PO4 were correlated with the level 2 normalized NRS score ($-0.943 < r < -0.886$, $p<0.050$) and at CP3, P3, Pz correlated with the level 3 normalized NRS score ($-0.943 < r < -829$, $p<0.050$). Finally, the mean amplitudes of P600 at CPz, Pz, F4, FC4, C4, CP4, P4, PO4 were correlated strongly with the level 1 normalized NRS score ($-0.984 < r < -0.864$, $p<0.050$)

For the non-respondent patient subjects, the mean amplitudes of P1 at all selected sites except TF9, F3, FC3, FC4, T8 were correlated with the normalized NRS score on level 3 nociceptive stimulus ($-0.795 < r < -0.614$, $p<0.050$). The amplitudes of P2 were much less strongly correlated with the normalized NRS scores. Only the

mean amplitudes at C4 ($r=-0.704$, $p<0.050$) and CP4 ($r=-0.604$, $p<0.050$) were moderately correlated with the normalized NRS score on level 3 nociceptive stimulus. The mean amplitudes of P3 elicited at PO3 were correlated moderately with the normalized NRS score level 3 ($r=-0.603$, $p<0.050$), those elicited at P3 and PO3 were correlated with the normalized NRS score level 4 nociceptive stimulus ($r=-0.682$ & $r=-0.671$, $p<0.050$, respectively). The C3 and CP3 mean amplitudes were correlated with the normalized NRS score on level 5 nociceptive stimulus ($r=-0.674$ & $r=-679$, $p<0.050$, respectively). Finally, there were no significant correlation findings for the mean amplitudes of N400 and P600 components and the normalized NRS scores on nociceptive stimuli ($p>0.050$).

In summary, in the respondent patient subgroup, the P2 and N400 possibly were the key components reflecting the pain modulation effects under focused attention and imagery as their amplitudes had stronger correlations with the normalized NRS scores. In contrast, the P300 and P600 components appeared to be less related to pain modulation as their amplitudes were found to have weaker correlations with the normalized NRS scores. These later components were also found to be significantly different between the imagery and perception conditions. On the other hand, the key ERP component to be related to the normalized NRS scores was the P1 component in the non-respondent patient group. The later ERP components were not strongly related to the amount of pain modulation. The associated pain levels were not limited to the weakest pain level 1.

CHAPTER SIX

DISCUSSION

In this chapter, the findings of focused attention using somatosensory imagery for modulating pain perception in pain-free subjects will be discussed. This will be followed by a discussion of the findings obtained from patient groups.

FOCUSED ATTENTION AND PAIN PERCEPTION MODULATION AMONG PAIN-FREE SUBJECTS

The aim of the study on pain-free subjects was to examine the effects of focused attention using generation of pre-learned somatosensory images on modulating the perception on recalled incoming nociceptive images. It was hypothesized that the pain-free subjects would modify the focus of the attention and would rehearse sub-nociceptive images. Further, it was hypothesized that the mental processes used would be reflected in the electrophysiological results. The modulation of the perception of the recalled nociceptive stimuli would also be shown in the differences in pain NRS ratings between the imagery and perception conditions. Due to the phasic characteristic (50 ms) of the nociceptive stimuli, the subjects were only asked to assign a pain NRS rating to the incoming nociceptive stimuli. This rating was recalled after the 3000 ms mental rehearsal of the nociceptive image (as in the Perception trials) or the sub-nociceptive image (as in the Imagery trials). Thus, the pain ratings obtained from the subjects might not be directly attributable to focused attention and sub-nociceptive imagery processes but also to the images of the nociceptive stimuli that were kept and recalled in the working memory in the trials. It

is noteworthy that the differences in NRS ratings between imagery and perception occurred with weaker intensity of electrical stimulation (Level 1-3). The magnitudes of the differences were also relatively small as they were less than 1 in the 11-point scale (Table 5.2). This could be due to the notion that the second electrical stimulation which the subject received before assigning a pain intensity rating on the recalled stimulation (presented at the beginning of the trial) could inflate the rating and hence weaken the effect of the pain modulation. Another possible reason is that the training which the subjects involved before the experiment - focused attention followed by sub-nociceptive imagery, was rather short for eliciting a strong effect. Nevertheless, there is consistent evidence attributing changes in the NRS ratings to focused attention and self-generation of the sub-nociceptive images. Besides the significant decreases in the NRS ratings, the amplitudes of the two key ERP components, i.e. P2 and N400, were found to be more highly correlated with the normalized NRS ratings compared to other two components, i.e. P300 and P600. The P2 component was associated with focused attention whilst the N400 component was related to image generation processes. The P300 and P600 components were found to relate to sensory evaluation and maintenance. These findings suggest that it is less likely that the reduction of NRS ratings would be due to the influence of subjects' ability to recall and hence change the original ratings. More detailed interpretations of the meaning behind the NRS ratings assigned by the pain-free subjects will be discussed in this chapter.

ERP Components and Focused Attention

There was a statistically significant difference between the results of the imagery and perception trials for the P2 component, signifying the reorientation of attention from external stimulus to internal generation of sub-nociceptive imagery. Prior studies have found that a positive P2 was associated with bringing spatial attention to the nociceptive stimulus (Dowman et al., 2007b). The fronto-central distributed P2 revealed in this study was similar to the waves elicited in infrequent and deviant no-go trials that required participants to inhibit responses in other studies (e.g. Hatem et al., 2007; Nataka et al., 2004). There have been similar findings in studies that used other senses: visual, auditory (Bruin et al., 2002; Eimer, 1993; Falkenstein et al., 1999), and somatosensory (Dowman et al., 2007a; Hatem et al., 2007; Nataka et al., 2004). The more frontal P2 distribution, which was somewhat different from the centro-parietal no-go component reported in these studies, suggests the possibility of a top-down orientation of attention in the subjects towards the incoming nociceptive stimulus. Findings from this study seem to support the hypothesis that the amplitude of P2 could serve as an electrophysiological marker for successful initiation of a focused attention process ((Dowman et al., 2007a; Hatem et al., 2007).

The P3 component was more positive-going distributed over the centro-parietal (CPz) sites. Both temporal and topographical characteristics suggested that the waveform elicited in the imagery trials would be a P3b, which is associated with evaluation and categorization of sensory stimuli by accessing to long-term memory (Donchin and Coles, 1988; Friedman et al., 2001; Goldstein et al., 2002; Kok, 2001; Legrain et al., 2002). Previous studies showed that the P3b was particularly strong

when the participants saw a rare target stimulus, regardless of its sensory modality (Friedman et al., 2001; Goldstein et al., 2002). Although the main differences between the imagery and perception trials were at the FC and Cz, the P3 component was shown peaking at the temporal and parietal regions. The results of dipole analysis on P3 suggested that the component is likely to originate from the temporal region including the parahippocampus and the right lingual gyrus. Many Go/Nogo studies have reported this P3b component (Bokura et al., 2001; Bekker et al., 2005; Friedman et al., 2001; Huster et al., 2010; Legrain et al., 2002; Polich, 2007). The locations of the dipoles revealed for P3 (such as the left parahippocampus) concur with these studies. Putting into the context of somatosensory imagery in this study, instead of appraising the incoming nociceptive stimulus, the subjects prepared to evaluate and categorize the somatosensory information (i.e. the level of nociceptive sensation) (Friedman et al., 2001; Goldstein et al., 2002; Polich, 2007) in order to generate the corresponding sub-nociceptive image previously learned. Nevertheless, it was not clear whether those processes were targeted at the external pain stimulus or the learned sub-nociceptive sensory images generated from within.

The imagery trials elicited less negative-going N400 than the perception trials over the fronto-central areas. According to the paradigm design, this late negative component could reflect the process in which the images that the subjects were told to retrieve from their memory in this study were the sub-nociceptive counterparts learned in the training before the experiment (Posner, 1994; Posner & Petersen, 1990). It is important to note that there is no conclusive evidence concerning the roles of N400 component (Kutas et al., 2011). The relationship between the N400 and the generation and rehearsal of the previous learnt sub-nociceptive or other somatosensory stimuli have not been substantiated in previous studies. The role of

this negative component in the present paradigm requires further deliberation. N400 was originally associated with the mental responses to meaningful stimuli (Kutas et al., 2011). These stimuli commonly involved semantic memory processing of linguistic stimuli in speech or reading (Debruille et al., 2007; Kutas et al., 1984; Qiu et al., 2007; West et al., 2000). Later studies further revealed that the elicitation of N400 was not limited to lexicon-related stimuli but non-linguistic stimuli, such as objects, line drawing and pictures (Metzler, 2011). Other studies have revealed that the N400 was a common event-related component found associated with imagery of different modalities (visual imagery: Qiu et al., 2007; West & Holcomb, 2000; vibrotactile imagery: Chow et al., 2007; motor imagery: Metzler, 2011). West et al. (2000) revealed that the frontally distributed N400 was associated with imagery of more substantiate images of words such as “shoes” than the less substantial images of words such as “bravery”. Similarly, Qiu et al. (2007) found that a frontal-central negativity elicited at around 520 ms post-stimulus was associated with generating lexicon-related images. In addition, a study conducted by Chow et al. revealed that frontally distributed N400 was elicited when subjects generated familiar vibrotactile images. These studies suggest that despite different modalities, the N400 component was consistently elicited over a similar topographical distribution (frontal region) with similar latency (300 to 500 ms). These observations further support the notion that the N400 can be imagery-related and is likely to be modality-independent (Debruille, 2007). The frontal-central distributed less-negative N400 component obtained from the current study was largely similar to those described for tasks involving generation and rehearsal of different mental images without a semantic component. This further suggests thatduring the imagery trials, the subjects generated the previously learnt sub-nociceptive images which were reflected in the less negative-going N400

component. The temporal course difference between P2 and N400 indicates that the image generation process is likely to follow the shifting of attention from the short incoming nociceptive stimuli.

Another argument that requires consideration is that the N400 obtained could have been elicited by semantic memory processing which is commonly associated with imagery of visual or auditory modality (Pylyshyn, 2002). In other words, could it be possible for the subjects to employ semantic memory processes when generating the previously learnt sub-nociceptive images in the imagery trials? This could be in the form of attaching a "semantic label" to each level of the nociceptive stimulus. A review of the experimental design and empirical results does not seem to support this speculation. First, the subjects in both the imagery and perception conditions were required to generate and maintain somatosensory images for a total of 3000 ms followed by making response to judge the intensity of the images. The response was based on comparing the intensity of the stimulus presented by the end of the 3000 ms imagery and that of the generated image. As both nociceptive and sub-nociceptive had been well learned before the experiment, it is less likely that the subject had used a semantic-related strategy when generating the sub-nocicpetive image (as in Imagery condition) but a different strategy when generating the nociceptive image (as in Perception condition) which would have elicited a significant between-condition N400. Second, the training of imagery for the sub-nociceptive sensation did not emphasize its labeling but its intensity, nature and location. It is less probable that the subjects would have consistently used a semantic-related strategy which was more sophisticated to perform in the imagery condition. Nevertheless, the results of this study cannot exclude the possibility that the significant N400 obtained in the imagery condition would be related to the integration of less congruent knowledge, i.e. sub-

nociceptive images into the perceptual experience gained from the incoming nociceptive stimulus. Previous studies suggested that N400 would index knowledge integration (Debruille et al., 2007; Kutas, 2011). In the domain of linguistic stimuli, DeLong and colleagues (2005) reported more negative-going N400s when subjects saw words that did not match with their knowledge or their expectations. Others have suggested that the N400 amplitude can be related to the amount of effort spent on integrating new or incongruent knowledge into existing representations (Barber et al., 2004; Debruille et al., 2007). In the context of this study, the significant N400 component obtained in the imagery condition could reflect knowledge integration when sub-nociceptive images were generated. It is however noteworthy that such a process would not involve significant semantic processing. This is because the incongruence is probably induced and reflected by N400 when the sub-nociceptive imagery internally generated conflicts with the external nociceptive stimulus. This speculation needs to be further substantiated in a future study.

The dipoles identified for the N400 component offer alternative support to the somatosensory imagery processes. The sources estimated at the posterior cingulate gyrus and the lingual gyrus are consistent with the centro-parietal distribution of N400. Previous studies indicated that these sources were likely to mediate modality-independent imagery processes (Daselaar et al., 2010). Furthermore, it has been suggested that the dipole identified around the caudate tail (as part of the striatum) relates to tactile sensation (Belardinelli et al., 2009). These dipole sourcing results support the idea that that N400 is more linked with imagery-related mental processes rather than semantic-related processes.

The mental processes of somatosensory imagery appear to end with a relatively long positive potentiation, P600. This LPC has been shown to represent

kinds of higher-level functions — such as reasoning (Qiu et al., 2008) or retention of images in working memory or further sensory manipulation (Ruchkin et al., 1992; Ventouras et al., 2002). The results obtained in this study tend to suggest it is the extension of the earlier P300 component. The reason is that the posterior sites at which the P600 were elicited were found to be similar to those of the P300. In functional terms, during the attention orientation (reflected by P2) and generation of the sub-nociceptive images (reflected by N400), sensory evaluation and interpretation processes would occur concurrently which are associated with the earlier P300 and later P600. This observation can be further substantiated by Legrain and colleagues' (2002) study which found that the P600 (called the P3b) was elicited when subjects were detecting the infrequent deviant of somatosensory stimuli. This LPC was also reported to relate to retaining of images in working memory for sensory manipulation (Ruchkin et al., 1992; Ventouras et al., 2002). The topography of the LPC revealed in this study is consistent with these studies. Its weak relationship with the magnitude of pain attenuation suggests that this late process plays a less important role in modulating pain perception.

As mentioned in the previous section, the behavioral results support the notion that the normalized NRS rating assigned to the recalled nociceptive images are likely to reflect the outcome of focused attention and imagery of sub-nociceptive images, i.e. pain attenuation. As the NRS rating given by each subject is based on the recall of the first stimulus intensity, the ratings could be influenced by working memory with which the somatosensory images were generated and rehearsed (nociceptive for the perception trials and sub-nociceptive for the imagery trials). The normalized NRS ratings computed by subtracting the NRS score obtained from the imagery condition from that obtained from the perception condition would possibly eliminate the

possible working memory effects, if any. The moderate-to-strong correlations between the normalized NRS ratings and the neurophysiological results further support the argument that the NRS ratings reflected the extent of modulation of pain perception as a result of focused attention and imagery. The P2 component, which is regarded as the "marker" of attention shifts, was found to be more positive-going and peaking at FCz and Cz in the imagery trials compared to the perception trials. This would be consistent with the initiation of sub-nociceptive image generation, reflected by frontal N400. The parietally distributed P300 and P600 could signify respectively the evaluation of sensation after the focused attention process and the maintenance of somatosensory images in working memory. In this study, the images are likely to be the self-generated images of the learnt sub-nociceptive sensation. The relationships between focused attention and normalized NRS ratings on the level 3 recalled nociceptive image was substantiated by its strong to moderate and negative correlations with the amplitudes of the P2 component. The amplitudes of the P300 and N400 components were also found to be moderately and negatively correlated with the normalized NRS ratings assigned by the pain-free subjects, as well as between the P2 and the NRS ratings of the level 3 recalled nociceptive image. The normalized NRS ratings were also correlated significantly with subjects' scores on the Stroop Test suggesting the rating assignment process possibly involved resolving conflicting stimuli measured by the test.

Different mental processes underpinning the Stroop Test have been proposed (Schack et al., 1999). More recent studies have revealed that Stoop effect relates to conflict monitoring and resolution sub served by the anterior cingulate gyrus (Floden et al., 2011; Swick & Jovanovic, 2002). It was further demonstrated that engaging in incongruent trials as in the Stroop task required subjects to energize the rule of color

naming instead of lexicon reading (Apkarian et al., 2009; Wiech et al., 2008; Stuss et al., 2001). In this study, the rule to be energized by the subjects was to generate the corresponding sub-nociceptive image instead of appraising the incoming nociceptive stimulus in the imagery trials. This required the subjects to inhibit appraisal of the incoming stimulus, shift the attention, and generate the sub-nocicpetive image (Filipović et al., 1999; Verleger et al., 2006). The results of dipole-source analysis also suggested the significant P2 waveform elicited over the fronto-central region would be associated with the right cingulate gyrus (BA 24). This offers convergent evidence on the process of conflict monitoring and resolution involved in the early part of the imagery trials after the presentation of the nociceptive stimuli. The lack of significant correlations with the magnitude of the normalized pain rating for other levels of nociceptive stimuli (levels 2 to 4) could be because the subjects found it difficult to differentiate between the intermediate intensity levels of the nociceptive sensation.

FOCUSED ATTENTION AND PAIN PERCEPTION MODULATION AMONG CHRONIC PAIN PATIENT SUBJECTS

The key question asked in the second part of the main study was whether focused attention via somatosensory imagery can modulate nociceptive perception among individuals experiencing chronic pain. A more fundamental question would be whether chronic pain patients could engage in focused attention and generation of sub-nociceptive images. The behavioral results suggested that the cognitive processes associated with focused attention and generation of sub-nociceptive images were largely diminished among the patient subjects (called non-respondents). The results further indicated that there were a sub-group of the patient subjects (about one third.

called respondents) who showed possible reduction of the NRS ratings. The down-modulation effects were found to exist at the Level 2 intensity of the stimulation. The small magnitude of the effect is likely not to be clinically meaningful. The differences in the electrophysiological and other behavioral findings between these two patient sub-groups can offer important and plausible explanations on whether chronic pain patients could engage in focused attention for down-modulation of pain perception. The results will be discussed in the following sections.

Non-responsiveness to Focused Attention of Patient Subjects with Chronic Pain

The results indicated that majority of the patient subjects did not show significant differences in the NRS ratings between the imagery and perception conditions. These findings suggested that despite engaging in the focused attention and generation of sub-nociceptive image protocols, patient subjects failed to down-regulate the pain perception. The behavioral results were different from those obtained from the non-pain subjects. In contrast, a small sub-group of the patient subjects (n=6) showed significant changes in the NRS ratings sharing comparable down-regulation of pain perception similar to that observed in the non-pain subjects. These two sub-groups of patient subjects were found to differ in various ways.

First, the two patient sub-groups were differed in the levels of pain perception. The non-respondent patient subjects reported relatively higher thresholds on the "very painful sensation" (23.13 mA) than the respondent counterpart (16.50 mA). The maximum intensity of the chronic pain (experienced at the time when they participated in the experiment) reported by the non-respondent sub-group was lower than that of the respondent sub-group, reaching a marginal statistical significance

[t(14)=2.01, p<0.055]. Second, the non-respondent patient subjects had significantly lower scores on the Catastrophizing subtest of the CSQ than the respondent patient subjects (p<0.05). These suggested that when compared with respondent patient subjects, non-respondent patient subjects appear to have a higher pain threshold as well as experience a lower intensity chronic pain. The non-respondent patient subjects also tended to be less sensitive and less reactive to pain experience. Putting these together, the non-respondent patient subjects might be less hypervigilant and less flexible dealing with the pain sensation than the respondent patient subjects (McCracken et al., 2010; Wicksell et al., 2008). In the context of this study, the non-respondent patient subjects might be less sensitive to the incoming nociceptive stimuli and less readily engaging in focused attention and manipulating the sub-nociceptive images. Catastrophising has been shown to be a key psychological factor that was positively associated with pain sensitivity among people with chronic pain (Sullivan et al., 2005; Turner et al., 2002; Weissman-Fogel et al., 2008). In other words, those who have a lower tendency for exaggerating negative thoughts and emotions in response to pain, such as the non-respondent patient subjects, would have attenuated pain perception.

The non-responsiveness in focused attention and imagery of sub-nociceptive stimuli manifested among the non-respondent patient subjects may be similar to what has been described as psychological inflexibility (Hayes et al., 1996, 2006; McCracken et al., 2010; Wicksell et al., 2008). It is suggested that, during the course of living with chronic pain, an individual might develop a mental state of acceptance to pain, which refers to the willingness of facing one's own unpleasant feelings arising from the chronic pain (Hayes et al., 2006; McCracken et al., 2006, 2010). These individuals might develop defensive behaviors so as to avoid being exposed to

unforeseeable circumstances that might result in negative psychological experience attributes such as fear and anxiety. As a result, individuals with chronic pain would tend to be less active in engaging in activities and seeking new experience. This is often associated with having an inflexible pattern of action. In this study, focused attention was a novel strategy to the patient subjects. Perceiving the nociceptive stimuli and generating sub-nociceptive images for rehearsal may be caught by the psychological inflexibility among the non-respondent patient subjects. This offers a plausible explanation for the non-effective pain modulation using focused attention among this sub-group of patient subjects. The concept of psychological inflexibility, apart from the significant results of the CSQ, is beyond the scope of this study. Further studies are called for to substantiate the validity of this proposition.

The ERP results shed light on the unique mental processes undergone within the non-respondent patient subjects. First, the amplitude of P2 component – a key marker associated with focused attention yielded non-significant interaction effects for the non-respondent patient subjects. It is noteworthy that the Condition × Laterality effect was statistically significant for the amplitude of P1 component, which peaked at fronto-central regions. Previous ERP studies on nociceptive sensation stipulated that significant P1 reflected the perception and emotional awareness of the incoming sensation, which involved the secondary somatosensory cortex (S2) and the cingulate gyrus (Hoshiyama et al., 2000; Howland et al., 1995; Kitamura et al., 1995, 1997; Yamasaki et al., 2000). It is plausible that the significant P1 elicited by the non-respondent patient subjects suggested an early orientation onto the affective aspect of the nociceptive stimulus. The early affective response might hinder the subsequent orienting processes for undergoing nociceptive imagery, which resulted in the non-significant differences in P2 amplitudes between the imagery and

perception conditions. Future studies should explore the role of psychological inflexibility in influencing focused attention and imagery of nociceptive stimuli. The Psychological Inflexibility in Pain Scale (PIPS) (Wicksell et al., 2008) can be employed for quantifying the extent of the psychological inflexibility in patients with chronic pain.

Responsiveness to Focused Attention of Patient Subjects with Chronic Pain

The small sample size of the respondent patient subjects (6 out of 17) limits drawing strong conclusions from the results of the present study. The trend of lower NRS ratings on the recalled nociceptive images in the imagery rather than the perception condition suggested possible down-regulation of pain perception particularly at the Level 2 electrical intensity by the selected patient subjects. The positive down-regulation is likely to be attributable to the shifting of attention from perceiving a nociceptive sensation to generation and rehearsal of sub-nociceptive images. The behavioral outcomes of the respondent patient subjects were largely similar to those of the pain-free subjects in this study.

Previous studies on focused attention demonstrated that its effects came from manipulating the intensity of the external pain stimulations instead of the emotion aroused from the stimulations (Moseley et al., 2008; Nouwen et al., 2006). The present study adopted this concept and the perception/imagery task involved shifting of attention across nociceptive stimuli and sub-nociceptive images. The nociceptive stimuli were externally presented and felt by the subjects whilst the sub-nociceptive images were internally generated and rehearsed subsequent to the perception of the nociceptive stimuli. As the subjects were required to evaluate the pain felt from

recalling the nociceptive images presented at the beginning of the trial, the reduction of pain NRS ratings is likely to be attributable to the shift from the nociceptive then sub-nociceptive attentional processes.

There were two main behavioral observations in the respondent patient subject group. First, they had higher scores on the Catastrophizing subscale of CSQ than the non-respondent counterparts (Sullivan et al., 1995; Weissman-Fogel et al., 2008), suggesting more exaggerated pain experience among the respondent patient subjects. These scores were moderately and negatively correlated with the normalized pain NRS ratings. In other words, respondent patient subjects who had a relatively less strong tendency for pain catastrophizing would achieve greater pain modulation. These findings are consistent with those reported in Weissman-Fogel et al.'s study (2008). This study employed contact heat and the level of pain modulation negatively correlated with scores on the Pain Catastrophizing Scale (PCS) ($r=–0.34$). Weissman-Fogel et al. explained that individuals with a high tendency of pain catastrophizing would overemphasize the affective component of pain which impaired the ability of modulating the pain felt.

The results of the current study are interesting. First, non-respondent patient subjects had the lowest tendency on pain catastrophizing, i.e. lowest scores on the Catastrophizing subscale of CSQ. The low tendency of pain catastrophizing could associate with psychological inflexibility resulting in diminished focused attention. Second, among the respondent patient subjects, lower tendency on pain catastrophizing was found to have greater down-regulation of the pain perception. It appears, therefore, that more intense pain catatrophizing could impede patient subjects shifting attention from perceiving incoming nociceptive stimulation to internally generate sub-nociceptive images. This would result in smaller down-regulation of the

pain perception. It is plausible that the patient subjects even though managed to engage in focused attention, as indicated by the stronger tendency of pain catastrophizing, could be distracted to the affective aspect of the nociceptive stimulation. The mechanism underlying pain catastrophizing in influencing focused attention and hence pain perception goes beyond the scope of this study. Future studies are called for on exploring the role of pain catastrophizing and pain modulation.

The significant modulation effect brought by focused attention was limited to the Level 2 intensity and within 1 out of 11-point on the NRS. The effects yielded from the respondent patient subjects were weaker than those from the pain-free subjects. The clinical significance of these positive results is less clear and needs to be tested in future clinical trials. Nevertheless, previous studies on focused attention suggested that its effect was associated with the duration of which the nociceptive stimuli were manipulated (Nouwen et al., 2006). The brief presentation (50 ms) of the nociceptive stimulations might hamper the effect of the focused attention. Another explanation for the behavioral differences between the respondent patient and pain-free subjects is the tendency of hypervigilance among the former group. Hypervigilance due to the chronic pain was found to hamper subjects' shifting attention towards external stimuli (Crombez et al., 1999; Karl et al., 2004; Snijders et al., 2010; Veldhuijzen et al., 2006a & b). According to these studies, the chronic pain felt by patients would consume attentional resources which in turn limited orienting attention other stimuli. In the context of this study, the patient subjects would have limited ability of disengaging from perceiving the external nociceptive stimulus for image generation as required in the imagery trials. The results showed that the hindrance of focused attention was stronger as the intensity of the nociceptive stimuli

increased. The higher pain thresholds reported by the respondent patient subjects (4.42 to 20.79 mA) compared to pain-free subjects (3.86 to 14.92 mA) further supported the notion of hypervigilance among the former group. The differences however cannot exclude the fact that the patient subjects took pain medication during the period of experiment which might heighten the pain thresholds.

Despite the small sample size, key findings from the electrophysiological markers in the pain modulation process suggested that the respondent patient subjects shared similar mental processes with the pain-free subjects. Similarities were revealed in the fronto-central distributed P2 and frontal distributed N400 during the imagery trials. Pain-free subjects who showed a down-modulation of pain perception on the recalled nociceptive images elicited more positive-going P2 within the fronto-central regions in the imagery condition compared to the perceptual condition (Table 5.7 & Appendix XXIII (d)). This was observed in the respondent patient group but not in the non-respondent patient subjects. As discussed in relation to the pain-free subjects, previous studies have suggested that a centrally distributed P2 is related to spatial shifting of attention to evoked stimuli (Dowman, 2007a; Friedman, Cycowicz, & Gaeta, 2001). The P2 component was found to relate functionally to inhibitory and response conflict (Hatem et al., 2007; Nataka et al., 2004). These support the notion that during the focused attention process the subjects were required to resolve conflict by shifting their attention from perceiving the incoming nociceptive stimulus to another somatosensory stimulus. It is likely that the respondent patient subjects inhibited the perception of the first incoming nociceptive stimulus but shifted the attention to the self-generated sub-nociceptive image in the imagery trial. The amplitudes of the positive-going P2 were found to be strongly correlated with the normalized pain NRS rating (i.e. levels 1 and 2) ($-0.957 < r < -0.857$, $p < 0.05$) over an

extensive cortical distribution among the respondent patient subjects. In contrast, such relationships were substantially weaker among the non-respondent patient subjects. This further suggests that the patient subjects who did not show positive modulation of pain perception might have experienced problems with shifting the attention.

What is also noteworthy is the Laterality × Site interaction effect found in P2 component in the respondent patient group with the sites on the left side more positive-going than those in right side. (Table 5.19 & Appendix XXVI (c) & (d)) This was not observed among pain-free subjects. The significant fronto-central laterality effect suggests that patients with chronic pain may have undergone plastic changes in the prefrontal regions under the prolonged influence of chronic pain (Apkarian et al., 2004 & 2009; Iadarola et al., 1995; Ducreux et al., 2006; May, 2008; Neugebauer, 2009; Wiech et al., 2008; Zhuo, 2008). The dorsolateral prefrontal cortex (DLPFC) has been regarded as one of the main regions showing neuro-degeneration among people with chronic pain (Apkarian et al., 2004 & 2009; Iadarola et al., 1995; Ducreux et al., 2006; May, 2008; Neugebauer, 2009; Wiech et al., 2008; Zhuo, 2008). Whether the patient subjects have undergone a similar degenerative process is beyond the scope of this study to establish. Nevertheless, evidence from existing literature suggests that people with chronic pain are likely to have some impairment in suppressing pain due to the plastic changes at the prefrontal regions (Apkarian et al., 2009; Lorenz et al., 2003; Wiech et al., 2008). Neuroimaging studies on placebo-induced analgesia have shown that the DLPFC was particularly activated before the noxious stimulation occurred, suggesting its role in pain attenuation.

The pain modulatory mechanism has been found to be mediated by its connections with the anterior cingulate gyrus and the descending pain modulatory system. Chronic pain patients have been shown to have asymmetrical decreased gray

matter density in the DLPFC and thalamic regions (Apkarian et al., 2004 & 2009). This is consistent with the laterality effect obtained in the P2 component analysis of this study, and it supports the view that the decrease in the pain NRS ratings in the imagery condition, the outcomes of the focused attention and imagery of sub-nociceptive sensation, is likely to reflect a pain attenuation effect. The behavioral results obtained from the respondent patient subgroup support this suggestion. First, the respondent patient subjects showed a significant decrease in the normalized pain NRS ratings (NRS in imagery trials minus NRS rating in perception trials) over a much narrower range (Level 2 stimulation) than the pain-free subjects (level 1-4 nociceptive stimulus). This result supports the impeded pain attenuation ability of the respondent patient subjects when compared with the pain-free subjects. Second, the non-respondent patient subjects failed to show significant decreases in the pain NRS ratings and at the same time elicited non-significant P2 and N400 in the imagery condition. This was contrary to the significant elicitation of P1, P300 and P600 in the imagery condition.

It was found that the amplitudes of the N400 component of the respondent subject subjects had significantly less negative-going at Fz and FC sites when compared with the non-respondent counterparts. This late negative component, previously found to be related to the generation and maintenance of visual images (Qiu et al., 2007; West & Holcomb, 2000) and vibrotactile images (Chow et al., 2007), was also revealed in the chronic pain respondents. It also reflects the process of image generation by accessing working memory (Chow et al., 2007; West, 2000). Taking these together, the process subsequent to the shifting of attention from the incoming nociceptive stimulus may be for the patient subjects to generate the image of a corresponding sub-nociceptive image. Due to pre-experiment training, it is likely that

the sub-nociceptive image originated from those well-learnt in the training. The significant N400 component found in the imagery condition in the respondent patient and pain-free subjects but not in the non-respondent patient subjects may suggest that generation of the sub-nociceptive images might be less effective among the latter subgroup.

GENERAL DISCUSSION

Patient Subject Characteristics

One of the merits of this study has been to elucidate the mental processes associated with focused attention and somatosensory imagery for pain modulation among patients with chronic pain. Due to the heterogeneous nature of chronic pain, there are a limited number of studies on this topic (McCaul et al., 1982 & 1984; Nouwen et al., 2006; Moseley et al., 2008). The current study only recruited patients with chronic pain at the lower lumbar region. The purpose was to control the heterogeneity of the subjects. However, there were still shortcomings in terms of the within-group variation and representativeness of the patient subjects. First, there was a wide range of pain history, ranging from 3 to 168 months. The differences in patient subjects' experience particularly the duration of the chronic pain can be a potential confounding factor in the results obtained from this study. For instance, those who experienced longer periods of chronic pain might be more likely to adopt a similar mental set such as inflexibility than those with less experience. This in turn could limit the readiness of learning new cognitive approaches (such as focused attention) to manage pain perception (McCracken et al., 2010; Wicksell et al., 2008). The

behavioral results also reveal that the tendency of pain catastrophizing could affect patient subjects' responses to focused attention and somatosensory imagery. Differences in experiences with chronic pain might also confound this tendency. The more than three-month history of chronic pain inclusion criterion made reference to the common clinical guideline (Hart et al., 2000). Previous literature indicated that patients with chronic pain appear to undergo plastic changes in their brain after three months of experiencing persistent pain (Apkarian et al., 2009; Zhuo, 2008). It is inconclusive, however, whether the plastic changes observed were due entirely to the chronic pain. Future studies will need to be conducted to verify the relationships between pain experience and plastic changes in the brain leading to impediment of fontal function and attention. Finally, as the patient subjects participated in this study were diagnosed with chronic low back pain, the results on focused attention, somatosensory imagery and pain modulation are specific to this group of patients and hence might not be generalized to chronic pain at different regions (e.g. neck and shoulder) or types of pain (e.g. neuropathic pain, fibromyalgic pain).

Experimental Design

Previous studies on focused attention mainly were predominantly behavioral. The subjects were exposed to persistent and tonic pain while they applied a focused attention technique for pain attenuation (McCaul et al., 1982 & 1984; Nouwen et al., 2006). The current study used event-related potential to further explore the mental processes behind focused attention on pain perception. The task design required the subjects to attend first to the nociception before generating a pre-learnt sub-nociceptive image. This not only made the pain become goal-relevant, but also

encouraged the subjects to perceive the nociceptive stimulus in a more controlled and structured way, compared to previous studies (McCaul et al., 1982 & 1984; Nouwen et al., 2006). For example, in Nouwen et al.'s study (2006), the subjects were asked to monitor continually and describe the cold pressor pain across an extended period of time (i.e. 7 minutes). The mental processes were not monitored in the experimental condition and the underlying mental processes were less well defined. The drawbacks of the design used in this study are two-fold. First, auditory prompts were used for the subjects to differentiate imagery or perception trials. This would cause a problem if a subject does not have satisfactory auditory acuity. Second, the type of stimulation might not be the most appropriate since electrical stimulus may only not exclusively trigger nociceptive signals but also mechanical ones. The similarity of this type of stimulus might not be as close to chronic pain as the other stimuli, such as thermal pain and contact heat pain (Kakigi et al., 2000).

Contribution to Theoretical Knowledge

Effects of Somatosensory Imagery through Focused Attention

The findings of this study contribute to the theoretical basis of the processes of somatosensory imagery modulating pain perception in people with chronic pain and the role of the higher cortical centers, including prefrontal cortex, in this kind of pain modulation. The findings shed light on the benefit of using somatosensory imagery as one of the therapeutic interventions to attenuate pain perception among people with chronic pain in the following ways.

This study investigated the attentional processing of painful sensation that was goal-relevant. In other words, pain sensation induced by the nociceptive stimuli was

the focus of the experiment in which the subjects were required to engage in self-regulation processes. A number of previous studies used stimuli other than somatosensory in nature (e.g. visual or auditory stimulus) to induce pain attenuation. Goal-irrelevant pain-related information in either chronic pain patients or healthy individuals may not induce the naturally driven interruption associated with perilous threats (van Damme et al., 2010). The somatosensory stimulus, on the other hand, would more likely induce evolutionary modulation on pain. The design of this experiment attempts to adhere to this notion. Among three attention-related models described in Chapter Two, the Cognitive-Affective Model of the Interruptive Function of Pain (Eccleston et al., 1999) appears to be more relevant to the pain self-regulation phenomenon revealed by our findings. The key findings from this study suggest that pain attenuation might be achieved by orientating attention to cognitive aspect of the nociceptive stimulus (P2 component) and bring attention internally to generate the sub-nociceptive image. This cognitive strategy leads to interruption of attention to the nociceptive sensation and then the perception of the same sensation which was recalled after a few seconds.

According to the extended theory from the Model of the Interruptive Function of Pain (Crombez et al., 2005), hypervigilance to pain occurs among patients with chronic pain. It seems they ruminate over pain processing and catastrophize the negative effect of the pain they bear. Since it is also suggested that drawing attention to pain is not under conscious control, this explains why a distraction strategy is not an effective means of pain modulation for patients with chronic pain. The somatosensory imagery paradigm, which relies on focused attention, basically avoids "enforcing" chronic pain patients to relocate attention away from nociceptive stimulus. Instead, the mental tasks encourage the subjects to focus on the intensity of the

stimulus (Levels 1 – 5) followed by interpretation. According to the parallel treatment model (Leventhal et al., 1989), this would encourage attentional focus on the objective side rather than the affective aspect. The attenuation of pain perception may be achieved by minimizing the effect of the affective aspect (Leventhal et al., 1989; Wiech, 2008). The processes of pain modulation still rely on attentional modulation in which a subject is distracted away from the emotional aspect toward the cognitive aspect. This makes pain sensation goal-relevant.

Neurophysiological Activities under Somatosensory Imagery

The results of this study also enrich knowledge on neurophysiological activities underlying pain attenuation via somatosensory imagery. The ERP component analysis suggested that the P2 component may be the key marker for initation of focused attention in the respondent patient group and the healthy group due to its higher correlated.compared to other components, i.e. P3 and P600. The saliency of the P2 component indicates the process in which the attentional shift is initiated away from the external stimulus and toward the internal images to be generated (Dowman, 2004a, 2007a & b). It has been suggested that the centro-frontal P2 component in imagery condition appeared to be related to the inhibitory process in other response inhibition paradigms (Hatem et al., 2007; Nataka et al., 2004). The dipole analysis revealed the source of P2 could be from anterior cingulate gyus, which has been shown to be related conflict resolution (Floden et al., 2010; Stuss et al., 2001; Swick & Jovanovic, 2002) while the attention needs to be switched to one of the conflicting stimuli. The strong associations between the amplitudes of the P2 component and the magnitude of pain attenuation further substantiate the functionality of this positive component.

Another key marker appears to be the less negative-going N400 in the frontal region. This might be reflecting the period in which the subject generates a pre-learnt sub-painful imagery. The dipole locations were found to be in the posterior cingulate gyurs (modality independent) and caudate nucleus (modality specific) (Belardinelli et al., 2009; Daselaar et al., 2010). This late negative component was also found to relate to pain attention but not as conspicuously as the P200 component. It is stipulated that being able to shift attention towards nociceptive stimulation would be more important for pain modulation

What particularly appeared to be different between the chronic pain respondents and the healthy group in terms of the neurophysiological data is more lateral distribution of the P2 component. This might reflect some plastic changes under the influence of chronic pain influence (Wiech et al., 2008). The similar dipole location in the later components confirms similar sources for the sub-painful imagery. More dipoles found in the chronic pain respondents might imply a broader area of neural substrates for the top-down cognitive task. Further studies are required to confirm the difference due to over-recruitment or insufficiency of related substrates.

Further, the mental processes of the non-respondent patient group differed rather remarkably from the respondent counterparts as revealed from the ERP analysis. For the early ERP components, such as SP2-3 and SP3/P1, there were no significant differences between the imagery and perception conditions for the non-respondent group. In addition, there were no significant differences in the attention-related components P2 for the two conditions. This suggests that this group of subjects with chronic pain may not undergo an attention shift in the first 100-200ms and subsequently did not elicit the salient inhibitory potential. The later components, such as P300, N400 and P600, also showed no significant differences different between the

two mental tasks. Unexpectedly, the only ERP component which was significantly different was the P1 component which appeared to be associated with the amount of pain down-regulation. Previous studies on pain attention (Dowman et al., 2004a and 2007a), suggested the P1 component is related to the emotional awareness of a pain experience. It could originate from the secondary somatosensory cortex (S2) and cingulate gyrus. (Hoshiyama et al., 2000; Howland et al., 1995; Kitamura et al., 1995, 1997; Yamasaki et al., 2000).

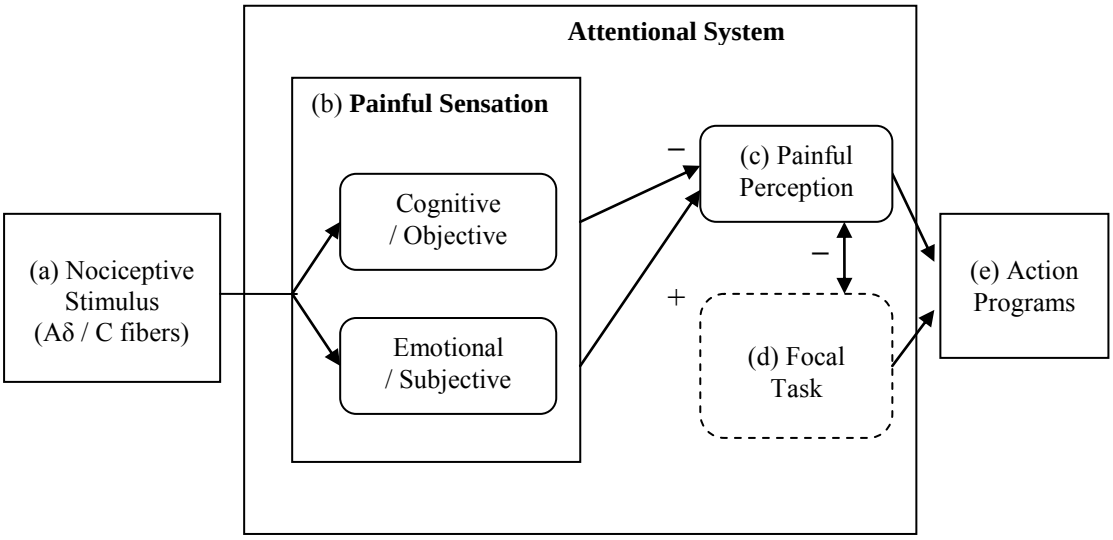
This implies that the subjects in the non-respondent group had more emotional awareness towards nociceptive stimulus rather than the cognitive aspect of it (such as intensity or location). Based on the processes depicted above, a modified conceptual model of pain modulation using focused attention is proposed in Figure 6.1A & B. Under only the perception condition (Figure 6.1A), was the nociceptive stimulus from the electrical stimulator transmitted to the Aδ / C fibers nociceptors (a). The nociceptive signals then reach the somatosensory cortices to form the painful sensation, which is composed of cognitive (objective) and emotional (subjective) components (b). The sensation would then be brought to the attentional system and form a painful perception (c). The painful perception would have negative affects on concurrent focal task(s) (d). This would lead to action programs that respond to the painful experience (e).

Under focused attention situation via somatosensory imagery (Figure 6.1B), the nociceptive signal would also be transmitted to the cortical level (a). Attention system shifts attention to the cognitive aspect of the painful sensation (thicker arrow) and away from the emotional aspect (dotted arrow) (b). With successful focused attention, the painful perception would then be reduced (c). The sub-nociceptive image (regarded as the focal task) based on the cognitive pain sensation would then be

rehearsed and brought to attention system and further negative affect the painful perception (d). The resultant somatosensory perception would lead to action program (if any).

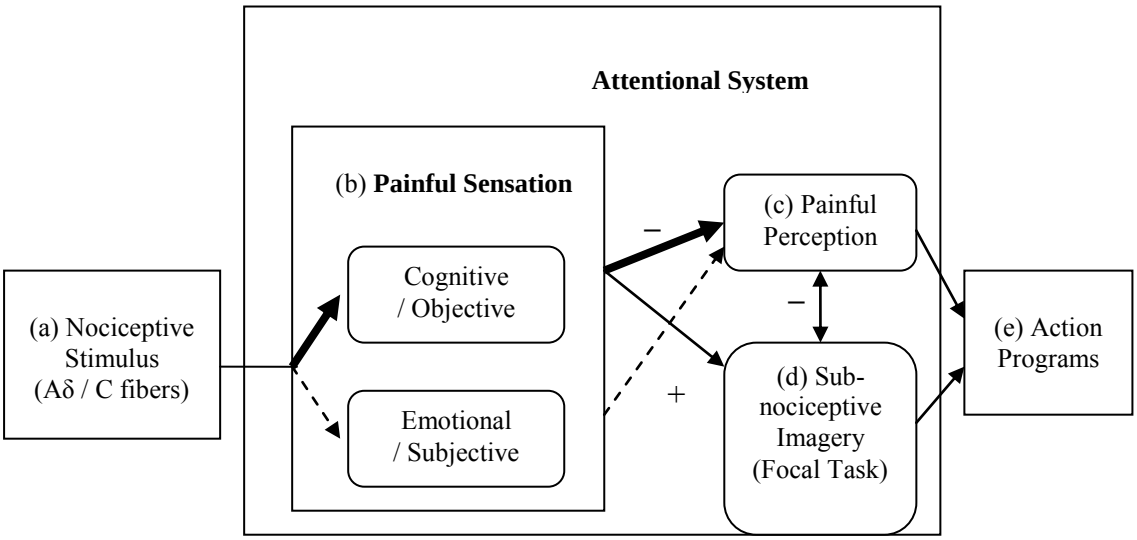
Figure 6.1 Conceptual model of attention-mediated pain modulation using focused attention (Concepts adapted from Eccleston et al., 1999; Leventhal et al., 1989). The strength of influence is indicated by the thickness of the arrows.

(A) Attentional System under Painful Perception



(a) In a perceptual trial, the nociceptive stimulus presented from the electrical stimulator transmitted signals to nociceptors vai Aδ / C fibers. (b) Cognitive (objective) and emotional (subjective) sensations are formed when the nociceptive signals reach the higher-level attentional system. (c) The pain was then perceived. (d) Focal task represents other concurrent cognitive tasks that may attract attention. This would be minimal during the experiment (dotted-line box). The focal task has a reciprocally inhibitory relationship with the painful perception (negative reciprocal arrow) (e) Action would be executed to respond to the pain perceived.

(B) Attentional System under the Influence of Focused Attention



(a) In an imagery trial, the nociceptive stimulus presented from the electrical stimulator transmitted signals to nociceptors via Aδ / C fibers. (b) When the painful sensation reaches somatosensory cortices, the attention system focuses on the cognitive aspect (thicker arrow) and set aside the emotional counterpart (dotted arrow). (c) The overall sensation is then perceived. (d) Based on the intensity of pain sensation (cognitive aspect), sub-nociceptive image is rehearsed by accessing to the working memory (not shown) and brought to the attention system. This focal task engagement may exert an inhibitory effect on the painful perception. (e) Action program is then executed.

Clinical Implications

Application of 11-point NRS for Quantifying Painful and Sub-painful Perception

In this study, the subjects were asked to rate nociceptive and sub-nociceptive stimuli using an 11-point NRS. Using the approximated agreement method, the kappa agreement was high with the weakest stimuli producing the highest agreement. The ICC statistics also revealed satisfactory reliability for lower tactile stimulus (ICC = 0.724; 95%CI = 0.395-0.913) but not so much for the higher-end tactile sensation (ICC = 0.315; 95%CI = -0.502-0.783). This suggests that, despite the barely detectable level, the weakest tactile sensation appears to be more distinctive to the pain-free subjects. As for the nociceptive stimulation, the reliability of rating was an even higher 0.662 (95%CI=0.259-0.893) (for Level 3 intensity) to 0.835 (95%CI=0.634-0.948) (for Level 1 intensity. The results suggested that the 11-point NRS for pain is a reliable scale for pain rating, concurring with previous findings (Jensen et al., 1986; Williamson et al., 2005). The scale seems to also be applicable on sub-painful perception. Since the consistency is somewhat lower, more training for familiarizing the weakest and strongest sub-nociceptive stimulus would be essential to ensure the reliability of the instrument.

Another important finding is that there is a wide between-subject variation in terms of pain tolerance. The current study adhered to the procedures proposed by De Pascalis et al. (2001 & 2008). There was a rather wide variation of voltages across subjects corresponding to the three critical sensory thresholds, i.e. minimal detectable stimuli, just noticeable pin-prick and very painful sensation (NRS = 7). Similar variations have also been reported in previous studies (Dowman et al., 2004a; De Pascalis et al., 2001 & 2008). This reflects that pain perception is subjective since the

same level of voltage elicits different nociceptive stimuli at the periphery and painful perception at the higher cognitive level. The advantage of determining the voltage level given during the experiment according to subjective judgment rather the objective physical nociceptive stimulation is to ensure the actual painful experience is controlled among subjects. As the experimental paradigm actually involved the subjects in modulating painful perception, controlling the subjective aspect of the painful stimulation seems more reasonable. The ERP analysis also suggested that the sub-painful imagery starts with an attentional orientation process which occurs much later than the offset of the somatosensory evoked potential (around 50-70 ms).

Patient Screening and Training

What is important to be aware of when implementing this focused attention strategy on patients with chronic pain? Since there were a fraction of patient subjects, i.e. non-respondents, shown not to benefit from focused attention, screening appropriate subjects might be necessary. This includes assessing baseline coping skills using CSQ or more specific instruments such as Pain Catastrophizing Scale (PCS) (Sullivan et al., 1995; Yap et al., 2004). Further, as non-respondent patient subjects appeared to manifest inflexibility to novel cognitive strategies, instruments that are designed for this particular attribute could be used. This includes Chronic Pain Acceptance Questionnaire (CPAQ) (McCracken et al., 2004; Ning et al., 2008) and newly validated instrument called Psychological Inflexibility in Pain Scale (PIPS) (Wicksell et al., 2008), might be used for screening appropriate patients. According to the presentation of the chronic pain respondents, the patients who are suitable for the focused attention strategy would bear with some level of chronic pain and catastrophizing to pain. If one reports low chronic pain and pain catastrophizing, he or

she might have already adopted certain kinds of coping strategies to deal with their chronic pain and have less potential to benefit from new cognitive strategies. More in-depth interview and psycho-educational approaches might be beneficial in order to prepare these individuals psychologically prior to the introduction of a new cognitive pain modulation technique.

After appropriate patients are screened, a proper training strategy is essential to ensure acquisition of focused attention strategy using somatosensory imagery. Two main stages of training are important. First, sufficient learning time should be given for the patient to get familiarized with the intensity and distinctiveness of different intensity of nociceptive and sub-nociceptive stimuli. Due to subtlety of the latter, extra time might be needed for subjects to encode different levels of sub-nociceptive stimuli. At least 80% accuracy of stimulus recognition is needed. Second, since rehearsing covert sub-nociceptive images would be novel to most of the patients, the training on matching the rehearsed images and the sub-nociceptive stimuli is indispensible for the subjects to consolidate the novel mental processes.

CHAPTER SEVEN

CONCLUSION

REVIEW OF MAJOR FINDINGS

Among the pain-free subjects, the behavioral results indicated their ability to employ focused attention and somatosensory imagery to modulate pain perception induced by external nociceptive stimuli. The results indicate that the effect of focused attention and imagery of sub-nociceptive sensation is influenced by the magnitude of the nociceptive stimuli to be perceived. It is plausible that the higher the level of nociceptive stimulus, the more that it would draw attention and the harder would be the attentional shift away from the stimulus. The consequence is that the higher level nociceptive stimuli would weaken the effect of modulating pain perception particularly down-regulating the intensity of the pain sensation felt from the recalled nociceptive images. The correlational findings from pain-free subjects also suggested that pain down-regulation also involves the ability of conflict resolution that is a frontal lobe function as the subjects were required to switch from the incoming nociceptive stimulus to internally generated image, and then to the recall of the nociceptive image.

The mental processes associated with focused attention and somatosensory imagery down-regulation are reflected in the electrophysiological findings. The fronto-central P2 might be the key ERP component for the focused attention process when it signifies a spatial attentional shift from the nociceptive stimulation felt at the right malleolus to the internally generated sub-nociceptive image. The sub-nociceptive image appears to occur after 400 ms, corresponding to the frontal N400

component. During the whole focused attention processes, the evaluation and categorization of the sensation continually occurs as reflected by parietally located P3 and P600 components. Correlational analyses show that the P2 and N400 were particularly associated with the normalized pain NRS ratings. This implies these attentional shift (P2) and image rehearsal (N400) might play important roles in creating the modulatory effect on pain perception. Behaviorally, pain modulation effects reflected by the differences in the NRS ratings between imagery and perception trials were only found within low intensity nociceptive stimulations. The magnitude of the pain modulation might not reach a level to be regarded as clinically significant. This could be due to the short duration of training received by the subjects, particularly the patient subjects. Another plausible reason is that the second stimulus presented before the rating of the recalled nociceptive stimulus (nociceptive for perception trials or sub-nociceptive for imagery trials) might attenuate their ratings.

The observations gained from the pain-free group form the basis for understanding the effect of mental processes associated with focused attention and somatosensory imagery for pain modulation among patients with chronic pain. Both behavioral and neurophysiological data indicated that the patient subjects' responses to focused attention and to a lesser extent pain down-regulation can be classified into two categories: responsive versus non-responsive. The non-respondent patient subjects were found to be less responsive to use focused attention and somatosensory imagery. This was different for the pain-free subjects. The non-respondent patient subjects tended to score lower on the Catastrophizing subscale of CSQ than the respondent counterparts, suggesting that they were less sensitive to the negativity of pain. While the P2 did not significantly differ between imagery and perceptual conditions, the P1 was found to be significantly different between the two task

conditions. This finding suggests that the non-respondent patient subjects might be more aware of the affective aspect of the nociceptive stimulus rather than its intensity when they underwent the shift of attention and imagery strategy. Although further investigations are definitely needed, non-respondent patient subjects are more likely to have psychological inflexibility that might hinder their ability to apply new cognitive techniques to modulate pain perception (McCracken et al., 2010). As a result, they tended to benefit less from learning the focused attention and somatosensory imagery for achieving the pain modulation**.**

The respondent patient subjects, constituting about one-third of the patient subjects appeared to be able to engage in focused attention and somatosensory imagery whilst the majority patient subjects failed to do so. In terms of pain rating, the effects of pain down-regulation seem to be confined to the lower level of nociceptive stimuli and a narrow range. The pain-related and frontal lobe function test results suggest that their discrepancies with the pain-free subjects might be attributable to patients' hypervigilance to pain phenomenon using a catastrophizing strategy when coping with pain. The results obtained from event-related potentials indicate that the respondent patient subjects are likely to undergo similar mental processes as the pain-free subjects when engaging in focused attention and somatosensory imagery for pain down-regulation. The P2 and N400 components were found to be significantly different, suggesting the involvement of attention orientation (Dowman, 2004b & 2007a; Polich, 2007) and generation of somatosensory images (Chow et al., 2007), respectively. The main differences between the pain-free subjects and the respondent patient subjects, was a Condition × Laterality effect in the P2 for the respondent patient subjects (attentional shift), suggesting possible modulation in the shift of attention processes possibly resulting from the chronic pain experience.

LIMITATIONS OF THE PRESENT STUDY

This study has a number of limitations. The discussion will be focused on three aspects: experimental design, stimulus and subject recruitment.

For ethical reasons, the experimental design was not a fully crossed design in the experimental paradigm. Subjects were asked to generate a nociceptive image while given a sub-nociceptive stimulus. The pain "up-regulation" strategy would have encouraged pain exaggeration or even catastrophizing to pain. This would be particularly contradictory for patients with chronic pain. It would lead to a stimulus bias in which more nociceptive stimuli would be presented to the subjects when compared to the sub-nociceptive counterparts. The pain rating would be skewed towards higher pain rating.

Another shortcoming in the experimental paradigm is that the subjects were instructed to rate the pain intensity perceived on the 50 ms nociceptive stimulus which was presented at the beginning of the trial. This would require the subjects to recall the image maintained and based on what had been recalled to assign a NRS rating. The pain perception process could have been influenced by the subjects' ability of recall and vividness of motor imagery. This might confound the pain NRS ratings. The normalized NRS ratings could possibly alleviate the biases associated with within-group variations in recall and motor imagery functions. To improve paradigm design in future studies, the nociceptive stimulus can be sustained throughout the imagery and subjects would need to simultaneously engage simultaniously in the imagery of sub-nociceptive images whilst exposed to the stimulus. The main obstacle for this design would be the tremendous interferences both in the mental processes

and the electrophysiological signals captured during the trial. This would impede the signal to noise ratio of the results. Future exploration is needed to resolve this issue.

A further disadvantage of the experimental design was the simultaneous presentation of the first nociceptive stimulus (S1) and the auditory cues. The auditory cue might draw a portion of the attention towards a nociceptive stimulus. Thus an auditory cue with the same duration might be more appropriate to present before the onset of the nociceptive stimulus and serve as a prime for either perception or imagery trials. Besides, the experimental task was relatively complex. The extent to which patients learned and then generated sub-nociceptive sensations during the imagery trials was not calibrated. This left the within-subject variation uncontrolled, which might weaken the power of the study.

Besides, in terms of stimulus presentation, a nociceptive sensation induced by an electrical stimulus might not be the most appropriate since the electrical stimulation may not only trigger nociceptors but also receptors, such as mechanoreceptors (Gugino, et al., 1990; Kakigi et al., 2000; Katayama, 1985). Due to technical limitations of the electrical stimulators, only phasic stimuli with duration of 50 ms were presented in the ERP experiment. The characteristics of the electrical stimulus presented in the experiment would be different from those of chronic pain, which appears to be long-lasting (tonic) and more purely nociceptive. The clinical implication of findings from this study would be limited since acute pain was not under study. This problem might be resolved if other types of nociceptive stimuli are used, such as laser (Forss et al., 2005, Hatem et al., 2007) and heat (Chen et al., 2005; Forss et al., 2005). Chemically induced pain (e.g. application of capsaicin) of persistent thermal pain may be used to simulate persistent tonic pain on subjects (Kóbor et al., 2009).

The sample size of the patient subjects was relatively small, particularly when the patient subjects were required to be divided further into the respondent and non-respondent subgroups. This weakened the power of the statistical analyses. The results should be interpreted with caution. For the subject selection, data on pain rating suggests that there might be heterogeneity among patients with chronic pain that might affect the effectiveness of somatosensory imagery on pain perception. This weakens the power of the analysis in the chronic pain group. In a future study, better screening methods would be needed to identify patients with chronic pain who might benefit from the novel somatosensory image technique. As mentioned in the previous chapter, instruments such as the Pain Catastrophizing Scale (Sullivan et al., 1995; Yap et al., 2004), Chronic Pain Acceptance Scale (McCracken et al., 2004; Ning et al., 2008) and Psychological Inflexibility in Pain Scale (PIPS) (Wicksell et al., 2008) would be used collectively to screen potential subjects for the new cognitive strategy. Based on the findings from chronic pain patients, it is suggested that some types of chronic pain patients who bear relatively low catastrophizing to pain and relatively high tolerance on external nociceptive pain, might have hindered ability to acquire new cognitive strategy to modulate pain. Finally, the findings can only be generalized to patients with chronic mechanical pain in nature since the chronic pain the patients had was mechanical.

SUGGESTION FOR FURTHER STUDY

This study offers some initial findings on the neural processes associated with the effects of focused attention and imagery on modulating pain perception. Further studies need to be conducted to enrich further the knowledge in the area. A study

using randomized controlled trial design could be conducted to examine the effectiveness of the somatosensory imagery strategies. With a more stringent screening method based on demographic data and neuropsychological scores (see previous section), patients with chronic pain can be randomly allocated to experimental and control in clinical settings. The experimental group would be training to use somatosensory imagery for pain modulation while the control group simply received conventional pharmaceutical interventions and physical therapy. Future studies should recruit participants with pathological pain, such as neuropathic pain, allodynia (i.e. painful sensation caused by innocuous stimuli), hyperalgia (an exaggerated response to noxious stimuli) to see if the intervention works for them. Future studies can test one of the proposed mechanisms by testing people with problems in inhibitory response, furthering our understanding of the neural processes of pain modulation. The findings shed light on the possible application of focused attention and self-generated sub-nociceptive images to individuals with chronic pain or frontal-lobe dysfunction. As has been discussed, the effect of pain modulation might be confounded by the recall process due to the short duration of electrical stimuli in this study, i.e. 50 ms, presenting at the beginning of each trial and the relatively long imagery period, i.e. 3000 ms. In future studies, more tonic electrical stimuli could be presented concurrently with the imagery period by subjects. The optimal intensity and duration of electrical stimuli need to be sought in order to enhance the signal-to-noise ratio for examine the temporal processes of focused attention on pain modulation.

Furthermore, validity studies on instruments that would help screen potential patients for the imagery technique are worthwhile studying. One of the relevant studies would be Psychological Inflexibility in Pain Scale (PIPS). This 16-item

instrument with two-factor structure can help to identify patients with chronic pain having propensity to avoid pain and cognitive fusion, in which they tend to merge personal thought with actual events (Wicksell et al., 2008). This would limit their capacity in adopting a new cognitive strategy to regulate pain modulation.

Neuroimaging studies could be carried out in the future to provide a better understanding about pain modulation and the role of frontal lobe function. ERP studies could be conducted to further examine the temporal processes of somatosensory imagery on tonic pain, i.e. pain sensation with prolonged duration (e.g. heat pain and drug-induced pain). The literature so far mainly focuses on the modulation of externally induced pain (e.g. Dowman, 2007a; Hatem et al., 2007; Legrain et al., 2002). It is worthwhile to investigate the mental processes of self-regulation on patients' actual chronic pain. This would substantiate the application value of the somatosensory imagery strategy to benefit patients with chronic pain in clinical settings. As the ERP component analysis suggested possible neuroplastic changes in people with chronic pain (as reflected by the laterality interaction in P2 and other earlier components), functional magnetic resonance imaging and diffusion tensor imaging techniques could be conducted to investigate the possible differences in chronic pain patients in terms of brain activations and connectivity during somatosensory imagery strategy. Since the ERP analysis suggested that the P2 component could be a key neurophysiological marker for successful initiation of attention focused process, biofeedback studies could also be designed in the future in order to specifically examine the saliency of this ERP components in relation to pain modulation.

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APPENDICES

Appendix I Letter of Ethics Approval of Department Committee, Department of Rehabilitation Sciences

THE HONG KONG
POLYTECHNIC UNIVERSITY
香港理工大學

MEMO

To : CHAN Che Hin, Department of Rehabilitation Sciences
From : NG Yin Fat, Chairman, Departmental Research Committee, Department of Rehabilitation Sciences

Ethical Review of Research Project Involving Human Subjects

I write to inform you that approval has been given to your application for human subjects ethics review of the following research project for a period from 13/06/2009 to 31/12/2012:

Project Title : Visualization Replacement Modulating Perception of Chronic Pain: An Event-related Potential Study

Department : Department of Rehabilitation Sciences

Principal Investigator : CHAN Che Hin

Please note that you will be held responsible for the ethical approval granted for the project and the ethical conduct of the research personnel involved in the project. In the case the Co-PI has also obtained ethical approval for the project, the Co-PI will also assume the responsibility in respect of the ethical approval (in relation to the areas of expertise of respective Co-PI in accordance with the stipulations given by the approving authority).

You are responsible for informing the Departmental Research Committee Department of Rehabilitation Sciences in advance of any changes in the research proposal or procedures which may affect the validity of this ethical approval.

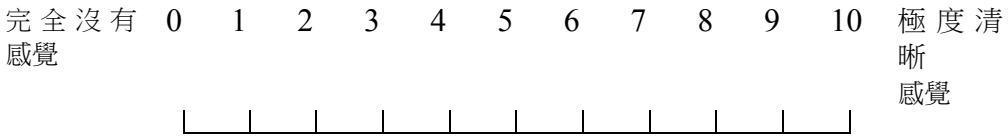
You will receive separate notification should you be required to obtain fresh approval.

NG Yin Fat
Chairman
Departmental Research Committee
Department of Rehabilitation Sciences

Appendix II An eleven-point Numeric Rating Scale (NRS) of Sub-painful Sensation (Chinese and English Versions)

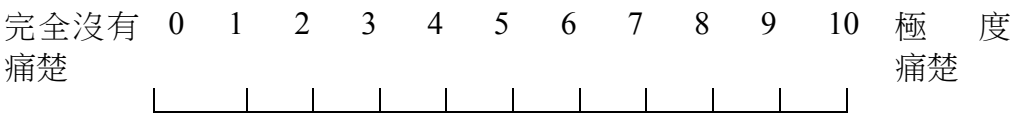
觸覺程度量表

Numeric Rating Scale (NRS) of Sub-painful Sensation (11-point scale)



Appendix III Eleven-point Numeric Rating Scale (NRS) of Pain

Numeric Rating Scale (NRS) of Pain Sensation (11-point scale)



Appendix IV Record Form of Sub-nociceptive and Nociceptive Rating during Training Session

Pilot #_____ Name: _____ Sex: _____ Age: _____

Recording Sheet

Min Detectable Stimulus (Asc.)	Min Detectable Stimulus (Desc.)	Min Detectable Stimulus (Average)	Just noticeable pinprick	Very painful pinprick (NRS=7)	Unbearable pain (NRS=10)

Rating Consistency

Starting Row: ___	Sub-nociceptive					Nociceptive				
	1	2	3	4	5	1	2	3	4	5
	2	3	5	4	1	2	3	5	4	1
1. NRS										
	3	4	1	5	2	3	4	1	5	2
2. NRS										
	1	2	4	5	3	1	2	4	5	3
3. NRS										
	3	2	5	4	1	3	2	5	4	1
4. NRS										
	2	5	3	1	4	2	5	3	1	4
5. NRS										
	5	4	2	3	1	5	4	2	3	1
6. NRS										
	3	2	1	5	4	3	2	1	5	4
7. NRS										
	4	1	3	5	2	4	1	3	5	2
8. NRS										
	2	5	1	3	4	2	5	1	3	4
9. NRS										
	4	3	1	2	5	4	3	1	2	5
10.NRS										

Appendix V Information Sheet for Control Group (Chinese Version)

香港理工大學復康治療科學系

研究項目介绍

研究題目
意象調整痛楚感知：事件相關腦電位研究

研究成員
陳子頌先生及陳智軒教授

研究目的
探討患有長期痛楚人士進行感覺意象取代以調整痛楚感知時，各個腦部區域活動的情況。

研究內容
本研究實驗分三節進行：

- 在第一節中，你須要填寫一連串有關個人資料、痛症的病歷 （如適用）、處理痛楚策略、產生意象清晰能力及額葉功能的問卷調查及測試。隨後你會接受不同程度的電刺激以分別確定你的觸覺及痛覺起端水平。然後，你會接受一小時使用觸覺及痛覺程度量表的訓練。隨後你便參與兩小時的接受觸感及痛感後評分的實驗，期間腦電活動將同時記錄下來。第一節需時四小時。

- 在第二節中，在研究員的指導下，你先須要記住不同程度電刺激感覺。並在感覺到不同程度觸覺及痛覺刺激的情況下，在腦海中想像先前記住的感覺以代替真實的感覺。第二節的訓練時間為兩小時。

- 在第三節中，你會參與第二次的腦電活動記錄的實驗。在接受不同電刺激的情況下，你須要在腦海想像出在第二節中記住觸覺及痛覺的意象，以代替真實的感覺。

實驗的總時間約為十小時。研究員會帶領你進行每個部份的實驗程序。若在過程中感到覺疲倦或不適時，你可稍作休息。

潛在危險及權利
縱使在實驗中涉及痛楚之刺激，我的身體將不會受到任何的損傷。參與本研究項目乃純屬自願性質。我有權利在任何時間及任何理由下終止實驗。

Appendix VI Information Sheet for Control Group (English Version)

The Hong Kong Polytechnic University
Department of Rehabilitation Sciences

Research Project Information Sheet

Project title:

Visualization Replacement Modulating Perception of Chronic Pain: An Event-related Potential Study

Investigators:

Mr. Sam C. C. Chan and Professor Chetwyn C. H. Chan

Purpose of the study:
To investigate the brain processes of people with chronic pain when being asked to imagine sensation to alter pain perception

Project information:
The experiments will be conducted in three sessions:

- On the first session, you will be first asked to complete a series of questionnaires concerning personal particulars, pain history (if applicable), pain coping strategies, vividness of sensory imagery and frontal lobe function. Afterward, you will receive a range of electrical stimuli applied by an electrical stimulator in order to determine tactile and pain thresholds. You will receive a one-hour training session to rate painful or below-pain stimuli given by a pain stimulator. A two-hour experiment will be conducted, in which you will be required to perceive tactile and pain sensation given by an electrical stimulator and give sensory rating for each sensation while electroencephalogram (EEG) is being recorded. The total time will be 4 hours.

- On the second session, with the investigator's instruction, you will be trained to remember the different levels of electrical intensities given by an electrical stimulator. You will be guided how to generate sensation image previously remembered in my mind and replace it with the perception give by the electrical stimulator. This will take about two hours.

- On the third session, there will be another EEG session. You will be given different intensities of sensory stimuli and you will be required to generate different sensory imagery learned in the second session. This session will last for four hours.

The total time will take approximately ten hours. The study investigator will guide you through the procedures in all sessions. I will be provided with breaks in case of tiredness or discomfort.

Potential Risks and Rights:
Although the study involves painful stimuli, no damages to your body will be the consequence of the experiments and you will not experience any unnecessary pain. Participation is completely on voluntary basis and subjects have the right to withdraw from study at any time or with any reason.

Appendix VII Informed Consent for Control Group (Chinese Version)

香港理工大學復康治療科學系

參加者同意書

研究題目
患有長期痛楚人士的感覺意象對痛楚感知調整之影響：事件相關腦電位研究

研究成員
陳子頌先生及陳智軒教授

研究目的
本是香港理工大學復康治療科學系之研究項目。其目的乃利用事件相關腦電位去尋求出患有長期痛楚人士進行感覺意象以調整痛楚時，各個腦部區域活動的過程。

研究內容
本研究實驗分兩天進行。在第一天實驗開始之前，我需要填寫一連串有關個人資料（如痛楚病歷）、處理痛楚策略、情緒及感覺意象能力的問卷調查。隨後，我將會參與兩小時有關觸感及痛感感知及意象的實驗，期間腦電活動將同時記錄下來。在第二天，我將參與一個需時約四小時有關兩種不同痛楚調整策略的實驗。總實驗的時間約為七小時。主研究員會帶領我進行所有的實驗程序。若感到覺疲倦或不適時，我可稍作休息。

潛在危險及權利
縱使在實驗中涉及痛楚之刺激，我的身體將不會受到任何的損傷。參與本研究項目乃純屬自願性質。我有權利在任何時間及任何理由下終止實驗。

同意書
本人 _____（香港身分證號碼：_____）明白此項研究之細節，並聲明自願參加此項研究。我明白可以隨時在不需作出解釋之情況下退出此項研究，而將不會受到處罰或歧視。我悉知參與本研究當中帶的潛在危險。我明白本人之個人資料將不會向本研究以外之人士公開，並且我的姓名或照片將不會出現於任何研究之報告內。所有資料會於研究完成後銷毀。

本人可致電 2766 4845 或 9745　　向研究員陳子頌先生查詢本研究事宜。若果我對研究員有任何投訴，可致電 27665397，與 Mrs. Michelle Leung 接洽。我將受予簽署同意書副本一份。

參加者簽署：_____　　日期：_____

見證人簽署：_____　　日期：_____

Appendix VIII Informed Consent for Control Group (English Version)

The Hong Kong Polytechnic University
Department of Rehabilitation Sciences

Research Project Informed Consent Form

Project title: The effect of Imagery on Modulation Pain Perception in People with Chronic Pain: An Event-related Potential Study

Investigators: Sam C. C. Chan and Professor Chetwyn C. H. Chan

Purpose of the study: To investigate the mental processes reflected by event-related potentials of somatosensensory imagery to modulate pain perception

Project information: The experiments take place in two days. On the first day, I will be asked to complete a series of questionnaires on personal particulars (e.g. pain history), pain coping strategies, emotion and self-perceived ability of sensory imagery before the experiment session. Afterward, a one-hour training session will be conducted in order to standardize my pain scale with painful or tactile stimuli given by a pain stimulator. A two-hour experiment will be conducted, in which I will be required to perceive tactile and pain sensation and generate the corresponding imagery while electroencephalogram (EEG) is recorded. On the second day, I will be in another four-hour EEG experiment, in which I will be required to modulate pain perception using two different strategies. The total time will take approximately seven hours. The chief investigator will guide me through the procedures. I will be provided with breaks in case of tiredness or discomfort.

Potential Risks and Rights: Although the study involves painful stimuli, no damages to my body will be the consequence of the experiments. Participation is completely on voluntary basis and subjects have the right to terminate from study at any time or any reason.

Consent: I, _____ (HKID no. _____), have been explained the details of this study. I voluntarily consent to participate in this study. I understand that I can withdraw from this study at any time without giving reasons and withdrawal will not lead to any punishment or prejudice against me. I am aware of any potential risk in joining this study. I also understand that my personal information will not be disclosed to people who are not related to this study and my name or photograph will not appear on any publications resulted from this study. All personal information will be discarded upon the completion of the study.

I can contact the study coordinator, Mr. Sam C.C. Chan at telephone 2766 4845 or 9745 , or the project supervisor Prof. Chetwyn C.H. Chan at 2766 6727 for any questions about this study. If I have complaints related to the investigator(s), I can contact Mrs. Michelle Leung, Secretary of Department Research Committee, at 2766 5397. I know I will be given a signed copy of this consent form.

Signature (subject): _____ Date: _____
Signature (witness): _____ Date: _____

Appendix IX Demographic Data Form (Chinese Versions)

參加者個人資料問卷

日 期 : _____

姓 名 : _____

1. 年 齡 _____

2. 性 別 □1.男 □2.女

3. 婚姻狀況 □1.未婚 □2.已婚 □3.分居／離婚
□4.喪偶 □5.其他 _____

4. 教育程度： □1.小學程度或以下
□2.小學畢業
□3.中學程度
□4.中學畢業
□5.預科
□6.大專／大學
□7.大學或以上

5. 就業情況
□1. 失業／沒有工作
□2. 兼 職 工 作, 你 的 工 作 是 _____
□3. 全 職 工 作, 你 的 工 作 是 _____
□4. 學 生
□5. 家 庭 主 婦
□6. 退 休

Appendix X Demographic Data Form (English Versions)

Personal Information

Name: _____

1. Age: _____

2. Sex: □ Male □ Female

3. Marital Status: □1.Single □2. Married □3.Separate／Divorced
□4.Widowed □5. Others _____

4. Education Level:
□ 1. Primary level or below
□ 2. Primary graduate
□ 3. Secondary level
□ 4. Secondary graduate
□ 5. Matriculation
□ 6. Undergraduate
□ 7. Postgraduate

5. Employment Status:
□ 1. Unemployment
□ 2. Part-time job (Occupation: _____)
□ 3. Full-time job (Occupation: _____)
□ 4. Student
□ 5. Homemaker
□ 6. Retired

Appendix XI Vividness of Visual Imagery (VVIQ) (Chinese Version)

視覺意象逼真程度問卷

請細閱以下 16 條題目，試想像每題目所描述的情景，然後就你所想像的景物之逼真程度，給予“1”至“5”分的評級，請把分數寫在該題目旁邊。

評分級別如下：
5 = 極度清晰和逼真，就如眼前所見一樣
4 = 很清晰和逼真
3 = 中度清晰和逼真
2 = 模糊不清和昏暗
1 = 在腦海裡完全沒有影像，只知道在想著一些物件

在第 1 至 4 題中，試想像一些你經常見到的親人及朋友(但此時他們並不是和你在一起的)，然後細想那在你腦海裡出現的影像。

題目	評　分 (1 至 5)
1. 他們的面貌、頭部、肩膊和身體的細緻輪廓。	_____
2. 他們的頭部、身體的姿勢特徵。	_____
3. 他們步行時的每一個步姿、踏步的闊度等。	_____
4. 一些他們慣常穿著之衣服的顏色。	_____

在第5至8題中，試想像一個初升的太陽。然後細想那在你腦海裡出現的影像。

題目	評分 (1 至 5)
5. 太陽正在水平線上升起，進入滿佈薄霧的天空。	_____
6. 天空變為晴朗，太陽給蔚藍的天空包圍著。	_____
7. 雲層漸厚，風暴和閃電來臨。	_____
8. 天空中出現一道彩虹。	_____

在第9至12題中，試想像一間你經常光顧的店舖的外觀，然後細想那在你腦海裡出現的影像。

題目	評分 (1 至 5)
9. 從對面馬路所見該店舖的外觀。	_____
10. 櫥窗的佈置，包括各種貨品的顏色、形狀和細節。	_____
11. 你正站在店舖門前，在你面前那扇門的顏色、形狀和細節。	_____
12. 你進入了店舖後走到櫃台，櫃台的職員接待你，並給你找續。	_____

在第 13 至 16 題中，試想像一下郊外的景物，包括樹木、山脈和湖泊，然後細想那在你腦海裡出現的影像。

題目	評分 (1 至 5)
13. 郊外地形的起伏。	_____
14. 樹木的顏色和形狀。	_____
15. 湖泊的顏色和形狀。	_____
16. 一陣強風吹向樹木和湖面，泛起陣陣波浪。	_____

問卷完。

Appendix XII Vividness of Visual Imagery (VVIQ) (English Version)

VIVIDNESS OF VISUAL IMAGERY QUESTIONNAIRE

Read each of the 16 items carefully. The items of the test will possibly bring certain images to your mind. You are asked to rate the vividness of each image a 5-point scale given below.

The image aroused by an item might be:
1 = Perfectly clear and as vivid as normal vision
2 = Clear and reasonably vivid
3 = Moderately clear and vivid
4 = Vague and dim
5 = No image at all, you only "know" that you are thinking of an object

In answering items 1 to 4, think of some relative or friend whom you frequently see (but who is not with you at present) and consider carefully the picture that comes before your mind's eye.

Item	Rating (1 至 5)
1. The exact contour of face, head, shoulders and body.	_____
2. Characteristic poses of head, attitudes of body etc.	_____
3. The precise carriage, length of step, etc. in walking.	_____
4. The different colours worn in some familiar clothes.	_____

For items 5 to 8, visualise the rising sun. Consider carefully the picture that comes before your mind's eye.

Item	Rating (1 至 5)
5. The sun is rising above the horizon into a hazy sky.	_____
6. The sky clears and surrounds the sun with blueness.	_____
7. Clouds. A storm blows up, with flashes of lightening.	_____
8. A rainbow appears.	_____

For items 9 to 12, think of the front of a shop which you often go to. Consider the picture that comes before your mind's eye.

Item	Rating (1 至 5)
9. The overall appearance of the shop from the opposite side of the road.	_____
10. A window display including colours, shape and details of individual items for sale.	_____
11. You are near the entrance. The colour, shape an details of the door.	_____
12. You enter the shop and go to the counter. The counter assistant serves you. Money changes hands.	_____

Finally, for items 13 to 16, think of a country scene which involves trees, mountains an a lake. Consider the picture that comes before your mind's eye.

Item	Rating (1 至 5)
13. The contours of the landscape	_____
14. The colour and shape of the trees	_____
15. The colour and shape of the lake	_____
16. A strong wind blows on the tree and on the lake causing waves	_____

End of Questionnaire

Appendix XIII Stroop Test

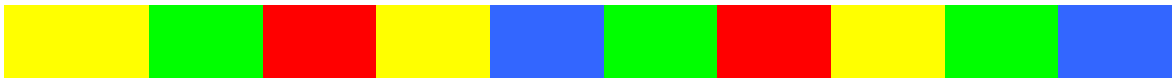
First ten stimuli (in Chinese) in word reading:

綠　紅　黃　藍　黃　紅　藍　綠　紅　黃

First ten stimuli (in English) in word reading:

green　red　yellow　blue　yellow　red　blue　green　red　yellow

First ten stimuli in color naming:



First ten stimuli (in Chinese) in incongruent color naming:

綠　紅　黃　藍　黃　紅　藍　綠　紅　黃

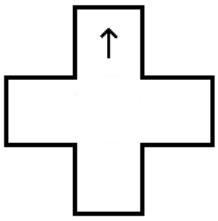
First ten stimuli (in English) in incongruent color naming:

green　red　yellow　blue　yellow　red　blue　green　red　yellow

Appendix XIV Two Samples of Trials Shown on the Monitor in Arrow Test

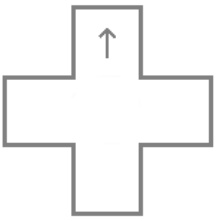
The left figure represents one sample of compatible trial with a black arrow and the right figure represents one sample of incompatible trial with grey arrow. The respondent is required to press the key with the same direction in compatible trials and to press the key with an opposite direction in incompatible trials.

黑色箭头的范例



因这箭头是**黑色**，所以应按与箭头方向相同的键（“上”键）。

灰色箭头的范例



因这箭头是**灰色**，所以应按与箭头方向相反的键（“下”键）。

Appendix XV Ethics Approval of Ethics Committee of Hospital Authority

基督教聯合醫院
UNITED CHRISTIAN HOSPITAL
香港九龍觀塘協和街一百三十號
130, Hip Wo Street, Kwun Tong, Hong Kong

Tel :
電話號碼 :
Fax :
圖文傳真 :

27 October 2009

Mr. CHAN Chi-chung Sam

Dear Mr. CHAN,

We are pleased to inform you that you will be permitted to attach in the Pain Clinic of United Christian Hospital of the Hong Kong Hospital Authority ("HA") for the period of 1 November 2009 to 31 October 2010.

During the above-mentioned period of attachment, you will be required to observe the instructions of the hospital and any house rules and regulations that may be applicable including any applicable clinical and non-clinical guidelines and infection control measures. Before commencement of your attachment, you will be required to undergo such necessary training as may be organized by the HA including infection control precautions.

For the avoidance of doubt, this arrangement does not create an employer-employee relationship between yourself and the HA and permission for such arrangement may be withdrawn at any time.

You will keep all information that you obtain whether directly or indirectly including those pertaining to patients confidential. Such obligation will survive after your attachment hereunder.

You acknowledge that copyright and ownership of all documents, medical or otherwise, that you create whilst on attachment to the hospital will vest in and belong to the HA.

As you are not an employee of the HA, you will not be entitled to receive any wages or benefits from the HA for the services performed.

Yours sincerely,

(Echo CHENG)
for Cluster General Manager(HR)
Kowloon East Cluster

I accept the offer on the terms and conditions as set out above.

Signature : _____

Name : _____

Date: _____

Appendix XVI Information Sheet for Chronic Pain Group (Chinese Version)

香港理工大學復康治療科學系

研究項目介绍

研究題目
意象干預長期痛楚感知：事件相關腦電位研究

研究成員
陳子頌先生、陳智軒教授、香港醫管局靈實醫院徐德義醫生及聯合醫院關少瓊醫生

研究目的
探討患有長期痛楚人士進行感覺意象取代以調整痛楚感知時，各個腦部區域活動的情況。

研究內容
本研究為靈實醫院、聯合醫院及香港理工大學復康治療科學系合作項目，以便資料有效地傳送。實驗過程分三節進行,，總時間約為十小時：

- 在第一節中，你須要填寫一連串有關個人資料、痛症的病歷 （如適用）、處理痛楚策略、產生意象清晰能力及額葉功能的問卷調查及測試。隨後你會接受不同程度的電刺激以分別確定你的觸覺及痛覺起端水平。然後，在研究員的指導下，你先須要記住不同程度電刺激感覺。並在感覺到不同程度觸覺及痛覺刺激的情況下，在腦海中想像先前記住的感覺以代替真實的感覺。第一節的程序需時三小時。

- 在第二節中，你會參與一個在腦電活動記錄下進行的實驗。在接受不同電刺激的情況下，你須要在腦海想像出在第一節中所記住的觸覺及痛覺意象，以干預電刺激所帶來的真實的感覺。第二節的實驗需時四小時。

- 在第三節中，你會被邀請出席一個訓練項目。當中你會學習如何將早前兩節中學到的觸覺及痛覺意象應用於你的長期痛楚上。第三節的訓練時間為三小時。

以上程序於理工大學應用認知神經科學實驗室內進行，你須前往該處參與訓練及實驗。研究員會帶領你進行每個程序。若在過程中感到覺疲倦或不適時，你可稍作休息；如有需要，設於理工大學校園內的診所亦可提供醫療的支援。

完成三節的研判過程後，你將會獲得港幣三百元的交通及饍食的補貼。

潛在危險及權利
縱使在實驗中涉及痛楚之刺激，你的身體將不會受到任何的損傷或接受到不需要的痛楚。參與本研究項目乃純屬自願性質。你有權利在任何時間及任何理由下終止實驗，而不會影響日後你在醫管局轄下醫院中接受的治療及有關的權利。為了保護我的私隱，你的個人資料（包括姓名、身分證號碼、地址、門診／住院編號）將不會記錄在任何紙張或電腦的檔案內，在記錄過程中只會採用到研究編號。此外，你的個人資料及研究編號的聯繫電子文件將會獨立儲存。以上談及的個人資料及研究記錄將會存放於有鎖的檔案櫃中。

Appendix XVII Information Sheet for Chronic Pain Group (English Version)

The Hong Kong Polytechnic University
Department of Rehabilitation Sciences

Research Project Information Sheet

Project title:
Visualization Replacement Modulating Perception of Chronic Pain: An Event-related Potential Study

Investigators:
Mr. Sam C. C. Chan, Professor Chetwyn C. H. Chan, Dr T. Y. Chui and Dr. Anne S. K. Kwan

Purpose of the study:
To investigate the brain processes of people with chronic pain when being asked to imagine sensation to alter pain perception

Project information:
This is a collaborative study of Haven among Hope Hospital, United Christian Hospital, and Department of Rehabilitation Sciences, Hong Kong Polytechnic University, to facilite the transfer of data. The experiments will be conducted in three sessions, taking approximately ten hours:

- In the first session, you will be first asked to complete a series of questionnaires concerning personal particulars, pain history (if applicable), pain coping strategies, vividness of sensory imagery and frontal lobe function. Afterward, you will receive a range of electrical stimuli applied by an electrical stimulator in order to determine tactile and pain thresholds. With the investigator's instruction, you will be trained to remember the different levels of electrical intensities given by an electrical stimulator. You will be guided how to generate sensation image previously remembered in my mind and replace it with the perception give by the electrical stimulator. This session will take three hours.
- In the second session, the electroencephalogram (EEG) will be recorded while you will be given different intensities of sensory stimuli and you will be required to generate different sensory imagery learned in the second session. This session will last for four hours.
- In the third session, you will be invited to attend a training session to learn how to apply the replacement imagery technique learned in the previous sessions on your chronic pain condition. The training session will last for three hours.

The procedure mentioned above will take place at the Applied Cognitive Neuroscience Laboratory in the Hong Kong Polytechnic University. You will need to travel there for training and experimental. The study investigator will guide you through the procedures in all sessions. You will be provided with breaks in case of tiredness or discomfort. The clinic located within the university campus could also provide medical backup if needed.

You will receive a total of HK$300.00 to cover for the traveling expenses to the laboratory and meals.

Potential Risks and Rights:
Although the study involves painful stimuli, no damages to your body will be the consequence of the experiments and you will not experience any unnecessary pain. Participation is completely on voluntary basis. You have the right to withdraw from study at any time or with any reason without affecting their rights and future treatment in HA Hospitals. In order to protect you privacy, my personal information (including name, HKID, address, OPD/hospital numbers) will not be recorded on data sheet electronic files. The document of electronic file containing the linkage information between the study code and my identity will be stored separately. All the personal information mentioned above will be stored in locked cabinets.

Appendix XVIII Consent Form for Chronic Pain Group (Chinese Version)

香港理工大學復康治療科學系

研究項目介绍

研究題目

意象干預長期痛楚感知：事件相關腦電位研究

研究成員

陳子颂先生、陳智軒教授、徐德義醫生及關少瓊醫生

同意書

本人 _____明白此項研究之細節，並聲明自願參加此項研究。我明白可以隨時在不需作出解釋之情況下退出此項研究，而將不會受到處罰或歧視。我悉知參與本研究當中帶的潛在危險。我明白本人之個人資料將不會向本研究以外之人士公開，並且我的姓名或照片將不會出現於任何研究之報告內。所有資料會於研究完成後銷毀。

本人可致電 2766 4845 或 9745 向研究員陳子颂先生查詢本研究事宜。若果我對研究員有任何投訴，可致電 27665397，與復康治療科學系研究委員會秘書 Mrs. Michelle LEUNG 接洽。我將受予簽署同意書副本一份。

參加者簽署：_____ 日期：_____

見證人簽署：_____ 日期：_____

Appendix XIX Consent Form for Chronic Pain Group (English Version)

The Hong Kong Polytechnic University

Department of Rehabilitation Sciences

Research Project Informed Consent Form

Project title:

Visualization Replacement Modulating Perception of Chronic Pain: An Event-related Potential Study

Investigators:

Mr. Sam C. C. Chan, Professor Chetwyn C. H. Chan, Dr T. Y. Chui and Dr. Anne S. K. Kwan

Consent:

I, _____, have been explained the details of this study. I voluntarily consent to participate in this study. I understand that I can withdraw from this study at any time without giving reasons and withdrawal will not lead to any punishment or prejudice against me. I am aware of any potential risk in joining this study. I also understand that my personal information will not be disclosed to people who are not related to this study and my name or photograph will not appear on any publications resulted from this study. All personal information will be discarded upon the completion of the study.

I can contact the study coordinator, Mr. Sam C.C. Chan at telephone 2766 4845 or 9745 , or the project supervisor Prof. Chetwyn C.H. Chan at 2766 6727 for any questions about this study. If I have complaints related to the investigator(s), I can contact Mrs. Michelle Leung, Secretary of Department Research Committee, at 2766 5397. I know I will be given a signed copy of this consent form.

Signature (subject): _____ Date: _____

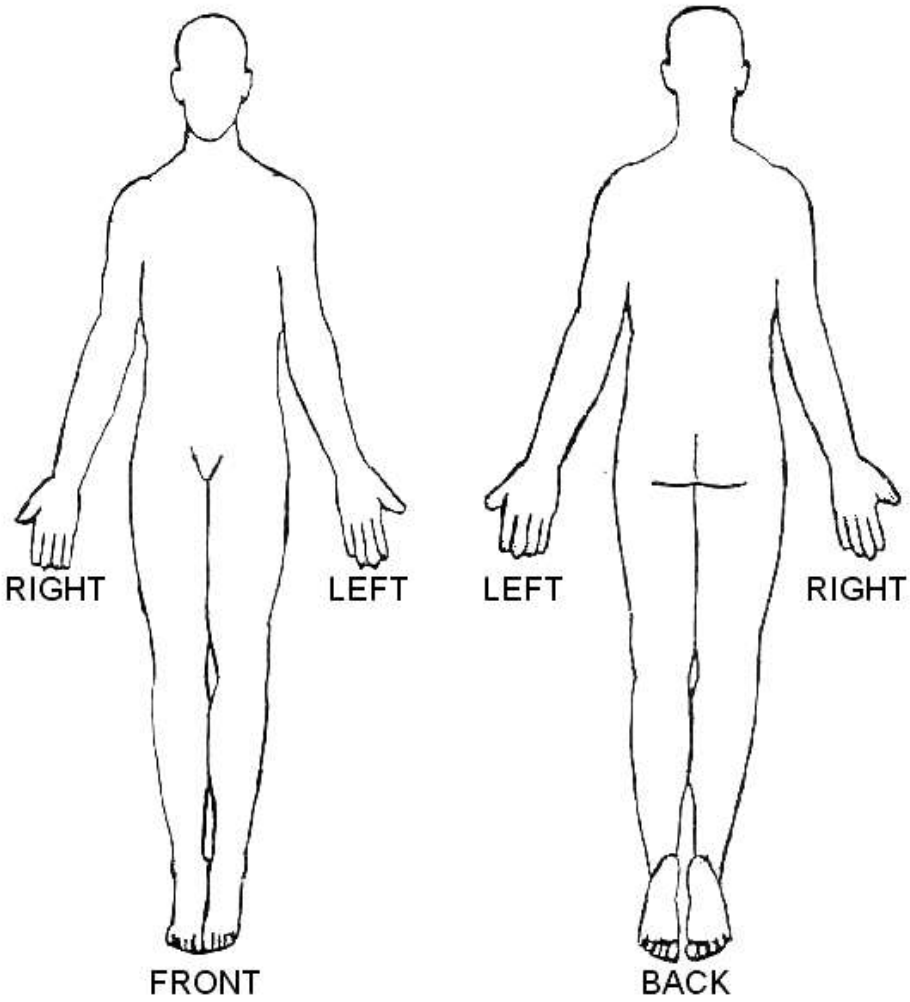
Signature (witness): _____ Date: _____

Appendix XX Pain Assessment Form – Body Chart

全身圖／Body Chart

請以下列的符號表示出身體上所有的不適，並寫下該部份的痛楚程度 (1 – 10)。
Use the symbols below to mark the areas on your body where you feel the following sensations. Include ALL affected areas. And give your pain ratings for that particular body part.

BURNING	NUMBNESS	PINS & NEEDLES	STABBING	ACHE
X	O	=	/	^



Appendix XXI Pain History Questionnaire

<u>有關病況的資料</u>

1. 你患病有多久？ _____年

2. 現時你有沒有去定期覆診（西醫）？
□1. 沒有
□2. 有，請問你現時在那裡覆診？**請圈出覆診地點：醫院／專科診所／私家醫生**

3. 你是否病人自助組織的會員？
□1. 是
□2. 否

4. 現時有否服用止痛藥
□1. 是 藥名：_____
□2. 否

5. 在過去一個月內，平均來說，你有幾唔舒服呢？（**請圈出正確答案**）

完全沒有 **差到難以想像**

1 2 3 4 5 6 7 8 9 10

6. 在過去一個月內，你最唔舒服的情況有幾嚴重呢？（**請圈出正確答案**）

完全沒有 **差到難以想像**

1 2 3 4 5 6 7 8 9 10

7. 在過去一個月內，你的唔舒服或痛楚感覺有幾經常出現 ？（**只圈出一個答案**）

完全沒有……	0
一或兩次……	1
數次……	2
頗為經常……	3
十分經常……	4
每一天或幾乎每一天……	5

8. 在過去一個月內，一般來說，你有幾唔舒服 ？（**只圈出一個答案**）

完全沒有…… 0
十分輕微…… 1
輕微…… 2
普通…… 3
嚴重…… 4
非常嚴重…… 5

9. 在過去一個月內，當你有唔舒服時，會維持多久？（**只圈出一個答案**）

完全沒有…… 0
幾分鐘…… 1
數分鐘至一小時…… 2
數小時…… 3
一或兩日…… 4
超過兩日…… 5

10. 在過去一個月內，你有幾多時間係 :（**請在每條問題後圈出最貼切的答案**）

	完全沒有	很少時間	有時	都幾多	很多	全部時間
1. 感到筋疲力盡	0	1	2	3	4	5
2. 充滿能量	0	1	2	3	4	5
3. 感到疲累	0	1	2	3	4	5
4. 有精神做你想做的事情	0	1	2	3	4	5
5. 感到精力充沛	0	1	2	3	4	5

11. 一般來說，你認為自己的健康狀況是 . ·（**只圈出一個答案**）

極佳…… 1
非常好…… 2
好…… 3
普通…… 4
惡劣…… 5

12. 在過去六個月內，你有冇去睇醫生（精神科醫生除外）？（**留院期間見醫生不計**）

【 】1. 沒有 【 】2. 有， 總共多少次 _____

13. 在過去六個月內，你有冇見過下列的醫療專業人士？ **（留院期間次數不計）**

1. 精神科醫生 【 】1.沒有【 】2.有，總共多少次 _____
2. 心理學家或心理輔導員 【 】2.沒有【 】2.有，總共多少次 _____
3. 社康護士 【 】1.沒有【 】2.有，總共多少次 _____
4. 物理／職業治療師 【 】1.沒有【 】2.有，總共多少次 _____

14. 在過去六個月內，你有冇去過急症室嗎？
【 】1.沒有 【 】2.有，總共多少次：_____
往急症室的原因：_____

15. 在過去六個月內，你總共留院（有過夜的）多少次？共多少晚？
【 】1.沒有【 】2.有，總共多少次：___ 總共多少晚：___ 原因：____

Appendix XXII Coping Strategy Questionnaire (CSQ) (Chinese Version)

策略與方針問卷

姓名 : _____

有痛症的朋友會使用不同的方法去應付或處理痛楚。以下是一些患有痛症的朋友於痛楚時會做的事情。請你指出當你遇到痛楚時，你會有幾經常做這些事情呢？

0 分代表當你痛楚時，你是完全不會做這樣的事情，6 分則代表當你痛楚時，你經常會做這樣事情的。你可以按不同的事情選擇 0-6 分內任何一個分數。

完全不會做　1　2　3　4　5　6　經常會做

當我覺得痛楚時：

1. 我嘗試令自己感到與痛楚是有距離的，就好像這些痛楚是出現在別人的身上。

完全不會做　1　2　3　4　5　6　經常會做

2. 我出街去做些事情，例如睇戲或購物。

完全不會做　1　2　3　4　5　6　經常會做

3. 我嘗試去想些令自己感到開心的事情。

完全不會做　1　2　3　4　5　6　經常會做

4. 我不會去想這是痛楚，反而我會當這些是麻木或溫暖的感覺。

完全不會做　1　2　3　4　5　6　經常會做

5. 它很恐佈及我感到這是永遠不會有改善的。

完全不會做　1　2　3　4　5　6　經常會做

6. 雖然遇到痛楚，我會告訴自己要勇敢及堅持。

完全不會做　1　2　3　4　5　6　經常會做

7. 我閱讀。

完全不會做　1　2　3　4　5　6　經常會做

8. 我告訴自己我是可以克服痛楚的。

完全不會做　1　2　3　4　5　6　經常會做

9. 我在腦海中數數字或想一首歌曲。

完全不會做　1　2　3　4　5　6　經常會做

10. 我想這只是一些感覺，例如麻痺。

完全不會做　1　2　3　4　5　6　經常會做

11. 它很可怕及令我感覺到不安。

完全不會做　1　2　3　4　5　6　經常會做

12. 我在腦海中幻想自己正在玩遊戲，從而令自己不再去想這些痛楚。

完全不會做　1　2　3　4　5　6　經常會做

13. 我覺得生無可戀。

完全不會做　1　2　3　4　5　6　經常會做

14. 我知道有朝一日會有人會幫助我，而痛楚亦會暫時消失。

完全不會做　1　2　3　4　5　6　經常會做

15. 我祈禱祈求痛楚不會持續太耐。

完全不會做　1　2　3　4　5　6　經常會做

16. 我嘗試想痛楚不是屬於我的身體，而是身體以外的東西。

完全不會做　1　2　3　4　5　6　經常會做

17. 我不去想這些痛楚。

完全不會做　1　2　3　4　5　6　經常會做

18. 我想想將來，當痛楚消失後的種種情況。

完全不會做　1　2　3　4　5　6　經常會做

19. 我告訴自己，痛楚不會對我有什麼影響。

完全不會做　1　2　3　4　5　6　經常會做

20. 我告訴自己，我不能讓痛楚阻止我去做我想做的事情。

完全不會做　1　2　3　4　5　6　經常會做

21. 我完全不會留意這些痛楚。

完全不會做　1　2　3　4　5　6　經常會做

22. 我相信有朝一日，醫生會有方法治好我的痛楚。

完全不會做　1　2　3　4　5　6　經常會做

23. 無論情況怎樣差，我知道我可以處理這些痛楚。

完全不會做　1　2　3　4　5　6　經常會做

24. 我裝作痛楚並不存在。

完全不會做　1　2　3　4　5　6　經常會做

25. 我時常擔心痛楚會否消失。

完全不會做　1　2　3　4　5　6　經常會做

26. 我常在腦海中想起已往快樂的經歷。

完全不會做　1　2　3　4　5　6　經常會做

27. 我會想那些和我合作愉快的人。

完全不會做　1　2　3　4　5　6　經常會做

28. 我祈禱祈求痛楚停止。

完全不會做　1　2　3　4　5　6　經常會做

29. 我幻想痛楚是出現在我身體之外。

完全不會做　1　2　3　4　5　6　經常會做

30. 我繼續平常生活，當作沒有任何事情發生。

完全不會做　1　2　3　4　5　6　經常會做

31. 我視痛楚為一個挑戰，不會讓它影響我。

完全不會做　1　2　3　4　5　6　經常會做

32. 雖然痛楚傷害我，我仍會繼續生活下去。

完全不會做　1　2　3　4　5　6　經常會做

33. 我覺得我已不可以繼續忍受下去。

完全不會做　1　2　3　4　5　6　經常會做

34. 我會嘗試到人多的地方。

完全不會做　1　2　3　4　5　6　經常會做

35. 我不理會這些痛楚。

完全不會做　1　2　3　4　5　6　經常會做

36. 我依靠對宗教的信任。

完全不會做　1　2　3　4　5　6　經常會做

37. 我覺得我不能繼續生活下去。

完全不會做　1　2　3　4　5　6　經常會做

38. 我想著那些我喜歡做的事情。

完全不會做　1　2　3　4　5　6　經常會做

39. 我去做任何事令我不會再想痛楚。

完全不會做　1　2　3　4　5　6　經常會做

40. 我去做些我享受的事情，如看電視、聽音樂。

完全不會做　1　2　3　4　5　6　經常會做

41. 我裝作這不是我身體的一部份。

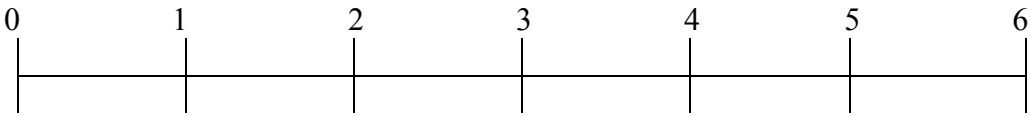
完全不會做　1　2　3　4　5　6　經常會做

42. 我做些需要活動的事情，如做家務。

完全不會做　1　2　3　4　5　6　經常會做

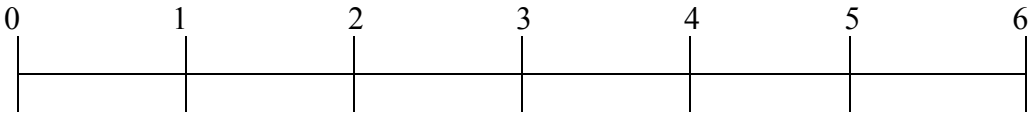
43. 基於你平日所用來處理痛楚的方法，你覺得你對於這些痛楚可以有<u>幾大的</u>控制呢？0 分代表完全不能夠控制，6 分則代表完全能夠控制，你可以揀 0 至 6 分的其中 1 個分數。**(請圈上正確答案)**

完全不能夠控制　　完全能夠控制



44. 另外，基於你平日所用來處理痛楚的方法，你覺得你可以把痛楚<u>減低多少</u>呢？0 分代表完全不能夠減低，6 分則代表完全減低，你可以揀 0 至 6 分的其中 1 個分數。**(請圈上正確答案)**

完全不能夠控制　　完全能夠控制



Appendix XXIII Analysis Results of Pain-free Group

Appendix XXIII (a) Repeated measures ANOVA model for main effects of Condition (Imagery vs Perception) and Pain (5 levels) and the interactions between them on pain NRS ratings in the pain-free subjectss

Effect	Control		
	Df	F-value	p-value
Condition	1, 17	10.666	0.006
Pain	1.24, 17.37	34.820	<0.0005
Condition $\times$ *Pain*	4,56	1.498	0.215

Appendix XXIII (b) Statistical results of repeated measures ANOVA with 2 (Perception vs Imagery condition) × 6 midline electrodes (Fz, FCz, Cz, CPz, Pz, and POz) and repeated measures ANOVA with 2 (Perception vs Imagery condition) × 2 (left vs right) × 7 lateral electrodes on the mean amplitudes of P1 component of the pain-free subjects

	Control		
Midline Sites	df	F-value	p-value
Within-Subjects Effect	1,17	0.133	0.720
Conditions	2.582,43.886	13.814	<0.0005
Electrode	1.317, 22.393	0.870	0.390
Condition × Electrode			
Lateral Sites			
Within-Subjects Effect			
Conditions	1,17	0.068	0.797
Laterality	1,17	1.632	0.219
Electrode	2.484, 42.234	15.031	<0.001**
Condition × Laterality	1,17	0.103	0.752
Condition × Electrode	1.449, 24.627	1.851	0.185
Laterality × Electrode	3.182, 54.100	2.154	0.101
Condition × Laterality × Electrode	2.485, 42.240	0.480	0.663

Appendix XXIII (c) Statistical results of repeated measures ANOVA with 2 (Perception vs Imagery condition) × 6 midline electrodes (Fz, FCz, Cz, CPz, Pz, and POz) and repeated measures ANOVA with 2 (Perception vs Imagery condition) × 2 (left vs right) × 7 lateral electrodes on the peak latencies of P1 component of the pain-free subjects

	Control		
Midline Sites	df	F-value	p-value
Within-Subjects Effect			
Conditions	1,17	6.824	0.018
Electrode	1.816, 30.878	1.086	0.345
Condition × Electrode	2.393, 40.686	0.570	0.639
Lateral Sites			
Within-Subjects			
Conditions	1,17	6.077	0.025
Laterality	1,17	0.426	0.523
Electrode	1.839, 31.271	1.243	0.300
Condition × Laterality	1,17	0.029*	0.867
Condition × Electrode	3.068, 52.148	0.688	0.455
Laterality × Electrode	1.962, 33.359	1.266	0.295
Condition × Laterality × Electrode	3.599, 61.180	0.457	0.747

Appendix XXIII (d) Statistical results of repeated measures ANOVA with 2 (Perception vs Imagery condition) × 6 midline electrodes (Fz, FCz, Cz, CPz, Pz, and POz) and repeated measures ANOVA with 2 (Perception vs Imagery condition) × 2 (left vs right) × 7 lateral electrodes on the mean amplitudes of P2 component of the pain-free subjects

	Control		
Midline Sites	df	F-value	p-value
Within-Subjects Effect			
Conditions	1,17	12.241	0.003**
Electrode	2.147, 36.502	7.706	0.001**
Condition × Electrode	1.224, 20.815	1.890	0.184
Lateral Sites			
Within-Subjects			
Conditions	1,17	12.480	0.003**
Laterality	1,17	0.722	0.467
Electrode	2.019	9.479	0.001**
Condition × Laterality	1,17	0.825	0.376
Condition × Electrode	2.307, 39.226	4.096	0.020*
Laterality × Electrode	3.689, 62.718	0.609	0.645
Condition × Laterality × Electrode	2.810, 47.762	0.133	0.931

Appendix XIX(e) Statistical results of repeated measures ANOVA with 2 (Perception vs Imagery condition) × 6 midline electrodes (Fz, FCz, Cz, CPz, Pz, and POz) and repeated measures ANOVA with 2 (Perception vs Imagery condition) × 2 (left vs right) × 7 lateral electrodes on the peak latencies of P2 component of the pain-free subjects

	Control		
Midline Sites	df	F-value	p-value
Within-Subjects Effect			
Conditions	1,17	0.970	0.339
Electrode	2.182, 37.094	7.822	0.001**
Condition × Electrode	1.951, 33.163	0.952	0.394
Lateral Sites			
Within-Subjects			
Conditions	1,17	0.040	0.844
Laterality	1,17	0.938	0.346
Electrode	2.643, 44.928	12.802	<0.001**
Condition × Laterality	1,17	0.587	0.454
Condition × Electrode	2.203, 37.458	0.467	0.649
Laterality × Electrode	2.615, 44.457	0.379	0.741
Condition × Laterality × Electrode	2.776, 47.189	0.320	0.796

Appendix XXIII (f) Statistical results of repeated measures ANOVA with 2 (Perception vs Imagery condition) × 6 midline electrodes (Fz, FCz, Cz, CPz, Pz, and POz) and repeated measures ANOVA with 2 (Perception vs Imagery condition) × 2 (left vs right) × 7 lateral electrodes on the mean amplitudes of P300 component of the pain-free subjects

	Control		
Midline Sites	df	F-value	p-value
Within-Subjects Effect			
Conditions	1,17	9.020	0.008**
Electrode	1.700, 28.902	10.853	0.001**
Condition × Electrode	1.506, 15.610	0.950	0.376
Lateral Sites			
Within-Subjects			
Conditions	1,17	9.265	0.007**
Laterality	1,17	0.031	0.862
Electrode	1.999, 33.981	10.567	<0.001**
Condition × Laterality	1,17	0.001	0.980
Condition × Electrode	2.015, 34.260	2.084	0.140
Laterality × Electrode	2.191, 54.242	1.986	0.123
Condition × Laterality × Electrode	2.768, 42.063	0.491	0.675

Appendix XXIII (g) Statistical results of repeated measures ANOVA with 2 (Perception vs Imagery condition) × 6 midline electrodes (Fz, FCz, Cz, CPz, Pz, and POz) and repeated measures ANOVA with 2 (Perception vs Imagery condition) × 2 (left vs right) × 7 lateral electrodes on the peak latencies of P300 component of the pain-free subjects

	Control		
Midline Sites	Df	F-value	p-value
Within-Subjects Effect			
Conditions	1,17	0.000	0.983
Electrode	1.751, 29.760	1.783	0.189
Condition × Electrode	2.010, 34.172	0.232	0.795
Lateral Sites			
Within-Subjects			
Conditions	1,17	0.138	0.715
Laterality	1,17	0.013	0.912
Electrode	2.723, 46.292	3.921	0.017*
Condition × Laterality	1,17	0.262	0.615
Condition × Electrode	3.383, 57.503	1.435	0.239
Laterality × Electrode	2.675, 45.467	0.243	0.844
Condition × Laterality × Electrode	2.832, 48.146	0.941	0.424

Appendix XXIII (h) Statistical results of repeated measures ANOVA with 2 (Perception vs Imagery condition) × 6 midline electrodes (Fz, FCz, Cz, CPz, Pz, and POz) and repeated measures ANOVA with 2 (Perception vs Imagery condition) × 2 (left vs right) × 7 lateral electrodes on the mean amplitudes of N400 component of the pain-free subjects

	Control		
Midline Sites	Df	F-value	p-value
Within-Subjects Effect			
Conditions	1,17	9.208	0.007**
Electrode	1.401, 23.819	13.860	<0.001**
Condition × Electrode	1.571, 26.815	1.205	0.306
Lateral Sites			
Within-Subjects			
Conditions	1,17	9.578	0.007**
Laterality	1,17	0.002	0.966
Electrode	1.421, 24.155	15.041	<0.001**
Condition × Laterality	1,17	0.013	0.910
Condition × Electrode	1.741, 50.118	2.193	0.135
Laterality × Electrode	2.948, 50.118	3.272	0.029*
Condition × Laterality × Electrode	2.676, 45.500	0.271	0.824

Appendix XXIII (i) Statistical results of repeated measures ANOVA with 2 (Perception vs Imagery condition) × 6 midline electrodes (Fz, FCz, Cz, CPz, Pz, and POz) and repeated measures ANOVA with 2 (Perception vs Imagery condition) × 2 (left vs right) × 7 lateral electrodes on the peak latencies of N400 component of the pain-free subjects

	Control		
Midline Sites	df	F-value	p-value
Within-Subjects Effect			
Conditions	1,17	0.055	0.818
Electrode	2.007, 34.115	2.315	0.114
Condition × Electrode	2.678, 45.527	1.037	0.379
Lateral Sites			
Within-Subjects			
Conditions	1,17	0.396	0.537
Laterality	1,17	1.104	0.308
Electrode	2.680, 45.555	3.498	0.027*
Condition × Laterality	1,17	0.151	0.702
Condition × Electrode	2.906, 49.400	1.076	0.366
Laterality × Electrode	3.296, 56.305	0.872	0.469
Condition × Laterality × Electrode	3.841, 65.290	1.350	0.262

Appendix XXIII (j) Statistical results of repeated measures ANOVA with 2 (Perception vs Imagery condition) × 6 midline electrodes (Fz, FCz, Cz, CPz, Pz, and POz) and repeated measures ANOVA with 2 (Perception vs Imagery condition) × 2 (left vs right) × 7 lateral electrodes on the mean amplitudes of P600 component of the pain-free subjects

	Control		
Midline Sites	df	F-value	p-value
Within-Subjects Effect			
Conditions	1,17	10.368	0.005**
Electrode	1.280, 21.765	14.101	0.001**
Condition × Electrode	2.091, 35.554	0.149	0.871
Lateral Sites			
Within-Subjects			
Conditions	1,17	9.688	0.006**
Laterality	1,17	0.032	0.861
Electrode	1.242, 21.117	16.420	<0.001**
Condition × Laterality	1,17	1.756	0.203
Condition × Electrode	2.236, 38.012	4.015	0.022*
Laterality × Electrode	3.322, 56.476	4.066	0.009**
Condition × Laterality × Electrode	2.704, 45.975	1.005	0.393

Appendix XXIII (k) Statistical results of repeated measures ANOVA with 2 (Perception vs Imagery condition) × 6 midline electrodes (Fz, FCz, Cz, CPz, Pz, and POz) and repeated measures ANOVA with 2 (Perception vs Imagery condition) × 2 (left vs right) × 7 lateral electrodes on the peak latencies of P600 component of the pain-free subjects

	Control		
Midline Sites	df	F-value	p-value
Within-Subjects Effect			
Conditions	1,17	3.373	0.084
Electrode	2.232, 37.939	4.428	0.016*
Condition × Electrode	2.433, 41.361	0.227	0.839
Lateral Sites			
Within-Subjects			
Conditions	1,17	0.848	0.370
Laterality	1,17	0.268	0.611
Electrode	2.750, 46.747	3.169	0.037*
Condition × Laterality	1,17	1.578	0.226
Condition × Electrode	2.143, 36.424	0.721	0.502
Laterality × Electrode	2.237, 38.036	0.140	0.890
Condition × Laterality × Electrode	3.029, 51.667	0.707	0.554

Appendix XXIV Pain-related Demographic Information of Chronic Pain Patients

Patient No.	R/NR	Sex / Age	Diagnosis	Pain Duration (months)	NRS pain	Current Analgesic medication / Therapeutic Interventions
1.	NR	F/52	Right LBP & limb pain	120	5.5	Cerebrex / PT & Acupuncture
2.	R	F/50	Lower/upper back pain, bilateral OA knee	60	9.0	Cerebrex, Amoxil, Paracetamol
3.	NR	F/40	LBP & left knee pain	3	1.5	None
4.	NR	M/49	LBP with L2 radiculopathy	60	3.0	Tramadol / PT
5.	NR	M/54	LBP with right shoulder tendonitis	3	2.5	None
6.	NR	M/29	LBP	60	3.5	None / PT
7.	NR	F/45	LBP with lumbar cyst at L5	108	7.5	Tramadol & Lyrica / PT
8.	R	F/35	LBP and left brachial plexis syndrome	120	1.5	Paracetamol
9.	NR	F/27	LBP with C7 radiculopathy	168	6.0	None
10.	R	M/36	LBP, right inguinal pain and bilateral knee pain	84	7.5	Paracetamol, Tramadol / PT
11.	NR	F/36	LBP at L5-L1 level	24	4.0	Gabapentin, Paracetamol, Tramadol
12.	R	M/43	LBP	30	7.5	Dologesic, Amitripyline / PT
13.	NR	M/49	LBP & coccygeal pain	18	5.0	Lyrica, Cymbalta / PT
14.	R	F/43	LBP	48	6.0	None / PT & Chinese massage therapy
15.	NR	F/44	LBP with L5/S1 radiculopathy	24	3.0	Tramadol / PT
16.	R	F/39	LBP	30	7.0	NSAID & Neuralgesic
17.	NR	M/35	LBP with radiculopathy	18	4.5	Lyrica, Cataflam

Key: R=Respondent; NR=Non-respondent; LBP=low back pain, OA=osteoarthritis

XXV (a-s) Analysis Results of Comparison of Chronic Pain and Pain-free Groups

Appendix XXV (a) Repeated measures ANOVA model for main effects of Condition (Imagery vs Perception), Pain (5 levels) and group (chronic vs pain-free) and the interactions between them on pain NRS ratings

Within-Subjects Effect	df	F-value	p-value
Conditions	1.00, 33.00	6.982	0.014*
Condition × Group	1.00, 33.00	0.838	0.368
Pain	1.29, 34.85	75.582	0.001**
Pain × Group	1.29, 34.85	1.497	0.235
Condition × Pain	3.32,89.65	1.457	0.229
Condition × Pain × Group	4.00, 132	1.610	0.188
Between-Subject Effects	1.00, 33.00	214.736	<0.001*

** p<0.01, * p<0.050

Appendix XXV (b) Repeated measures ANOVA model for main effects of Condition (Imagery vs Perception) and Pain (5 levels) and the interactions between them on pain NRS ratings in chronic pain and pain-free groups

Effect	Chronic			Pain-free		
	df	F-value	p-value	df	F-value	p-value
Within-Subjects Main effect						
Conditions	1, 16	1.019	0.331	1, 17	10.666	0.006**
Pain	1.30, 16.70	52.012	<0.001**	1.24, 7.37	34.820	<0.001**
Condition × Pain	4,52	1.576	0.194	4,56	1.498	0.215

** p<0.01

Appendix XXV (c) Repeated measures ANOVA model for main effects of Condition (Imagery vs Perception), Pain (5 levels) and group (respondents vs non-respondents) and the interactions between them on pain NRS ratings

Within-Subjects Effect	df	F-value	p-value
Conditions	1.00,15.00	0.044	0.837
Condition × Group	1.00,15.00	0.018	0.894
Pain	1.283,19.250	64.877	<0.001**
Pain × Group	1.283,19.250	0.323	0.862
Condition × Pain	3.280,49.199	1.658	0.184
Condition × Pain × Group	3.280,49.199	0.198	0.911
Between-Subject Effects	1,15	1.907	0.187

** p<0.01

Appendix XXV (d) Repeated measures ANOVA model for main effects of Condition (Imagery vs Perception) and Pain (5 levels) and the interactions between them on pain NRS ratings in respondents and non-respondent

Effect	Respondent			Non-Respondent		
	df	F-value	p-value	df	F-value	p-value
Within-Subjects Main effect						
Conditions	1,5	0.005	0.947	1,10	0.066	0.802
Pain	1.320,6.602	24.404	<0.005**	1.242,12.425	19.143	<0.005**
Condition × *Pain*	2.042,10.209	0.674	0.535	2.948,29.484	1.086	0.369

** $p<0.01$

Appendix XXV (e) The mean amplitude (in μV) and peak latency (in ms) of the six midline electrodes and seven pairs of lateral (left and right) electrodes for Perception and Imagery trial for P1 component in chronic pain group and pain-free groups

Electrode sites	Chronic				Pain-free			
	Mean Amplitude		Peak Latency		Mean Amplitude		Peak Latency	
	Perception	Imagery	Perception	Imagery	Perception	Imagery	Perception	Imagery
Midline								
Fz	10.83 (7.09)	11.31 (7.19)	233.12 (22.38)	236.35 (25.89)	14.90 (6.80)	14.84(6.13)	**233.00(21.57)**	**244.39 (20.49)**
FCz	10.96 (6.66)	11.34 (6.84)	233.47 (22.30)	236.47 (25.89)	16.36 (7.09)	16.42(6.22)	230.83 (21.54)	237.22 (23.22)
Cz	**11.43 (6.90)**	**11.40 (6.75)**	234.12 (23.11)	237.29 (25.67)	16.28 (7.16)	16.54(6.12)	230.89 (21.38)	235.56 (22.26)
CPz	10.04 (5.85)	10.81 (6.56)	**233.06(22.03)**	**238.82(25.09)**	**16.42 (7.97)**	**16.88(7.05)**	**227.11(21.24)**	235.11 (22.01)
Pz	7.64 (6.18)	6.87 (5.66)	**229.65(21.91)**	235.35 (25.13)	13.29 (6.84)	14.02(6.26)	229.83(22.92)	**235.00 (20.90)**
POz	6.30 (6.30)	5.72 (5.36)	225.47 (24.20)	**231.00(26.15)**	10.38 (6.08)	11.04(5.63)	230.67 (22.95)	237.11 (19.86)
Left								
F3	9.64 (5.98)	9.82 (5.90)	232.18 (22.15)	232.88 (24.58)	12.45 (5.88)	12.08(5.34)	235.17 (19.57)	**241.83 (20.68)**
FC3	**10.05 (5.95)**	**9.95 (5.96)**	**234.29(23.39)**	**233.06(24.87)**	**14.81 (7.21)**	**14.41(6.16)**	229.50 (19.93)	239.94 (22.69)
C3	8.78 (5.70)	8.35 (5.61)	226.76 (22.31)	230.12 (22.42)	12.24 (6.60)	11.96(5.65)	**229.33(18.91)**	236.06 (19.67)
CP3	7.49(6.45)	7.14 (5.95)	**224.24(20.01)**	**226.06(19.55)**	10.83 (6.50)	10.77(5.77)	230.00 (18.31)	**234.72 (18.32)**
P3	6.79 (6.15)	6.22 (5.94)	229.41 (21.80)	231.65 (22.37)	8.52 (5.61)	9.27 (5.22)	**235.78(21.64)**	238.50 (18.97)
PO3	5.21 (5.76)	4.69 (5.34)	226.29 (20.08)	226.94 (20.23)	5.46 (4.57)	5.89 (4.36)	233.94 (21.66)	235.06 (18.58)
T7	5.27 (5.05)	5.33 (4.66)	227.94 (20.82)	229.88 (21.39)	7.11 (4.54)	7.12 (4.00)	231.39 (17.80)	235.33 (17.85)
Right								
F4	7.62 (6.94)	7.52 (7.10)	**231.76(21.50)**	235.29 (25.17)	11.52 (5.74)	11.17(5.58)	**234.06(22.21)**	**243.72(20.61)**
FC4	**8.53 (6.60)**	**8.42 (6.58)**	231.35 (22.57)	235.41 (25.05)	**12.61 (6.35)**	**12.55(6.02)**	232.11 (21.56)	240.33 (21.44)
C4	6.44 (6.57)	5.95 (6.68)	230.71 (22.30)	**238.88 (24.18)**	9.93 (7.14)	10.24(6.29)	232.94 (19.74)	236.28 (23.37)
CP4	5.66 (5.97)	5.26 (5.41)	228.47 (21.46)	237.18 (23.29)	8.70 (5.95)	9.19 (5.26)	**231.67(19.97)**	233.00 (26.24)
P4	5.16 (6.03)	4.39 (5.22)	225.00 (24.82)	232.59 (27.23)	8.11 (5.59)	9.19 (5.07)	231.78 (24.71)	232.61 (24.40)
PO4	4.29 (6.10)	3.43 (5.26)	**224.94(25.02)**	**232.47 (27.10)**	6.23 (5.40)	7.02 (5.08)	223.33 (28.07)	**228.17(29.50)**
T8	4.03 (4.91)	3.49 (4.57)	233.18 (23.11)	237.47 (23.38)	4.47 (5.13)	4.75 (5.00)	232.00 (17.60)	236.50 (19.75)

Key: Standard deviations are in parenthesis; bold figure indicates the site with the peak amplitude(s) or indicates the largest and smallest peak latencies

Appendix XXV (f) Statistical results of between group and within-group repeated measures ANOVA with 2 (conditions) × 6 (midline electrodes sites) and repeated measures ANOVA with 2 (conditions) × 2 (laterality) × 7 (lateral electrode sites) on the mean amplitudes of P1 component of the chronic pain and pain-free groups

	Chronic vs Pain-free			Chronic			Pain-free		
Midline	df	F-value	p-value	df	F-value	p-value	df	F-value	p-value
Within-Subjects Effect									
Conditions	1,33	0.173	0.680	1,16	1.281	0.274	1,17	0.133	0.720
Condition × Group		0.965	0.333						
Electrode	2.550, 84.138	26.566	<0.005**	1.875, 29.998	15.880	<0.005**	2.582, 43.886	13.814	<0.001
Electrode × Group		2.209	0.103						
Condition × Electrode	1.605, 52.957	1.013	0.355	1.268, 20.290	1.350	0.269	1.317, 22.393	0.870	0.390
Condition × Electrode × Group		1.598	0.214						
Between-Subject Effects	1,33	5.568	0.024*						
Lateral									
Within-Subjects									
Conditions	1,33	1.079	0.307	1,16	2.382	0.142	1,17	0.068	0.797
Condition × Group		1.876	0.180						
Laterality	1,33	12.839	0.001**	1,16	42.721	<0.005**	1,17	1.632	0.219
Laterality × Group		1.609	0.213						
Electrode	2.643, 87.226	21.133	<0.005**	2.2175, 34.794	6.679	0.003**	2.484, 42.234	15.031	<0.001**
Electrode × Group		2.030	0.123						
Condition × Laterality	1,33	0.162	0.690	1,16	0.428	0.522	1,17	0.103	0.752
Condition × Laterality × Group		0.542	0.467						
Condition × Electrode	1.592, 55.821	0.503	0.576	26.443	0.224	0.759	1.449, 24.627	1.851	0.185

Condition × Electrode × Group		1.544	0.224						
Laterality × Electrode	3.718, 122.707	2.166	0.082	3.067, 49.079	0.545	0.658	3.182, 54.100	2.154	0.101
Laterality × Electrode × Group		1.148	0.337						
Condition × Laterality × Electrode	1.895, 62.529	0.438	0.637	1.433, 22.924	0.476	0.564	2.485, 42.240	0.480	0.663
Condition × Laterality × Electrode × Group		0.531	0.581						
Between-Subject Effects	1,33	2.996	0.093						

Key: ** p<0.01, ** p<0.050

Appendix XXV (g) Statistical results of between group and within-group repeated measures ANOVA with 2 (conditions) × 6 (midline electrodes sites) and repeated measures ANOVA with 2 (conditions) × 2 (laterality) × 7 (lateral electrode sites) on the peak latencies of P1 component of the chronic pain and pain-free groups

	Chronic vs Pain-free			Chronic			Pain-free		
Midline	df	F-value	p-value	df	F-value	p-value	df	F-value	p-value
Within-Subjects Effect									
Conditions	1,33	10.853	0.002**	1,16	4.187	0.058	1,17	6.824	0.018
Condition × Group		0.567	0.457						
Electrode	1.869, 61.676	1.109	0.000	1.601, 25.618	1.156	0.320	1.816, 30.878	1.086	0.345
Electrode × Group		1.147	0.321						
Condition × Electrode	2.461, 81.219	0.411	0.706	1.939, 31.026	0.488	0.613	2.393, 40.686	0.570	0.639
Condition × Electrode × Group		0.562	0.607						
Between-Subject Effects	1,33	0.001	0.974						
Lateral									
Within-Subjects									
Conditions	1,33	8.709	0.006**	1,16	3.021	0.101	1,17	6.077	0.025
Condition × Group		0.413	0.707						
Laterality	1,33	0.281	0.600	1,16	1.243	0.281	1,17	0.426	0.523
Laterality × Group		1.684	0.203						
Electrode	1.917, 63.258	1.863	0.165	1.760, 28.154	0.845	0.427	1.839, 31.271	1.243	0.300
Electrode × Group		0.220	0.794						
Condition × Laterality	1,33	1.294	0.263	1,16	4.422	0.052*	1,17	0.029*	0.867
Condition × Laterality × Group		1.972	0.170						
Condition × Electrode	3.377, 111.451	0.240	0.889	2.077, 33.231	0.608	0.557	3.068, 52.148	0.688	0.455
Condition × Electrode ×		1.316	0.272						

Group									
Laterality × Electrode	2.657, 87.670	2.017	0.125	3.317, 50.187	1.793	0.158	1.962, 33.359	1.266	0.295
Laterality × Electrode × Group		0.868	0.450						
Condition × Laterality × Electrode	3.836, 126.583	0.286	0.880	2.486, 39.769	0.265	0.821	3.599, 61.180	0.457	0.747
Condition × Laterality × Electrode × Group		0.461	0.757						
Between-Subject Effects	1,33	0.318	0.577						

Key: ** p<0.01, ** p<0.050

Appendix XXV (h) The mean amplitude (in μV) and peak latency (in ms) of the six midline electrodes and seven pairs of lateral (left and right) electrodes for Perception and Imagery trial for P2 component in chronic pain group and pain-free groups

Electrode sites	Chronic				Pain-free			
	Mean Amplitude		Peak Latency		Mean Amplitude		Peak Latency	
	Perception	Imagery	Perception	Imagery	Perception	Imagery	Perception	Imagery
Midline								
Fz	8.86 (4.42)	10.61 (4.71)	**298.82(25.46)**	**293.35(18.84)**	11.35 (6.90)	13.92 (6.32)	**289.83 (21.90)**	**290.39 (16.65)**
FCz	9.18 (4.26)	10.60 (4.81)	301.65 (25.76)	296.18(21.78)	13.01 (7.31)	15.69 (6.59)	291.28 (22.53)	296.89 (19.09)
Cz	**9.84 (4.18)**	10.39 (4.98)	305.41 (27.03)	298.82(23.78)	13.75 (6.76)	16.31 (6.05)	296.67 (21.97)	297.89 (19.79)
CPz	8.94 (3.70)	**10.81 (5.02)**	308.65 (26.10)	307.94 (24.88)	**14.80 (7.63)**	**17.17 (6.97)**	299.50 (21.72)	300.44 (21.22)
Pz	6.48 (3.78)	6.37 (4.84)	311.59 (24.58)	309.18 (25.32)	12.43 (6.37)	14.63 (6.08)	304.28 (20.66)	304.00 (20.23)
POz	5.35 (4.35)	5.29 (4.96)	**314.12(24.79)**	**309.88(26.69)**	10.35 (5.89)	12.34 (5.75)	**304.89(22.02)**	**304.61(20.80)**
Left								
F3	7.90 (4.23)	**9.81 (4.09)**	**300.00(23.05)**	297.71(22.24)	9.06 (5.42)	11.23 (4.87)	**290.22(21.81)**	291.94 (19.63)
FC3	**8.40 (4.03)**	9.79 (4.23)	300.29 (22.88)	**296.00(21.53)**	**11.06 (6.15)**	**13.48 (5.73)**	291.00 (21.64)	**291.89(19.73)**
C3	7.02 (3.51)	7.76 (4.37)	303.65 (22.75)	296.71 (21.04)	9.67 (4.78)	11.31 (5.05)	300.89 (19.77)	299.39 (22.10)
CP3	6.08 (4.19)	6.64 (4.42)	306.47 (25.29)	305.12 (25.57)	9.33 (5.46)	10.66 (6.00)	304.89 (17.54)	305.39 (20.81)
P3	5.86 (4.11)	5.94 (4.78)	313.47 (23.82)	312.06 (25.31)	9.13 (5.39)	11.09 (5.75)	311.56 (22.51)	309.67 (20.95)
PO3	4.22 (3.85)	4.55 (4.16)	**316.71(22.40)**	**316.59(21.56)**	6.47 (4.78)	7.93 (5.59)	**316.22(21.63)**	**314.72(20.94)**
T7	3.58 (4.52)	4.40 (3.93)	306.00 (26.18)	302.71 (24.82)	4.82 (3.88)	5.78 (3.85)	300.17 (22.44)	297.44 (24.24)
Right								
F4	5.26 (5.27)	6.36 (5.30)	**293.06(24.60)**	**290.71(17.55)**	8.48 (6.35)	10.45 (6.12)	**291.61(24.64)**	296.72 (20.54)
FC4	**6.37 (4.47)**	**7.12 (5.24)**	298.12 (25.84)	291.41 (17.70)	**9.48 (6.39)**	**11.95 (5.65)**	292.56 (23.98)	**295.39(18.29)**
C4	4.96 (4.61)	4.29 (5.46)	307.65 (26.54)	296.71 (24.14)	9.22 (6.13)	11.08 (5.11)	304.61 (21.85)	303.39 (22.23)
CP4	4.38 (3.92)	3.79 (4.32)	308.12 (27.06)	306.35 (28.10)	8.99 (5.42)	10.71 (4.29)	307.83 (22.96)	309.06 (19.80)
P4	4.32 (3.90)	3.70 (4.86)	**312.59(24.11)**	**312.59(26.38)**	8.89 (5.42)	10.97 (4.97)	312.11 (22.13)	312.17 (19.97)
PO4	3.37 (4.02)	2.87 (4.82)	312.24 (23.70)	311.12 (26.06)	6.80 (5.11)	8.38 (4.82)	**314.67(21.71)**	**313.00(21.38)**
T8	2.76 (3.87)	1.82 (4.04)	303.29 (26.68)	293.12 (18.41)	3.72 (4.40)	5.03 (4.63)	300.94 (23.16)	303.89 (20.38)

Key: Standard deviations are in parenthesis; bold figure indicates the site with the peak amplitude(s) or indicates the largest and smallest peak latencies

Appendix 8.22 XXV (i) Statistical results of between group and within-group repeated measures ANOVA with 2 (conditions) × 6 (midline electrodes sites) and repeated measures ANOVA with 2 (conditions) × 2 (laterality) × 7 (lateral electrode sites) on the mean amplitudes of P2 component of the chronic pain and pain-free groups

	Chronic vs Pain-free			Chronic			Pain-free		
Midline	df	F-value	p-value	df	F-value	p-value	df	F-value	p-value
Within-Subjects Effect									
Conditions	1,33	11.214	0.002**	1,16	0.973	0.339	1,17	12.241	0.003**
Condition × Group		4.662	0.038*						
Electrode	2.235, 73.744	17.460	<0.001**	1.959, 31.339	17.776	<0.001**	2.147, 36.502	7.706	0.001**
Electrode × Group		3.880	0.021*						
Condition × Electrode	1.918, 63.287	2.442	0.097	1.175, 18.797	1.650	0.217	1.224, 20.815	1.890	0.184
Condition × Electrode × Group		1.081	0.343						
Between-Subject Effects	1,33	10.176	0.003**						
Lateral									
Within-Subjects									
Conditions	1,33	3.023	0.091	1,16	0.240	0.631	1,17	12.480	0.003**
Condition × Group		6.396	0.016*						
Laterality	1,33	12.472	0.001*	1,16	18.406	0.001**	1,17	0.722	0.467
Laterality × Group		5.244	0.029*						
Electrode	2.350, 77.564	17.912	<0.005**	2.476, 39.616	10.840	<0.001**	2.019	9.479	0.001**
Electrode × Group		1.575	0.210						
Condition × Laterality	1,33	0.111	0.742	1,16	0.693	0.417	1,17	0.825	0.376
Condition × Laterality × Group		1.386	0.249						
Condition × Electrode	2.098, 69.245	3.278	0.041*	1.609	0.903	0.398	2.307, 39.226	4.096	0.020*
Condition × Electrode ×		0.472	0.635						

Group									
Laterality × Electrode	3.966, 130.863	1.610	0.176	3.243, 51.891	2.117	0.105	3.689, 62.718	0.609	0.645
Laterality × Electrode × Group		0.618	0.649						
Condition × Laterality × Electrode	2.194, 72.392	0.388	0.699	1.743, 27.883	0.566	0.551	2.810, 47.762	0.133	0.931
Condition × Laterality × Electrode × Group		0.426	0.673						
Between-Subject Effects	1,33	8.886	0.005**						

Key: ** p<0.01, ** p<0.050

Appendix XXV (j) Statistical results of between group and within-group repeated measures ANOVA with 2 (conditions) × 6 (midline electrodes sites) and repeated measures ANOVA with 2 (conditions) × 2 (laterality) × 7 (lateral electrode sites) on the peak latencies of P2 component of the chronic pain and pain-free groups

	Chronic vs Pain-free			Chronic			Pain-free		
Midline	df	F-value	p-value	df	F-value	p-value	df	F-value	p-value
Within-Subjects Effect									
Conditions	1,33	0.852	0.363	1,16	2.107	0.166	1,17	0.970	0.339
Condition × Group		3.108	0.087						
Electrode	2.124, 70.096	13.292	<0.005**	1.896, 30.330	5.943	0.007**	2.182, 37.094	7.822	0.001**
Electrode × Group		0.167	0.858						
Condition × Electrode	2.890, 95.368	0.474	0.694	2.518, 40.293	0.570	0.607	1.951, 33.163	0.952	0.394
Condition × Electrode × Group		0.971	0.407						
Between-Subject Effects	1,33	0.872	0.375						
Lateral									
Within-Subjects									
Conditions	1,33	1.033	0.317	1,16	1.618	0.221	1,17	0.040	0.844
Condition × Group		1.485	0.232						
Laterality	1,33	0.007	0.933	1,16	1.432	0.249	1,17	0.938	0.346
Laterality × Group		2.297	0.139						
Electrode	2.789, 92.032	19.502	<0.001	2.452, 39.224	7.488	0.001**	2.643, 44.928	12.802	<0.001**
Electrode × Group		0.233	0.860						
Condition × Laterality	1,33	0.000	0.990	1,16	0.246	0.627	1,17	0.587	0.454
Condition × Laterality × Group		0.716	0.403						
Condition × Electrode	2.572, 84.882	0.878	0.442	2.583, 41.320	1.078	0.362	2.203, 37.458	0.467	0.649
Condition × Electrode ×		0.779	0.491						

Group									
Laterality × Electrode	3.304, 109.033	1.137	0.340	3.416, 54.652	1.602	0.194	2.615, 44.457	0.379	0.741
Laterality × Electrode × Group		0.754	0.534						
Condition × Laterality × Electrode	3.676, 121.324	0.256	0.892	3.698, 59.168	0.617	0.640	2.776, 47.189	0.320	0.796
Condition × Laterality × Electrode × Group		0.676	0.597						
Between-Subject Effects	1,33	0.030	0.865						

Key: ** p<0.01, ** p<0.050

Appendix XXV (k) The mean amplitude (in μV) and peak latency (in ms) of the six midline electrodes and seven pairs of lateral (left and right) electrodes for Perception and Imagery trial for P300 component in chronic pain group and pain-free groups

Electrode sites	Chronic				Pain-free			
	Mean Amplitude		Peak Latency		Mean Amplitude		Peak Latency	
	Perception	Imagery	Perception	Imagery	Perception	Imagery	Perception	Imagery
Midline								
Fz	3.42 (3.16)	4.31 (3.53)	356.47 (14.10)	**361.65(16.02)**	3.62 (5.68)	5.86 (4.47)	356.11 (10.50)	356.72 (12.51)
FCz	3.75 (3.17)	4.25 (3.63)	351.65 (4.74)	360.12(16.32)	4.97 (5.41)	7.50 (4.04)	**355.44(10.62)**	356.28 (12.43)
Cz	5.02 (2.49)	5.38 (3.46)	**351.24 (4.59)**	355.06 (14.54)	6.80 (5.11)	9.17 (4.21)	355.67 (10.51)	**355.39 (12.63)**
CPz	**5.77 (2.64)**	**7.61 (4.28)**	354.41(10.31)	**353.24(8.00)**	**8.74 (5.94)**	**10.83 (4.93)**	357.00 (10.36)	355.94 (13.44)
Pz	4.14 (3.05)	4.08 (3.95)	357.82 (16.26)	355.41 (14.81)	7.79 (5.75)	9.67 (5.05)	357.06 (10.63)	357.11 (13.65)
POz	3.72 (3.62)	3.54 (4.28)	**357.94(15.27)**	355.35 (14.82)	7.17 (5.26)	8.70 (4.74)	**358.61(12.45)**	**358.83 (15.14)**
Left								
F3	3.68 (3.25)	4.14 (4.37)	364.94(18.49)	363.00 (18.01)	3.19 (4.29)	4.79 (3.38)	357.22 (10.84)	359.61 (16.75)
FC3	3.98 (2.99)	4.22 (4.00)	359.12 (16.16)	362.88 (18.04)	4.16 (4.63)	6.21 (3.71)	**356.11(10.64)**	357.89 (14.93)
C3	3.71 (2.60)	4.09 (3.84)	359.06 (15.48)	365.24 (19.05)	4.95 (3.53)	6.88 (3.64)	357.94 (11.75)	357.33 (14.86)
CP3	3.50 (2.94)	3.79 (3.86)	355.82 (12.59)	364.00 (20.13)	5.12 (3.73)	6.78 (4.34)	360.89 (15.12)	**356.89 (14.45)**
P3	**4.29 (3.16)**	**4.22 (3.70)**	**358.06(16.84)**	**359.29(19.44)**	**6.58 (4.15)**	**8.22 (4.56)**	358.89 (13.18)	360.78 (17.66)
PO3	3.32 (3.04)	3.20 (3.27)	358.41 (16.73)	362.88 (19.99)	4.78 (3.31)	5.84 (3.98)	**363.33(15.99)**	361.78 (17.42)
T7	1.62 (3.10)	1.60 (4.41)	**365.76(18.10)**	**371.00(23.66)**	2.05 (2.78)	2.86 (2.33)	363.06 (19.35)	**363.39 (18.53)**
Right								
F4	1.01 (3.51)	0.77 (3.33)	359.59 (14.76)	367.82 (20.74)	2.53 (5.35)	4.37 (4.71)	357.33(10.54)	358.33 (16.04)
FC4	1.68 (3.02)	1.69 (3.25)	(**356.47 (9.86)**	361.29 (17.78)	3.05 (5.53)	5.48 (4.46)	**356.72(10.78)**	**356.61 (12.78)**
C4	1.72 (2.75)	1.17 (3.37)	357.24 (12.63)	358.72 (16.98)	5.48 (5.13)	7.06 (4.22)	358.00 (10.44)	359.22 (15.02)
CP4	1.90 (2.75)	1.57 (3.22)	358.06 (12.19)	360.24 (17.34)	5.69 (4.79)	7.44 (4.32)	358.56 (12.20)	357.56 (15.79)
P4	**2.66 (3.17)**	**2.12 (4.18)**	359.59 (15.25)	**355.76(14.80)**	**6.72 (5.15)**	**8.27 (4.72)**	358.72 (12.52)	362.06 (19.27)
PO4	1.96 (3.27)	1.33 4.11)	361.71 (15.14)	**355.76(14.74)**	5.45 (4.82)	6.43 (4.66)	360.06 (12.29)	363.56 (20.86)
T8	0.18 (2.75)	-0.66 (2.83)	**364.59(14.97)**	**365.88(18.24)**	2.05 (3.89)	3.25 (3.85)	**361.28(17.61)**	**370.17 (23.28)**

Key: Standard deviations are in parenthesis; bold figure indicates the site with the peak amplitude(s) or indicates the largest and smallest peak latencies

Appendix XXV (l) Statistical results of between group and within-group repeated measures ANOVA with 2 (conditions) × 6 (midline electrodes sites) and repeated measures ANOVA with 2 (conditions) × 2 (laterality) × 7 (lateral electrode sites) on the mean amplitudes of P3 component of the chronic pain and pain-free groups

	Chronic vs Pain-free			Chronic			Pain-free		
Midline	df	F-value	p-value	df	F-value	p-value	df	F-value	p-value
Within-Subjects Effect									
Conditions	1,33	10.631	0.001**	1,16	2.010	0.175	1,17	9.020	0.008**
Condition × Group		3.585	0.067						
Electrode	1.838, 60.645	14.710	<0.005**	1.740, 27.844	7.624	0.003**	1.700, 28.902	10.853	0.001**
Electrode × Group		4.380	0.001**						
Condition × Electrode	1.587, 52.358	1.979	0.157	1.239, 18.817	1.580	0.228	1.506, 15.610	0.950	0.376
Condition × Electrode × Group		1.107	0.326						
Between-Subject Effects	1,33	3.526	0.069						
Lateral									
Within-Subjects									
Conditions	1,33	2.445	0.127	1,16	0.152	0.702	1,17	9.265	0.007**
Condition × Group		4.771	0.036*						
Laterality	1,33	7.320	0.011*	1,16	15.257	0.001**	1,17	0.031	0.862
Laterality × Group		8.699	0.006**						
Electrode	2.005, 66.160	13.203	<0.005**	1.803	3.829	0.037*	1.999, 33.981	10.567	<0.001**
Electrode × Group		3.210	0.047*						
Condition × Laterality	1,33	0.659	0.423	1,16	0.789	0.388	1,17	0.001	0.980
Condition × Laterality × Group		0.695	0.411						
Condition × Electrode	1.873, 61.803	2.066	0.138	1.461, 23.380	0.792	0.428	2.015, 34.260	2.084	0.140
Condition × Electrode ×		0.377	0.674						

Group									
Laterality × Electrode	3.506, 115.698	3.189	0.020*	3.102, 49.634	1.885	0.142	2.191, 54.242	1.986	0.123
Laterality × Electrode × Group		0.682	0.613						
Condition × Laterality × Electrode	1.892, 62.441	0.758	0.466	1.353, 21.652	0.409	0.590	2.768, 42.063	0.491	0.675
Condition × Laterality × Electrode × Group		0.135	0.863						
Between-Subject Effects	1,33	4.849	0.035*						

Key: ** p<0.01, ** p<0.050

Appendix XXV (m) Statistical results of between group and within-group repeated measures ANOVA with 2 (conditions) × 6 (midline electrodes sites) and repeated measures ANOVA with 2 (conditions) × 2 (laterality) × 7 (lateral electrode sites) on the peak latencies of P300 component of the chronic pain and pain-free groups

	Chronic vs Pain-free			Chronic			Pain-free		
Midline	df	F-value	p-value	df	F-value	p-value	df	F-value	p-value
Within-Subjects Effect									
Conditions	1,33	0.320	0.575	1,16	1.555	0.230	1,17	0.000	0.983
Condition × Group		0.279	0.601						
Electrode	2.303, 76.003	2.194	0.111	1.896, 30.012	1.572	0.225	1.751, 29.760	1.783	0.189
Electrode × Group		1.147	0.328						
Condition × Electrode	2.546, 84.016	2.347	0.088	2.261, 36.171	2.307	0.108	2.010, 34.172	0.232	0.795
Condition × Electrode × Group		1.679	0.185						
Between-Subject Effects	1,33	0.065	0.800						
Lateral									
Within-Subjects									
Conditions	1,33	0.820	0.372	1,16	1.058	0.319	1,17	0.138	0.715
Condition × Group		0.100	0.754						
Laterality	1,33	0.448	0.508	1,16	1.454	0.245	1,17	0.013	0.912
Laterality × Group		0.709	0.406						
Electrode	2.993, 98.765	6.165	0.001 **	2.643, 42.148	4.216	0.014*	2.723, 46.292	3.921	0.017*
Electrode × Group		2.023	0.116						
Condition × Laterality	1,33	0.004	0.952	1,16	1.128	0.304	1,17	0.262	0.615
Condition × Laterality × Group		0.890	0.352						
Condition × Electrode	4.035, 133.153	0.814	0.519	3.404, 54.456	1.297	0.284	3.383, 57.503	1.435	0.239
Condition × Electrode ×		1.918	0.111						

Group									
Laterality × Electrode	3.010, 99.345	0.101	0.960	2.148, 34.368	0.338	0.730	2.675, 45.467	0.243	0.844
Laterality × Electrode × Group		0.475	0.701						
Condition × Laterality × Electrode	3.729, 123.054	0.819	0.508	4.007, 64.117	2.395	0.059	2.832, 48.146	0.941	0.424
Condition × Laterality × Electrode × Group		2.725	0.036*						
Between-Subject Effects	1,33	0.151	0.700						

Key: ** p<0.01, ** p<0.050

Appendix XXV (n) The mean amplitude (in μV) and peak latency (in ms) of the six midline electrodes and seven pairs of lateral (left and right) electrodes for Perception and Imagery trial for N400 component in chronic pain group and pain-free groups

Electrode sites	Chronic				Pain-free			
	Mean Amplitude		Peak Latency		Mean Amplitude		Peak Latency	
	Perception	Imagery	Perception	Imagery	Perception	Imagery	Perception	Imagery
Midline								
Fz	**-4.84 (3.99)**	**-3.63 (5.31)**	458.71 (15.62)	455.41 (18.80)	**-5.30 (6.39)**	**-3.84 (6.70)**	**462.00 (15.58)**	**459.61 (15.95)**
FCz	-4.46 (4.21)	-3.55 (5.46)	458.82 (15.48)	**453.18(17.81)**	-3.94 (5.64)	-2.19 (6.04)	456.72 (19.35)	458.50 (17.84)
Cz	-3.13 (3.64)	-2.23 (4.68)	**460.06(14.96)**	457.82 (18.53)	-1.86 (4.57)	-0.32 (4.72)	456.78 (20.40)	458.78 (17.63)
CPz	-1.58 (3.42)	0.24 (4.41)	454.41 (18.60)	**459.24(16.39)**	0.33 (4.57)	1.76 (4.76)	457.89 (20.87)	456.61 (18.16)
Pz	-2.47 (2.84)	-1.95 (3.47)	454.82 (18.64)	456.47 (18.13)	0.27 (5.07)	1.45 (4.90)	456.06 (21.26)	**452.83(19.48)**
POz	-2.22 (2.95)	-1.90 (3.55)	**450.12(23.01)**	456.29 (20.21)	0.49 (4.79)	1.46 (4.70)	**455.72(21.04)**	453.00 (19.29)
Left								
F3	**-3.97 (3.89)**	**-3.14 (5.82)**	458.82 (15.59)	456.29 (16.29)	**-4.95 (5.44)**	**-3.97 (5.68)**	**458.06(17.38)**	**462.17(17.57)**
FC3	-3.89 (3.78)	-3.11 (5.42)	458.76 (15.59)	457.71 (16.82)	-4.22 (5.25)	-2.78 (5.82)	454.17 (19.73)	459.89 (18.76)
C3	-3.13 (3.08)	-2.11 (4.56)	458.53 (15.00)	**457.88(17.88)**	-1.69 (2.74)	-0.57 (3.28)	454.00 (21.13)	453.17 (21.56)
CP3	-2.57 (2.62)	-1.51 (4.12)	459.47 (14.83)	454.82 (20.28)	-1.14 (2.35)	-0.26 (3.31)	454.06 (21.34)	**448.33(23.07)**
P3	-1.20 (2.17)	-0.83 (2.69)	**460.06(15.31)**	455.29 (14.93)	0.97 (3.56)	1.89 (4.09)	448.28 (22.33)	455.94 (19.33)
PO3	-1.41 (2.07)	-1.27 (2.74)	457.82 (16.73)	**454.06(15.06)**	0.21 (2.81)	0.82 (3.47)	**447.22(21.67)**	449.11 (20.37)
T7	-3.42 (2.95)	-2.83 (5.51)	**457.41(19.91)**	454.88 (17.42)	-3.13 (3.08)	-2.76 (2.96)	452.44 (20.44)	458.22 (19.63)
Right								
F4	**-6.08 (4.10)**	**-5.70 (4.88)**	456.71 (18.12)	454.11 (18.48)	**-3.84 (6.70)**	**-4.90 (6.89)**	459.72 (17.95)	**461.72(13.44)**
FC4	-5.87 (3.63)	-5.30 (4.36)	457.88 (17.01)	456.24 (16.86)	-2.19 (6.04)	-3.75 (6.45)	**462.39(15.35)**	457.11 (16.76)
C4	-3.77 (2.98)	-3.53 (3.13)	**452.12(19.30)**	**459.06(19.65)**	-0.32 (4.72)	-0.31 (4.54)	458.67 (18.14)	457.89 (19.46)
CP4	-3.27 (2.75)	-2.94 (2.79)	453.82 (18.44)	457.29 (19.73)	1.76 (4.76)	0.76 (4.21)	454.94 (20.26)	457.22 (18.16)
P4	-2.58 (2.65)	-2.57 (3.09)	452.47 (21.13)	454.88 (17.75)	1.45 (4.90)	2.00 (4.54)	451.17 (22.10)	453.78 (20.88)
PO4	-2.72 (2.62)	-2.90 (2.93)	451.11 (21.02)	**452.00(20.81)**	1.46 (4.70)	1.11 (3.64)	**444.61(20.70)**	**451.00(19.79)**
T8	-4.42 (2.97)	-4.66 (2.80)	**458.35(18.31)**	457.88 (19.29)	-3.84 (6.70)	-2.33 (3.74)	456.39 (18.46)	458.17 (20.32)

Key: Standard deviations are in parenthesis; bold figure indicates the site with the peak amplitude(s) or indicates the largest and smallest peak latencies

Appendix XXV (o) Statistical results of between group and within-group repeated measures ANOVA with 2 (conditions) × 6 (midline electrodes sites) and repeated measures ANOVA with 2 (conditions) × 2 (laterality) × 7 (lateral electrode sites) on the mean amplitudes of N400 component of the chronic pain and pain-free groups

	Chronic vs Pain-free			Chronic			Pain-free		
Midline	df	F-value	p-value	df	F-value	p-value	df	F-value	p-value
Within-Subjects Effect									
Conditions	1,33	15.553	<0.001**	1,16	7.611	0.014*	1,17	9.208	0.007**
Condition × Group		1.530	0.255						
Electrode	1.483, 48.953	21.821	<0.001**	1.142, 22.599	9.950	0.002**	1.401, 23.819	13.860	<0.001**
Electrode × Group		2.945	0.076						
Condition × Electrode	1.878, 61.963	2.114	0.132	1.379, 22.070	1.493	0.243	1.571, 26.815	1.205	0.306
Condition × Electrode × Group		0.828	0.435						
Between-Subject Effects	1,33	2.575	0.118						
Lateral									
Within-Subjects									
Conditions	1,33	8.087	0.008**	1,16	1.121	0.305	1,17	9.578	0.007**
Condition × Group		1.550	0.222						
Laterality	1,33	6.862	0.013**	1,16	10.271	0.006**	1,17	0.002	0.966
Laterality × Group		6.597	0.015*						
Electrode	1.519, 50.128	22.283	<0.005**	1.640, 26.237	8.088	0.003**	1.421, 24.155	15.041	<0.001**
Electrode × Group		3.159	0.064						
Condition × Laterality	1,33	0.161	0.691	1,16	0.324	0.577	1,17	0.013	0.910
Condition × Laterality × Group		0.287	0.596						
Condition × Electrode	1.881, 62.064	2.414	0.101	1.461, 23.379	0.880	0.397	1.741, 50.118	2.193	0.135
Condition × Electrode ×		0.530	0.581						

Group									
Laterality × Electrode	3.528, 116.421	3.923	0.007**	2.663, 42.596	1.100	0.355	2.948, 50.118	3.272	0.029*
Laterality × Electrode × Group		0.600	0.680						
Condition × Laterality × Electrode	2.032, 67.049	0.393	0.680	1.464, 23.422	0.244	0.716	2.676, 45.500	0.271	0.824
Condition × Laterality × Electrode × Group		0.121	0.889						
Between-Subject Effects	1,33	3.661	0.064						

Key: ** p<0.01, ** p<0.050

Appendix XXV (p) Statistical results of between group and within-group repeated measures ANOVA with 2 (conditions) × 6 (midline electrodes sites) and repeated measures ANOVA with 2 (conditions) × 2 (laterality) × 7 (lateral electrode sites) on the peak latencies of N400 component of the chronic pain and pain-free groups

	Chronic vs Pain-free			Chronic			Pain-free		
Midline	df	F-value	p-value	df	F-value	p-value	df	F-value	p-value
Within-Subjects Effect									
Conditions	1,33	0.013	0.909	1,16	0.003	0.960	1,17	0.055	0.818
Condition × Group		0.037	0.848						
Electrode	2.420, 79.860	2.588	0.071	2.370, 37.920	1.041	0.373	2.007, 34.115	2.315	0.114
Electrode × Group		0.592	0.587						
Condition × Electrode	3.041, 100.360	0.814	0.491	2.284, 36.546	1.747	0.185	2.678, 45.527	1.037	0.379
Condition × Electrode × Group		2.347	0.076						
Between-Subject Effects	1,33	0.028	0.869						
Lateral									
Within-Subjects									
Conditions	1,33	0.065	0.801	1,16	0.050	0.826	1,17	0.396	0.537
Condition × Group		0.346	0.561						
Laterality	1,33	0.003	0.960	1,16	1.476	0.242	1,17	1.104	0.308
Laterality × Group		2.466	0.126						
Electrode	2.801, 92.448	3.618	0.018*	1.998, 31.963	0.626	0.541	2.680, 45.555	3.498	0.027*
Electrode × Group		1.275	0.288						
Condition × Laterality	1,33	0.199	0.659	1,16	0.640	0.435	1,17	0.151	0.702
Condition × Laterality × Group		0.790	0.380						
Condition × Electrode	3.699, 133.052	0.411	0.786	2.746, 43.929	0.601	0.603	2.906, 49.400	1.076	0.366
Condition × Electrode ×		1.300	0.375						

Group									
Laterality × Electrode	3.775, 124.579	1.024	0.395	3.094, 49.509	0.673	0.577	3.296, 56.305	0.872	0.469
Laterality × Electrode × Group		0.504	0.722						
Condition × Laterality × Electrode	4.331, 142.917	1.671	0.155	2.784, 44.545	0.701	0.546	3.841, 65.290	1.350	0.262
Condition × Laterality × Electrode × Group		0.483	0.762						
Between-Subject Effects	1,33	0.100	0.754						

Key: ** p<0.01, ** p<0.050

Appendix XXV (q) The mean amplitude (in μV) and peak latency (in ms) of the six midline electrodes and seven pairs of lateral (left and right) electrodes for Perception and Imagery trial for P600 component in chronic pain group and pain-free groups

Electrode sites	Chronic				Pain-free			
	Mean Amplitude		Peak Latency		Mean Amplitude		Peak Latency	
	Perception	Imagery	Perception	Imagery	Perception	Imagery	Perception	Imagery
Midline								
Fz	-3.02 (4.18)	-1.48 (4.78)	585.35 (47.57)	**597.53(41.52)**	-1.93 (5.77)	0.76 (5.76)	596.67 (34.58)	612.67 (30.08)
FCz	-2.58 (4.15)	-1.25 (4.81)	**589.47(41.66)**	596.06 (40.27)	-0.38 (4.83)	2.70 (5.03)	**601.72(36.37)**	**614.39(28.11)**
Cz	-1.02 (3.34)	0.24 (4.02)	583.12 (33.65)	584.18 (43.12)	1.82 (4.20)	4.78 (4.50)	587.00 (47.97)	609.06 (29.55)
CPz	**0.27 (3.26)**	**2.47 (3.27)**	573.71 (36.38)	**581.18(48.13)**	**3.92 (4.23)**	**6.71 (4.25)**	580.50 (50.55)	602.33 (33.16)
Pz	-0.42 (2.35)	0.29 (3.32)	573.82 (30.39)	584.65 (46.02)	3.74 (4.71)	6.49 (4.82)	582.83 (46.05)	597.94 (39.37)
POz	-0.03 (2.28)	0.36 (3.39)	**567.18(31.71)**	583.29 (45.82)	3.72 (4.41)	6.04 (4.37)	**577.39(44.64)**	**596.28(35.43)**
Left								
F3	-2.21 (3.90)	-1.27 (5.25)	587.12 (50.38)	591.24 (49.71)	-2.05 (4.55)	0.25 (4.99)	591.50 (38.48)	593.78 (45.63)
FC3	-1.98 (3.62)	-1.08 (4.81)	587.06 (50.20)	595.12 (42.29)	-1.07 (4.75)	1.80 (5.49)	**591.72(38.67)**	**595.22(40.21)**
C3	-1.21 (2.94)	-0.21 (4.48)	**592.88(41.60)**	601.71 (42.09)	1.08 (2.79)	3.92 (3.97)	581.67 (46.21)	**588.50(43.66)**
CP3	-0.62 (2.85)	0.30 (4.12)	586.47 (46.55)	**602.88(42.31)**	1.70 (3.03)	4.26 (4.91)	570.17 (40.50)	589.44 (43.54)
P3	0.55 (2.36)	**1.14 (2.77)**	567.29 (37.39)	586.94 (49.46)	**3.94 (3.96)**	**6.25 (5.16)**	**566.22(42.52)**	590.89 (39.70)
PO3	**0.57 (2.44)**	0.82 (2.45)	**566.88(37.54)**	**585.53(47.74)**	3.04 (3.24)	4.70 (4.76)	568.72 (37.57)	588.78 (39.62)
T7	-1.88 (3.49)	-1.50 (5.07)	581.82 (47.44)	592.41 (46.76)	-0.62 (3.08)	0.80 (3.44)	586.89 (39.72)	**588.50(50.52)**
Right								
F4	-4.45 (4.43)	-3.99 (4.30)	**571.18(52.70)**	588.47 (48.28)	-2.68 (5.73)	-0.96 (5.81)	**603.33(39.68)**	591.94 (50.80)
FC4	-4.06 (3.72)	-3.26 (3.87)	570.35 (45.82)	582.59 (48.69)	-2.03 (5.50)	0.67 (5.15)	602.28 (40.48)	**597.28(48.36)**
C4	-2.56 (3.33)	-2.04 (3.26)	**560.71(35.20)**	582.94 (49.48)	2.00 (4.23)	3.53 (3.78)	586.61 (50.51)	590.06 (43.50)
CP4	-1.96 (2.92)	-1.46 (3.00)	562.59 (35.56)	583.06 (49.50)	2.79 (3.77)	4.59 (3.89)	**580.28(48.33)**	586.28 (40.09)
P4	**-0.68 (2.23)**	**-0.42 (2.98)**	558.65 (31.43)	582.00 (45.49)	**4.25 (4.50)**	**6.11 (4.81)**	580.78 (48.26)	**584.44(41.88)**
PO4	-0.85 (2.23)	-0.74 (2.84)	564.41 (31.17)	**588.76(46.45)**	3.68 (3.96)	4.98 (3.79)	583.56 (46.39)	574.67 (40.94)
T8	-3.53 (3.58)	-3.59 (3.10)	569.47 (45.70)	**581.18(48.20)**	0.15 (4.04)	0.27 (3.97)	595.17 (48.07)	597.61 (46.04)

Key: Standard deviations are in parenthesis; bold figure indicates the site with the peak amplitude(s) or indicates the largest and smallest peak latencies

Appendix XXV (r) Statistical results of between group and within-group repeated measures ANOVA with 2 (conditions) × 6 (midline electrodes sites) and repeated measures ANOVA with 2 (conditions) × 2 (laterality) × 7 (lateral electrode sites) on the mean amplitudes of P600 component of the chronic pain and pain-free groups

	Chronic vs Pain-free			Chronic			Pain-free		
Midline	df	F-value	p-value	df	F-value	p-value	df	F-value	p-value
Within-Subjects Effect									
Conditions	1,33	13.659	0.001**	1,16	3.703	0.072	1,17	10.368	0.005**
Condition × Group		3.128	0.086						
Electrode	1.336, 44.072	24.927	<0.005**	1.439, 23.032	14.453	<0.001**	1.280, 21.765	14.101	0.001**
Electrode × Group		3.573	0.106						
Condition × Electrode	1.783, 58.830	1.266	0.281	1.388, 22.211	1.379	0.264	2.091, 35.554	0.149	0.871
Condition × Electrode × Group		1.090	0.337						
Between-Subject Effects	1,33	7.557	0.010**						
Lateral									
Within-Subjects									
Conditions	1,33	5.307	0.028*	1,16	0.045	0.835	1,17	9.688	0.006**
Condition × Group		3.987	0.054						
Laterality	1,33	7.202	0.011**	1,16	14.266	0.002**	1,17	0.032	0.861
Laterality × Group		5.868	0.021*						
Electrode	1.355, 44.699	29.480	<0.001**	1.638, 26.205	17.660	<0.001**	1.242, 21.117	16.420	<0.001**
Electrode × Group		2.758	0.093						
Condition × Laterality	1,33	2.653	0.113	1,16	1.003	0.331	1,17	1.756	0.203
Condition × Laterality × Group		0.010	0.920						
Condition × Electrode	1.990, 65.657	3.018	0.056	1.436, 22.971	0.561	0.522	2.236, 38.012	4.015	0.022*
Condition × Electrode ×		1.050	0.355						

Group									
Laterality × Electrode	3.484, 114.956	4.922	0.002**	2.721, 43.538	1.495	0.232	3.322, 56.476	4.066	0.009**
Laterality × Electrode × Group		0.560	0.668						
Condition × Laterality × Electrode	2.115, 69.800	1.400	0.253	1.403, 22.449	0.545	0.526	2.704, 45.975	1.005	0.393
Condition × Laterality × Electrode × Group		0.136	0.883						
Between-Subject Effects	1,33	9.827	0.004**						

Key: ** p<0.01, ** p<0.050

Appendix XXV (s) Statistical results of between group and within-group repeated measures ANOVA with 2 (conditions) × 6 (midline electrodes sites) and repeated measures ANOVA with 2 (conditions) × 2 (laterality) × 7 (lateral electrode sites) on the peak latencies of P600 component of the chronic pain and pain-free groups

	Chronic vs Pain-free			Chronic			Pain-free		
Midline	df	F-value	p-value	df	F-value	p-value	df	F-value	p-value
Within-Subjects Effect									
Conditions	1,33	3.170	0.084	1.16	0.605	0.448	1,17	3.373	0.084
Condition × Group		0.336	0.566						
Electrode	3.331, 76.937	5.506	0.004*	2.140, 34.246	1.820	0.175	2.232, 37.939	4.428	0.016*
Electrode × Group		0.058	0.962						
Condition × Electrode	2.737, 90.329	0.259	0.837	2.393	0.559	0.607	2.433, 41.361	0.227	0.839
Condition × Electrode × Group		0.474	0.684						
Between-Subject Effects	1,33	2.790	0.104						
Lateral									
Within-Subjects									
Conditions	1,33	2.931	0.096	1,16	2.024	0.174	1,17	0.848	0.370
Condition × Group		0.798	0.378						
Laterality	1,33	0.478	0.495	1,16	2.263	0.152	1,17	0.268	0.611
Laterality × Group		2.030	0.164						
Electrode	2.838, 93.668	3.679	0.016*	2.071	1.376	0.267	2.750, 46.747	3.169	0.037*
Electrode × Group		1.005	0.391						
Condition × Laterality	1,33	0.232	0.633	1,16	0.743	0.401	1,17	1.578	0.226
Condition × Laterality × Group		2.276	0.141						
Condition × Electrode	2.413, 79.624	1.282	0.286	2.262, 36.189	0.735	0.502	2.143, 36.424	0.721	0.502
Condition × Electrode ×		0.143	0.901						

Group									
Laterality × Electrode	2.810, 92.732	0.841	0.468	2.783, 44.533	1.957	0.138	2.237, 38.036	0.140	0.890
Laterality × Electrode × Group		1.061	0.367						
Condition × Laterality × Electrode	2.954, 97.472	0.423	0.734	2.290, 36.636	0.143	0.892	3.029, 51.667	0.707	0.554
Condition × Laterality × Electrode × Group		0.395	0.754						
Between-Subject Effects	1,33	0.665	0.421						

Key: ** p<0.01, ** p<0.050

Appendix XXVI (a – j) ERP Analysis Results of respondent and non-respondent groups of Chronic Pain Groups

Appendix XXVI (a) The mean amplitude (in μV) and peak latency (in ms) of the six midline electrodes and seven pairs of lateral (left and right) electrodes for Perception and Imagery trial for P1 component in respondent and non-respondent groups

Electrode Site	Respondent		Non-respondent	
	Mean Amplitude		Mean Amplitude	
Central	Perception	Imagery	Perception	Imagery
Fz	9.22 (3.00)	10.45 (3.22)	**11.71 (8.58)**	**11.78 (8.76)**
FCz	9.90 (2.63)	10.74 (2.17)	11.55 (8.16)	11.67 (8.49)
Cz	**11.22 (3.88)**	11.17 (2.37)	11.54 (8.29)	11.53 (8.37)
CPz	10.47(3.13)	**12.02 (3.06)**	9.81 (7.05)	10.15 (7.93)
Pz	8.88 (4.41)	7.59 (2.53)	6.96 (7.07)	6.48 (6.90)
POz	8.29 (4.55)	6.80 (2.68)	5.21 (7.04)	5.14 (6.43)
Left				
F3	8.15(2.88)	**9.50 (3.03)**	10.44 (7.15)	9.99 (7.14)
FC3	**8.44 (2.65)**	9.28 (3.27)	**10.94 (7.12)**	**10.32 (7.15)**
C3	8.35 (2.30)	8.93 (2.09)	9.02 (7.01)	8.04 (6.91)
CP3	5.64 (4.40)	6.66 (2.40)	8.50 (7.33)	7.41 (7.32)
P3	6.86 (3.21)	6.14 (1.53)	6.75(7.44)	6.27 (7.43)
PO3	4.71 (4.30)	4.25 (2.22)	5.49 (6.60)	4.93 (6.56)
T7	3.46 (3.44)	5.49(2.49)	6.27 (5.64)	5.25 (5.62)
Right				
F4	5.68 (2.74)	4.45 (3.49)	8.68 (8.36)	**9.19 (8.11)**
FC4	**7.75 (4.24)**	**7.17 (3.38)**	**8.96 (7.75)**	9.10 (7.88)
C4	5.23 (3.37)	3.80 (2.74)	7.11 (7.88)	7.13 (7.96)
CP4	5.59 (3.82)	4.22 (2.03)	5.70 (7.05)	5.83 (6.62)
P4	5.53 (4.35)	3.64 (1.62)	4.95 (6.97)	4.79 (6.46)
PO4	5.03(4.36)	2.93 (1.98)	3.88 (7.04)	3.70 (6.48)
T8	4.94(3.82)	2.85 (3.24)	3.53 (5.52)	3.83 (5.27)

Key: Standard deviations are in parenthesis; bold figure indicates the site with the peak amplitude(s) or indicates the largest and smallest peak latencies

Appendix XXVI (b) Statistical results of between group and within-group repeated measures ANOVA with 2 (conditions) × 6 (midline sites) and repeated measures ANOVA with 2 (conditions) × 2 (laterality) × 7 (lateral sites) on the mean amplitudes of P1 component of respondent and non-respondent groups

	Chronic vs Pain-free			Respondent			Non-respondent		
Midline	df	F-value	p-value	df	F-value	p-value	df	F-value	p-value
Within-Subjects Effect									
Conditions	1,15	0.018	0.894	1,5	0.016	0.903	1,10	0.000	0.988
Condition × Group		0.022	0.884						
Electrode	1.813, 27.191	17.752	<0.001**	1.480, 7.400	3.096	0.113	1.801, 18.013	24.649	<0.001**
Electrode × Group		2.870	0.079						
Condition × Electrode	1.318, 19.764	3.019	0.089	1.051, 5.254	1.974	0.218	1.299, 3.068	0.423	0.617
Condition × Electrode × Group		1.520	0.239						
Between-Subject Effects	1,15	0.007	0.934						
Lateral									
Within-Subjects									
Conditions	1,15	0.445	0.515	1,5	0.111	0.752	1,10	0.479	0.505
Condition × Group		0.010	0.921						
Laterality	1,15	20.198	<0.001**	1,5	10.733	0.022*	1,10	11.312	0.007**
Laterality × Group		0.118	0.736						
Electrode	2.461, 36.922	9.758	<0.001**	1.598, 7.992	4.034	0.068	2.327, 23.266	8.487	0.001**
Electrode × Group		0.584	0.597						
Condition × Laterality	1,15	1.616	0.223	1,5	2.686	0.162	1,10	7.398	0.022*
Condition × Laterality × Group		8.374	0.011*						
Condition × Electrode	1.956, 29.346	1.829	0.179	1.752, 8.761	1.376	0.298	2.069, 20.690	0.489	0.626

Condition × Electrode × Group		1.309	0.286						
Laterality × Electrode	2.795, 41.929	1.422	0.251	2.200, 10.998	3.351	0.070	2.585, 25.849	0.266	0.821
Laterality × Electrode × Group		2.440	0.082						
Condition × Laterality × Electrode	1.874, 28.115	0.937	0.398	1.409, 7.044	1.286	0.316	2.579, 25.791	1.933	0.156
Condition × Laterality × Electrode × Group		3.246	0.057						
Between-Subject Effects	1,15	0.171	0.685						

**p<0.01; *p<0.050

Appendix XXVI (c) The mean amplitude (in μV) and peak latency (in ms) of the six midline electrodes and seven pairs of lateral (left and right) electrodes for Perception and Imagery trial for P2 component in respondent and non-respondent groups

Electrode Site	Respondent		Non-respondent	
	Mean Amplitude		Mean Amplitude	
Central	Perception	Imagery	Perception	Imagery
Fz	6.68 (3.16)	10.68 (3.59)	10.05 (4.68)	10.57 (5.39)
FCz	7.19 (2.50)	10.42 (3.67)	10.26 (4.72)	**10.70 (5.50)**
Cz	8.34 (1.72)	9.88(4.17)	**10.67 (4.94)**	10.67 (5.55)
CPz	**8.57 (2.18)**	**12.85 (3.02)**	9.14 (4.40)	9.70 (5.65)
Pz	6.92 (2.03)	6.97 (5.41)	6.24 (4.54)	6.04 (4.75)
POz	6.96 (2.10)	6.70 (5.41)	4.47 (5.07)	4.52 (4.79)
Left				
F3	5.90 (3.40)	**10.92 (3.24)**	8.99 (4.37)	9.20 (4.52)
FC3	6.20 (3.04)	10.28 (4.30)	**9.59 (4.11)**	**9.53 (4.38)**
C3	6.40 (1.92)	9.35 (4.35)	7.36 (4.19)	6.90 (4.34)
CP3	4.56 (3.37)	7.11 (4.32)	6.91 (4.50)	6.38 (4.65)
P3	**6.39 (2.59)**	6.43 (5.60)	5.57 (4.84)	5.67 (4.55)
PO3	3.93 (2.91)	4.41 (4.59)	4.38 (4.40)	4.63 (4.13)
T7	1.64 (4.75)	5.26 (4.23)	4.63 (4.23)	3.93 (3.88)
Right				
F4	2.33 (3.64)	3.69 (2.95)	6.87 (5.46)	7.82 (5.84)
FC4	**4.24 (4.16)**	**5.63 (5.75)**	**7.53 (4.37)**	**7.93 (5.04)**
C4	2.53(1.41)	1.38 (3.62)	6.28 (5.26)	5.88 (5.76)
CP4	3.24 (1.51)	2.27 (3.51)	5.00 (4.72)	4.62 (4.64)
P4	4.25 (2.40)	2.94 (5.82)	4.35 (4.63)	4.11 (4.50)
PO4	3.56 (2.37)	2.37 (5.78)	3.26 (4.80)	3.14 (4.51)
T8	1.84 (1.55)	-0.07 (3.22)	3.26 (4.69)	2.85 (4.19)

Key: Standard deviations are in parenthesis; bold figure indicates the site with the peak amplitude(s) or indicates the largest and smallest peak latencies

Appendix XXVI (d) Statistical results of between group and within-group repeated measures ANOVA with 2 (conditions) × 6 (midline sites) and repeated measures ANOVA with 2 (conditions) × 2 (laterality) × 7 (lateral sites) on the mean amplitudes of P2 component of respondent and non-respondent groups

	Chronic vs Pain-free			Respondent			Non-respondent		
Midline	df	F-value	p-value	df	F-value	p-value	df	F-value	p-value
Within-Subjects Effect									
Conditions	1,15	6.374	0.023	1,5	3.899	0.105	1,10	0.360	0.542
Condition × Group		4.415	0.060[m]						
Electrode	2.157, 32.348	24.902	<0.001**	1.110, 5.549	7.530	0.013*	1.764, 17.639	28.750	<0.001**
Electrode × Group		5.246	0.0009						
Condition × Electrode	1.191, 17.868	3.063	0.092	1.110, 5.549	1.503	1.503	1.528, 15.179	0.540	0.547
Condition × Electrode × Group		1.680	0.214						
Between-Subject Effects	1,15	0.001	0.973						
Lateral									
Within-Subjects									
Conditions	1,15	25.402	0.438	1,5	0.470	0.523	1,10	0.085	0.776
Condition × Group		39.932	0.351						
Laterality	1,15	24.336	<0.001**	1,5	16.870	0.009**	1,10	6.485	0.029*
Laterality × Group		3.920	0.066						
Electrode	2.884, 43,272	13.296	<0.001**	1.685, 8.426	6.256	0.025*	2.599, 25.988	11.101	<0.001**
Electrode × Group		1.025	0.389						
Condition × Laterality	1,15	19.156	0.001**	1,5	14.584	0.012*	1,10	0.314	0.587
Condition × Laterality × Group		22.953	<0.001**						
Condition × Electrode	1.698, 25.476	5.355	0.015*	1.393, 6.967	2.775	0.136	1.587, 15.875	2.104	0.161

Condition × Electrode × Group		3.003	0.075						
Laterality × Electrode	3.439, 51.582	2.477	0.064	2.208, 11.042	3.834	0.051*	2.993, 29.929	0.252	0.859
Laterality × Electrode × Group		2.491	0.063						
Condition × Laterality × Electrode	2.506, 37.592	2.660	0.072	1.985, 9.926	2.510	0.131	2.455, 24.547	1.954	0.156
Condition × Laterality × Electrode × Group		5.001	0.008**						
Between-Subject Effects	1,15	0.565	0.464						

**p<0.01;*p<0.050

Appendix XXVI (e) The mean amplitude (in μV) and peak latency (in ms) of the six midline electrodes and seven pairs of lateral (left and right) electrodes for Perception and Imagery trial for P3 component in respondent and non-respondent groups

Electrode Site	Respondent		Non-respondent	
	Mean Amplitude		Mean Amplitude	
Central	Perception	Imagery	Perception	Imagery
Fz	3.41 (3.59)	6.68 (3.16)	3.43 (3.08)	3.01(3.13)
FCz	4.03 (3.40)	6.41 (3.55)	3.60 (3.21)	3.08 (3.24)
Cz	5.66 (2.52)	7.35 (4.07)	4.68 (2.53)	4.30 (2.70)
CPz	**6.26 (2.65)**	**11.08 (4.27)**	**5.50 (2.72)**	**5.72 (3.00)**
Pz	5.14 (2.11)	5.49 (5.15)	3.59 (3.43)	3.31 (3.15)
POz	5.41 (2.11)	5.32 (5.08)	2.81 (4.02)	2.56 (3.67)
Left				
F3	3.45 (3.06)	6.26 (5.04)	3.80(3.48)	2.99 (3.71)
FC3	3.64 (2.77)	5.73 (4.93)	**4.16 (3.22)**	**3.39 (3.37)**
C3	**4.60 (1.52)**	**6.32 (4.66)**	3.22 (2.99)	2.88 (2.86)
CP3	3.82 (2.77)	5.36 (5.26)	3.32 (3.15)	2.94 (2.77)
P3	5.46 (2.47)	5.57 (4.45)	3.65 (3.41)	3.49 (3.21)
PO3	3.81 (2.94)	3.87 (4.06)	3.06 (3.20)	2.83 (2.91)
T7	1.58 (4.05)	2.70 (6.55)	1.65 (2.68)	1.00 (2.91)
Right				
F4	.52 (3.27)	-.32 (2.71)	1.28 (3.75)	1.37 (3.61)
FC4	1.41(3.34)	1.79 (3.74)	1.83 (2.99)	1.63 (3.15)
C4	1.43 (2.41)	0.09 (4.17)	1.88 (3.02)	1.75 (2.91)
CP4	2.07 (2.12)	1.33 (3.74)	1.80 (3.13)	1.70 (3.08)
P4	**3.01 (1.89)**	**2.00 (5.66)**	**2.47 (3.77)**	**2.19 (3.45)**
PO4	2.66 (1.76)	1.26 (5.57)	1.57(3.89)	1.37 (3.39)
T8	0.77 (1.98)	-1.82(3.48)	-0.15 (3.13)	-0.01 (2.34)

Key: Standard deviations are in parenthesis; bold figure indicates the site with the peak amplitude(s) or indicates the largest and smallest peak latencies

Appendix XXVI (f) Statistical results of between group and within-group repeated measures ANOVA with 2 (conditions) × 6 (midline sites) and repeated measures ANOVA with 2 (conditions) × 2 (laterality) × 7 (lateral sites) on the mean amplitudes of P3 component of respondent and non-respondent groups

	Chronic vs Pain-free			Respondent			Non-respondent		
Midline	df	F-value	p-value	df	F-value	p-value	df	F-value	p-value
Within-Subjects Effect									
Conditions	1,15	7.144	0.017*	1,5	7.859	0.038*	1,10	0.816	0.388
Condition × Group		12.126	0.003**						
Electrode	1.840, 27.602	7.761	0.003**	2.006, 10.029	6.033	0.019*	1.507, 15.068	3.606	0.063
Electrode × Group		0.357	0.686						
Condition × Electrode	1.279, 19.185	2.243	0.147	1.123, 5.614	1.247	0.318	1.661, 16.605	0.378	0.653
Condition × Electrode × Group		1.743	0.204						
Between-Subject Effects	1,15	2.818	0.114						
Lateral									
Within-Subjects									
Conditions	1,15	0.021	0.886	1,5	0.012	0.917	1,10	0.551	0.475
Condition × Group		0.167	0.689						
Laterality	1,15	24.037	<0.001**	1,5	12.240	0.017*	1,10	8.769	0.014*
Laterality × Group		3.079	0.100						
Electrode	2.202, 33.023	4.881	0.012	2.126, 10.629	3.012	0.090	1.993, 19.926	2.442	0.113
Electrode × Group		0.179	0.856						
Condition × Laterality	1,15	2.880	0.110	1,5	2.172	0.201	1,10	4.181	0.068
Condition × Laterality × Group		5.378	0.035*						
Condition × Electrode	1.578, 23.670	0.863	0.411	1.448, 7.240	0.709	0.479	1.814, 18.144	0.143	0.849

Condition × Electrode × Group		1.306	0.283						
Laterality × Electrode	3.399, 50.980	2.223	0.089	2.305, 11.523	2.024	0.173	2.544, 25.436	0.666	0.557
Laterality × Electrode × Group		1.643	0.186						
Condition × Laterality × Electrode	1.330, 19.955	0.948	0.369	1.226, 6.130	0.982	0.380	2.307, 23.070	3.446	0.043*
Condition × Laterality × Electrode × Group		2.845	0.098						
Between-Subject Effects	1,15	0.188	0.671						

**p<0.01; *p<0.050

Appendix XXVI (g) The mean amplitude (in μV) and peak latency (in ms) of the six midline electrodes and seven pairs of lateral (left and right) electrodes for Perception and Imagery trial for N400 component in respondent and non-respondent groups

Electrode Site	Respondent		Non-respondent	
	Mean Amplitude		Mean Amplitude	
Central	Perception	Imagery	Perception	Imagery
Fz	**-4.65 (4.17)**	-1.13 (4.97)	**-4.95(4.09)**	**-5.00 (5.20)**
FCz	-4.10 (4.23)	**-1.41(5.09)**	-4.65(4.39)	-4.71(5.52)
Cz	-2.59 (3.63)	-0.48 (4.26)	-3.42 (3.79)	-3.19 (4.80)
CPz	-1.65 (3.74)	2.34 (4.94)	-1.55 (3.42)	-0.91 (3.84)
Pz	-1.98 (2.69)	-1.03 (3.58)	-2.73(3.02)	-2.46 (3.47)
POz	-1.25 (2.43)	-0.67 (3.61)	-2.75 (3.18)	-2.56 (3.50)
Left				
F3	-3.96 (3.81)	-1.14 (6.95)	**-3.97 (4.12)**	**-4.24 (5.12)**
FC3	**-4.00 (3.71)**	**-1.58 (6.49)**	-3.82(4.00)	-3.95 (4.87)
C3	-2.99 (2.90)	-0.36 (5.21)	-3.20 (3.30)	-3.06 (4.11)
CP3	-2.59 (2.72)	0.07 (5.15)	-2.56 (2.70)	-2.38 (3.40)
P3	-.33 (2.45)	0.28 (3.34)	-1.67 (1.96)	-1.43 (2.20)
PO3	-.85 (2.62)	-0.62 (3.82)	-1.72 (1.77)	-1.62 (2.07)
T7	-3.31 (3.46)	-0.93 (7.42)	-3.48 (2.81)	-3.87 (4.22)
Right				
F4	**-6.13 (3.58)**	**-5.77 (4.17)**	**-6.05 (4.52)**	**-5.67 (5.42)**
FC4	-5.96 (3.41)	-5.02 (2.86)	-5.83 (3.90)	-5.46 (5.13)
C4	-3.74 (2.75)	-3.85 (2.70)	-3.79 (3.22)	-3.36 (3.45)
CP4	-3.16 (2.49)	-3.12 (1.90)	-3.33 (3.00)	-2.84 (3.25)
P4	-1.89 (1.57)	-2.59 (3.05)	-2.95 (3.09)	-2.56 (3.27)
PO4	-1.96(1.43)	-3.07 (2.86)	-3.14 (3.07)	-2.80 (3.11)
T8	-4.20 (2.20)	-5.35(2.14)	-4.54 (3.41)	-4.28(3.14)

Key: Standard deviations are in parenthesis; bold figure indicates the site with the peak amplitude(s) or indicates the largest and smallest peak latencies

Appendix XXVI (h) Statistical results of between group and within-group repeated measures ANOVA with 2 (conditions) × 6 (midline sites) and repeated measures ANOVA with 2 (conditions) × 2 (laterality) × 7 (lateral sites) on the mean amplitudes of N400 component of respondent and non-respondent groups

	Chronic vs Pain-free			Respondent			Non-respondent		
Midline	df	F-value	p-value	df	F-value	p-value	df	F-value	p-value
Within-Subjects Effect									
Conditions	1,15	13.490	0.002**	1,5	14.482	0.013*	1,10	0.284	0.606
Condition × Group		9.451	0.008**						
Electrode	1.457, 21.854	9.080	0.003**	1.498, 7.491	7.795	0.019	1.411, 14.109	5.801	0.022*
Electrode × Group		0.161	0.784						
Condition × Electrode	1.620, 24.296	1.922	0.173	1.202, 6.008	1.218	0.326	1.678, 16.781	0.461	0.605
Condition × Electrode × Group		1.731	0.201						
Between-Subject Effects	1,15	0.861	0.368						
Lateral									
Within-Subjects									
Conditions	1,15	1.537	0.234	1,5	1.389	0.292	1,10	0.144	0.713
Condition × Group		0.654	0.431						
Laterality	1,15	10.149	0.006**	1,5	4.196	0.096	1,10	4.610	0.057[m]
Laterality × Group		1.347	0.264						
Electrode	1.664, 24.957	9.124	0.002**	1.877, 9.385	4.234	0.051*	1.559, 15.591	5.770	0.018*
Electrode × Group		0.038	0.941						
Condition × Laterality	1,15	2.615	0.127	1,5	2.238	0.195	1,10	3.216	0.047
Condition × Laterality × Group		5.398	0.035*						
Condition × Electrode	1.311, 19.659	1.198	0.303	1.170, 5.848	0.752	0.402	1.531, 15.306	0.497	0.569

Condition × Electrode × Group		1.354	0.270						
Laterality × Electrode	2.519, 37.779	1.299	0.288	1.592, 7.859	0.583	0.544	2.619, 26.186	1.195	0.328
Laterality × Electrode × Group		0.349	0.755						
Condition × Laterality × Electrode	1.310, 19.652	1.013	0.349	1.183, 5.916	0.759	0.440	2.031, 20.306	1.003	0.385
Condition × Laterality × Electrode × Group		1.690	0.212						
Between-Subject Effects	1,15	0.231	0.637						

**p<0.01; *p<0.050

Appendix XXVI (i) The mean amplitude (in μV) and peak latency (in ms) of the six midline electrodes and seven pairs of lateral (left and right) electrodes for Perception and Imagery trial for P600 component in respondent and non-respondent groups

Electrode Site	Respondent		Non-respondent	
	Mean Amplitude		Mean Amplitude	
Central	Perception	Imagery	Perception	Imagery
Fz	-2.28 (4.71)	1.78 (4.40)	-3.43 (4.05)	-3.26 (4.12)
FCz	-1.63 (4.33)	1.63 (4.64)	-3.10 (4.16)	-2.82 (4.31)
Cz	0.07 (3.07)	2.36 (4.59)	-1.61 (3.47)	-0.91(3.33)
CPz	0.43 (4.14)	**4.63 (3.13)**	**0.18 (2.90)**	**1.30 (2.81)**
Pz	0.48 (1.99)	1.28 (4.61)	-0.90 (2.48)	-.26 (2.47)
POz	**1.01(1.97)**	1.51 (4.50)	-0.60 (2.32)	-.27 (2.64)
Left				
F3	-1.45 (4.33)	1.88 (5.73)	-2.62 (3.79)	-2.98 (4.30)
FC3	-1.45 (4.03)	1.47 (5.85)	-2.26 (3.55)	-2.46 (3.72)
C3	0.04 (2.86)	2.93 (5.06)	-1.90 (2.87)	-1.92 (3.20)
CP3	0.62 (2.93)	**3.09 (5.09)**	-1.29 (2.70)	-1.22 (2.66)
P3	2.19(2.09)	2.75 (3.62)	**-0.34 (2.06)**	**0.26 (1.82)**
PO3	**2.30(2.53)**	2.32 (2.91)	-0.37 (1.89)	0.00 (1.82)
T7	-0.56 (4.46)	1.59 (6.32)	-2.61(2.82)	-3.19(3.50)
Right				
F4	-3.44 (3.92)	-2.83 (3.37)	-5.01 (4.77)	-4.62 (4.76)
FC4	-3.43 (3.33)	-2.19 (3.31)	-4.41 (4.03)	-3.85 (4.17)
C4	-2.28(2.72)	-2.24 (3.98)	-2.71 (3.74)	-1.93 (3.01)
CP4	-1.55 (2.16)	-1.36 (3.47)	-2.19 (3.34)	-1.52 (2.88)
P4	-0.08 (0.70)	**-0.22 (4.00)**	**-1.00 (2.72)**	**-0.53 (2.49)**
PO4	**-0.06 (0.51)**	-0.58 (3.83)	-1.27 (2.69)	-0.82 (2.36)
T8	-2.76 (2.15)	-3.83 (3.43)	-3.94 (4.21)	-3.47 (3.08)

Key: Standard deviations are in parenthesis; bold figure indicates the site with the peak amplitude(s) or indicates the largest and smallest peak latencies

Appendix XXVI (j) Statistical results of between group and within-group repeated measures ANOVA with 2 (conditions) × 6 (midline sites) and repeated measures ANOVA with 2 (conditions) × 2 (laterality) × 7 (lateral sites) on the mean amplitudes of P600 component of respondent and non-respondent groups

	Chronic vs Pain-free			Respondent			Non-respondent		
Midline	df	F-value	p-value	df	F-value	p-value	df	F-value	p-value
Within-Subjects Effect									
Conditions	1,15	17.238	0.001**	1,5	14.807	0.012*	1,10	1.727	0.218
Condition × Group		7.256	0.017*						
Electrode	1.530, 22.951	10.507	0.001**	1.161, 5.806	7.459	0.033*	1.579, 15.790	8.556	0.005**
Electrode × Group		0.786	0.436						
Condition × Electrode	1.450, 21.754	2.806	0.096	1.089, 54.416	1.640	0.256	1.647, 16.471	1.095	0.346
Condition × Electrode × Group		2.476	0.120						
Between-Subject Effects	1,15	2.107	0.167						
Lateral									
Within-Subjects									
Conditions	1,15	1.786	0.201	1,5	1.202	0.323	1,10	0.266	0.617
Condition × Group		0.640	0.436						
Laterality	1,15	23.104	<0.001**	1,5	12.442	0.017*	1,10	5.728	0.038*
Laterality × Group		6.063	0.026*						
Electrode	1.758, 26.364	1.659	<0.001**	1.941, 9.707	4.265	0.048*	1.490, 14.898	9.251	0.004**
Electrode × Group		0.129	0.854						
Condition × Laterality	1,15	1.591	0.226	1,5	1.969	0.219	1,10	2.246	0.165
Condition × Laterality ×		5.002	0.041*						

Group									
Condition × Electrode	1.405, 14.051	1.692	0.211	1.121, 5.604	1.408	0.290	1.684, 16.844	0.833	0.433
Condition × Electrode × Group		2.516	0.118						
Laterality × Electrode	2.710, 21.072	0.834	0.473	2.166, 10.830	0.499	0.635	2.162, 21.622	2.109	0.143
Laterality × Electrode × Group		1.269	0.297						
Condition × Laterality × Electrode	1.712, 25.682	1.019	0.364	1.339, 6.694	1.516	0.273	3.477, 34.767	3.849	0.014**
Condition × Laterality × Electrode × Group		4.537	0.025*						
Between-Subject Effects	1,15	1.781	0.202						

**p<0.01; *p<0.050