Pain & Attention

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PAIN AND ATTENTION

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Chapter 1

General introduction

Imagine the last time you knocked one of your toes against the bed or when you accidentally took a sip from your coffee that was still a little too hot to drink. Although the experience of pain caused by these actions is commonly denoted as unwanted, the ability to sense pain and react to it is a prerequisite for human survival. It helps us humans to avoid the execution of actions that can seriously endanger our life, like picking up a pan from the stove without potholders. The importance of this ability is best visualised by people with congenital insensitivity to pain (or CIP), which is a rare clinical syndrome characterized by an impairment of pain perception. Due to their inability to sense pain and consequently being unable to avoid wear and tear done to their bodies or hyperthermia patients with CIP often do not make it past an age of 3 and the ones that do unfortunately nearly all die before the age of 25 years (Mardy, Miura, Endo, Matsuda, & Indo, 2001; Nagasako, Oaklander, & Dworkin, 2003; Dazinger, Prkachin, & Willer, 2006). Without the ability to sense pain, individuals are not motivated to withdraw themselves from a possible harmful situation, to protect a damaged body part while it heals or to avoid similar experiences in the future. This underlines the importance of being able to sense pain and react to it by attending the affected body part. Pain therefore serves as an important warning signal and is evolutionarily predisposed to interrupt and capture attention, making it a powerful motivator for action and escape behaviours (Eccleston & Crombez, 1999).

Attention is considered to be a complex cognitive function or process and is essential for human behavior and cognitive functioning in general. Attention can be described as the process of selection of information for further processing. This selection can be initiated voluntarily by directing attention to a specific task or a certain location (top-down or endogenous attention) or involuntarily in response to certain external events (bottom-up or exogenous attention). Different definitions have been proposed to describe this important cognitive function that is required in almost all actions we execute. The Cambridge Dictionary of Psychology defines 'Attention' as: "Focusing the apparently limited capacities of consciousness on a particular set of stimuli more of whose features are noted and processed in more depth than is true of nonfocal stimuli" (Matsumoto, 2009). Another dictionary defines it as "the process of selecting one aspect of the complex sensory information from the environment to focus on, while disregarding others for the time being" (Statt, 1998). Interestingly, according to the 19th century psychologist William James attention needs no definition at all: "Everyone knows what attention is. It is the taking possession by the mind, in clear vivid form, of one out of what seem several simultaneously possible objects or trains of thought. Focalization, concentration of consciousness are of its essence. It implies withdrawal from some things in order to deal effectively with others, and is a condition which has a real opposite in the confused, dazed, scatterbrain state." (James, 1890).

In this dissertation I will further focus on the concepts of attention and pain, and their supposed interconnectedness. Up to this date, a large number of studies have been

performed in order to further comprehend the mechanisms of attention or the mechanisms of pain individually. Only a limited number of studies have been performed to examine the apparent interaction between pain and attention. Even less studies examined the link between pain and attention on a neural level, while a systematic examination of the neural processes could provide much more insight on this supposed interconnectedness between the neural processes related to pain and attention. As a result of this omission in the research performed thus far, the main purpose of this dissertation and the performed studies was to gain further insight and understanding on the interconnectedness between attention and pain processing on a neurophysiological level. The electroencephalography technique (see section 1.6.3. for more information on this neural imaging technique) was employed to further examine this interaction between attention and pain processing. First the mechanisms underlying the processing of pain and the possible important role or influence of attention on this processing will be further introduced in this general introduction.

1.1 Pain and nociception: The experience of pain

The International Association for the Study of Pain (IASP) defines pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage”. According to this definition actual or potential tissue damage is the primary cause or at least the trigger of the unpleasant sensory and emotional experience. The effect (the pain experience) of this tissue damage is twofold and consists of two components of which one is an objective component (sensory experience) and the other a more subjective one (emotional experience). The elicited sensory experience is in most cases directly linked to the amount of tissue damage. The detection and transmission of tissue damage along pain specific fibers is called nociception (Turk & Melzack, 2001) and will be further explained in the next paragraph. The emotional component on which the pain experience is based is very subjective and may differ highly from person to person. Namely, an emotional value given to the tissue damage is dependent on many, for the outside, uncontrollable aspects like an individual’s genetic composition, prior learning history, current psychological status, and many sociocultural influences. The large influence of these aspects makes it therefore impossible to deduct the amount of pain someone is experiencing solely on the amount of tissue damage (i.e., sensory information). For example, one person may label a certain amount of pain as unbearable while another might label the same ‘painful event’ as insignificant or in some cases as pleasurable (e.g., sadomasochism). So in order to receive an answer on the amount of pain someone is experiencing the person needs to be conscious, has to attend the pain and must be able to communicate. This highlights a major fundamental problem in research on pain and attention. Namely, it is impossible for a person to rate the intensity of distracted pain as the person is required to attend the to-be-ignored pain

stimulus to form a rating. By using a more objective measure, the electrophysiological responses, it is may be possible to measure the processing of painful stimuli even while they are ignored or unattended.

1.2 Pain and nociception: the mechanisms of pain

The detection, transmission and subsequent conscious perception of sensory information are conducted by the peripheral and the central nervous system. In the two following sections the role of these nervous systems will be further detailed.

1.2.1 Peripheral nervous system

Sensory information, produced by tissue damage or touch, is detected by special receptors located directly under the skin and near the joints and organs. These receptors enable the detection of modalities like touch, pressure, vibration, temperature, and pain. Each receptor is in principle specifically tailored to detect one of the following modalities: mechano, thermo or nociception. In some cases, a single receptor is able to detect multiple modalities (Handwerker, 2008). Mechanoreceptors perceive changes in texture, sustained touch, pressure, rapid vibrations, and tension depth of the skin. Thermoreceptors identify absolute and relative changes in temperature (Mashour & Lydic, 2011). Nociceptors are the sensory receptors that detect the potential or actual damage to tissue leading to the experience of pain. The word nociceptor comes from the Latin word 'noci': to injure or damaging. Nociceptors can detect mechanical (responding to excess pressure or mechanical deformation), thermal (signalling noxious heat and cold), and chemical stimuli (responding to chemical stimulants like capsaicin, the active component of chili peppers that makes them hot).

The basic function of a nociceptor is to detect and to subsequently transmit the information onwards to higher-order neurons via the release of neurotransmitters. This is controlled by the synaptic membrane potential of the nociceptor, which is regulated by propagating action potentials along the axon to the synapse. Without stimulation, nociceptors are silent and produce no action potentials, whereas in response to receptor stimulation this rate is increased to around 10 action potentials per second (Woolf & Ma, 2007).

The sensory region of nociceptors consists of the free-nerve endings of A δ -, A β - and C-fibers. These free-nerve endings are extremely fine and are embedded in the epidermis (see Figure 1.1). Mechanical information is detected and handled by the thickly myelinated A β -fibers, which have a diameter of 5-12 μm and conduct information with a speed of 30-70 m/s. The free-nerve endings of A δ - and C-fibers detect and handle nociceptive information. A δ -fibers are 1-5 μm in diameter and are only sparsely myelinated, which has an impact on the conduction speed (5-30 m/s). The unmyelinated C-fibers are 0.1-1.3 μm in diameter and transmit information even slower at only 0.6-2.0 m/s (Millan,

1999; Manzano, Giuliano, & Nobrega, 2008). The A(δ or β) and C-fibers all have their endings in the spinal cord, which is part of the central nervous system, and which is responsible for further processing of the information.

Figure 1.1. A schematic representation of different stimulation techniques: laser stimulation, intracutaneous electrical stimulation and transcutaneous electrical stimulation. A δ - and C-fiber nociceptors can be found in the epidermis. Non-nociceptive free-nerve endings are located deep in the dermis. Left panel: The laser stimulus activates heat-sensitive nociceptive afferents located in the epidermis selectively. Center panel: Intracutaneous stimulation generates a current, which is spatially restricted to the epidermis. Therefore, it selectively activates the free-nerve endings in the epidermis. Right panel: Transcutaneous electrical stimulation activates deeper non-nociceptive fibers in the dermis as these have a lower electrical activation threshold than the nociceptive fibers. Adapted from Mouraux et al., (2010).

1.2.2 Central nervous system

The central nervous system includes the spinal cord and the brain. The spinal cord, a long tubular bundle of nervous tissue, supports cells that extend down from the brain. The primary function of the spinal cord is to coordinate the transmission of neural signals between the brain and the rest of the body and vice versa. It also contains neural circuits that can independently control numerous reflexes.

The tactile and nociceptive sensory information is transferred via two sensory pathways in the dorsal horn of the spinal cord: the dorsal spinothalamic tract and the ventral spinothalamic tract (Millan, 2002). The dorsal tract handles the transmission of tactile information. The tract enters the spinal cord through the dorsal root ganglion and synapses ipsilaterally in the dorsal column nuclei. The axons of the dorsal column nuclei cross in the brainstem and continue to ascend contralaterally in a pathway called the medial lemniscus. The axons finally synapse in the ventrolateral thalamus. Nociceptive information is transmitted through the ventral tract. The information enters

the spinal cord also through the dorsal root ganglion, however it ascends the spinal cord contralaterally. In the brainstem it joins the dorsal tract at the medial lemniscus and also synapses in the ventrolateral thalamus (Almeida, Roizenblatt, & Tufik, 2004).

Next, after arriving in the brain the nociceptive information is processed in various areas (Bromm & Lorenz, 1998; Peyron, Laurent, & Garcia-Larrea, 2000; Treede, Kenshalo, Gracely, & Jones, 1999). An overview of the cortical and sub-cortical areas involved in pain perception and processing, their-connectivity and ascending pathways is displayed in Figure 1.2. The areas involved in the perception and processing of nociceptive information is very complex (Iannetti & Mouraux, 2010; Willis & Westlund, 1997; Peyron et al., 2000; Apkarian, Bushnell, Treede, & Zubieta, 2005). Furthermore, all areas included in this network also handle information not related to nociceptive stimuli. This means that there is no specific area in the brain that exclusively handles the processing of nociceptive information as well as the generation of the pain experience.

Figure 1.2. Cortical and sub-cortical areas involved in pain perception and processing, their connectivity and ascending pathways. Primary areas involved in pain perception are the primary and secondary somatosensory cortices (SI and SII), anterior cingulate cortex (ACC), insula, thalamus, and prefrontal cortex (PF). The secondary areas indicated: primary and supplementary motor cortices (MI and SMA), posterior parietal cortex (PPC), posterior cingulate cortex (PCC), basal ganglia (BG), hypothalamus (HT), amygdala (Amyg), parabrachial nuclei (PB), and periaqueductal gray (PAG). Adapted from Apkarian, Bushnell, Treede, and Zubieta (2005).

The ventrolateral thalamus projects the incoming information to the primary somatosensory cortex (SI), the secondary somatosensory cortex (SII), the insular cortex

(IC), and the anterior cingulate cortex (ACC). The SI is primarily involved in the discrimination of stimulus location and intensity (Sambo & Forster, 2011; Inui, Wang, Qiu, Nguyen, Ojima, Tamura et al., 2003), and is somatotopically organized, meaning that it is divided in multiple partitions that handle information from specific anatomical body parts. For example, sensory information from the right hand is processed in the contralateral part of the SI next to the part in control for the processing of information from the right arm (see Figure 1.3). The size of the specific parts that maps to certain areas of the body is dependent on the importance of adequate processing of information from the related body part. There is a large area of the SI devoted to processing of information from the inside of the hands, while the area devoted to processing information from the back of the hand is much smaller.

Figure 1.3. Somatotopical organisation of the primary somatosensory cortex (SI).

Similar to SI, SII is somatotopically organized, however the organization is less fine-grained than in SI (Torquati, Pizzella, Penna, Franciotti, Babiloni, Rossini et al., 2002; Ploner, Schmitz, Freund, & Schnitzler, 2000; Ruben, Schwiemann, Deuchert, Meyer, Krause, Curio et al., 2001). Activity in SII, in relation to the processing of nociceptive information, is thought to reflect nociceptive learning and memory (Ploner, Schmitz, Freund, & Schnitzler, 1999). In addition, SI and SII are reciprocally connected (Liang, Mouraux, & Iannetti, 2011; Hannula, Neuvonen, Savolainen, Tukiainen, Salonen, Carlson et al., 2008). Nociceptive information referred to the SI and SII is processed in parallel (Liang et al., 2011). Successively, the thalamus and SII both connect to the IC. The IC is part of a complex set of brain structures, which are suggested to play a primary role in attention, motivation, emotion, learning, and memory. More specifically, the IC in combination with amygdala plays an important role in the affective and cognitive

aspects of the nociceptive information (Starr, Sawaki, Wittenberg, Burdette, Oshiro, Quevedo et al., 2009).

A central hub in the processing of nociceptive information is the ACC, as it receives and processes information from the thalamus, IC, SI and SII. The ACC is suggested to be involved in the emotional and cognitive evaluative aspects of nociception (Rainville, Duncan, Price, Carrier, & Bushnell, 1997; Ohara, Crone, Weiss, Kim, & Lenz, 2008; Yesudas & Lee, 2015). At this point it is relevant to note that the neural function of the ACC is not limited to associating unpleasantness with nociceptive information. Namely, the ACC has been shown to be involved in many more cognitive functions including attention (i.e. Bush, Luu, & Posner, 2000; Botvinick, Cohen, & Carter, 2004; Womelsdorf, Ardid, Everling, & Valiante, 2014), conflict monitoring (Botvinick et al., 2004), error detection (Falkenstein, Hoormann, Christ, & Hohnsbein, 2000; Gehring, Goss, Coles, Meyer, & Donchin 1993), learning and memory (Løvstad, Funderud, Meling, Krämer, Voytek, Due-Tønnessen, et al., (2012). The involvement of the ACC in determining the pain experience in addition to its involvement in many other cognitive functions like attention supports the suggestion that there is a close relation between pain processing and other cognitive processes. However, the exact role of the ACC, due to its concurrent involvement in attention, on the processing of pain is still undetermined, and will therefore be further examined in this dissertation.

The described mechanisms of pain processing in this part have, with hindsight, long been misunderstood. Over the course of centuries many different ideas and theories on the experience of pain and nociceptive processing have been proposed.

1.3 History of pain

The pain experience and its likely causes were for a long time believed to be the work of evil, magic, and demons. Therefore, the only way to get relief from pain was through help of shamans, magicians or priests. At this point, pain was believed to be the result of penalty or punishment, and not the result of tissue damage. The word pain is derived from the Latin word 'poene', which means fine, penalty or punishment.

It was around 400 BC when the ideas on pain and its causes started to change. Around that time the Greek physician Hippocrates said: "Pain is a clue to disease". Hippocrates was one of the first to believe that pain was not the result of superstition or punishment, but the result of a disease. The French philosopher René Descartes was in 1664 the first to propose a 'modern theory' on pain. Descartes thought that although humans have a soul (or a mind), the human body might work as a machine. He proposed that there was a direct connection between the cause of pain and the feeling it produces. Descartes drew up an example of a hot particle erupting from a fire that comes in contact with the skin. The fast moving particle causes a displacement of the skin and triggers a painful feeling in the brain through a direct connection, analogous to ringing the bell in the top of a church

by hanging on to a rope below (see Melzack & Wall, 1965). Nevertheless, the search for these specific pain pathways (the rope) and the pain centre in the brain (the bell) really started in the first half of the 20th century. The result of this search was a concept of pain as a straight-through sensory projection system. This 'specificity theory' assumed that pain was a modality like vision or hearing, with its own peripheral and central nervous system.

Some researchers believed that there was no separate system for perceiving pain, but that the system was shared with the system that conveys tactile information and proposed the 'pattern theory'. According to this pattern theory, which was the proposed alternative to the specificity theory, pain is experienced when a specific pattern of nerve impulse activity is produced in response to intense stimulation. Differences in the patterns of neural activity cause a stimulus to be perceived as low or high intensity (Albe-Fessard & Fessard, 1975).

A similarity between all of these early theories on the development of pain is the absence for psychological or cognitive contributions. Namely, none of these theories contained or incorporated an explicit role for the brain other than being a passive receiver of information from the periphery. In 1965, Melzack and Wall proposed a new theory, inspired by the observation made by dr. Beecher in 1946. As a doctor in the Second World War he observed that people were able to somehow interfere with the direct relationship between their injuries and the experienced pain. Soldiers who were brought in for medical help reported feeling less pain than was to be expected by their injuries. Of the seriously wounded soldiers only 27% requested pain-relieving medication. In contrast, 80% of the civilians who were brought in with similar injuries requested pain-relieving medication. To explain this discrepancy, Beecher suggested that the pain was somehow blocked by emotional factors (Beecher, 1946). Melzack and Wall (1965) tried to incorporate this cognitive factor in a new pain model, the Gate Control Theory, which probably is the most influential and productive model of pain to date. Foremost, it has led to a widespread recognition of the necessity for the inclusion of psychological factors when studying pain.

1.3.1 Gate Control Theory

The Gate Control Theory proposes that the transmission of nerve impulses from the afferent fibers to the first central transmission cells (T-cells) of the spinal cord is modulated by a gating mechanism in the spinal dorsal horn (see Figure 1.4). This gating mechanism is most likely the substantia gelatinosa (SG), which is an area of neurons in the spinal cord that receives peripheral afferent fibers (Wall, 1980). The influence of the SG on T-cells is modulated by the relative amount of activity in A β -, A δ - or C-fibers that result in the SG. First of all, stimulation of all fibers increases the activity in the T-cells (see Figure 1.4). In addition, stimulation of the A β -fibers increases the activity in the SG, whereas stimulation of the A δ -fibers and C-fibers decreases this activity. Normally, the positive

and negative influence of the fibers on the SG counteracts each other. However, A β -fibers tend to adapt by prolonged stimulation, which results in a decreased influence on the SG by these fibers and an increase in the influence of A δ -fibers or C-fibers (pain specific fibers) on the SG. This finally results in decreased influence of the SG on the input of the T-cells and in turn results in an increase in output of T-cells to the action system (opening the gate). However, the adaption of A β -fibers can be countered by applying vibration or scratching, which increases the influence of the SG on T-cells input again (closing the gate). This mechanism explains the pain relieve that is experienced when rubbing your knee when you knocked it.

The cognitive factor that would have an effect on pain processing was incorporated in this model as the 'central control' (see Figure 1.4). No further role or explanation was presented, so the influence of this control was a black box. The main systems involved in this modulation were assumed to be the dorsal column-medial lemniscus system and the dorsolateral path, which carry precise information about the nature and location of a stimulus to and from the periphery to the cortex. Their influence on the pain experience is the result of their higher conduction speed that may set the receptivity of cortical neurons for subsequent afferent stimuli. Another theory is that these systems activate selective brain processes that influence information arriving over slower conducting fibers or slower conducting pathways. In the years following the proposal of the gate control theory it became clear that the theory had a number of shortcomings. One of which was the still ill defined influence of the central control on the pain experience. Years followed until in 1990 the neuromatrix concept was proposed (Melzack, 1990).

Figure 1.4. A schematic representation of the Gate Control Theory as proposed by Melzack and Wall (1965). The substantia gelatinosa (SG) accepts input both from large (A β) and small (A δ and C) fibers. Based on the rate of input, the SG allows the stimulus to be passed on to the transmission cell (T cell) and up to the action system (the brain). Adapted from Melzack and Wall (1965).

1.3.2 Neuromatrix

The Neuromatrix was originally proposed to substitute the failed attempt to identify spatially segregated cortical regions specifically devoted to the perception and processing of pain. The Neuromatrix theory suggests that pain is a multidimensional experience produced by a characteristic “neurosignature”, a pattern of nerve impulses, generated by a widely distributed neural network in the brain (Melzack, 1990). According to this theory, pain is not a direct sensory consequence evoked by damage to tissue, but the result of a specific neural pattern that is generated by the neuromatrix (see Figure 1.5). The output pattern of the neuromatrix is modulated by multiple influences, of which the somatic sensory input is only a part (Melzack, 2001). The cognitive-evaluative and the motivational-affective part of the input are just as important in this theory. These recent theories on pain further emphasize the role of cognitive factors on the formation of a pain experience.

Figure 1.5. Factors that contribute to the patterns of activity generated by the neuromatrix. The neuromatrix comprises cognitive (C), sensory (S) and affective (A) modules. The output patterns for the neuromatrix produce multiple dimensions of pain experience as well as behavioural and homeostatic responses. Adapted from Melzack (2001).

1.4 Modulating pain

As discussed earlier in this introduction, the ability to sense pain is important for survival. However, a prolonged experience of pain is commonly denoted as unpleasant and unwanted. As such, humans will do anything to attenuate the pain they are experiencing. Relief from this unwanted and unpleasant experience of pain can be achieved via a number of methods, of which the use of medication is probably the best-known method.

1.4.1 Medication

Relief from pain can be achieved through the administration of medical drugs. These drugs (commonly known as painkillers) interfere with the messages, either at the site of

the injury, in the spinal cord or in the brain itself. The existing medical drugs used for pain relief can be divided into three broad categories with descending pain killing effects; strong-opioids, weak-opioids, and non-opioids.

Strong-opioids drugs are able to attenuate severe pain. Two familiar examples of strong-opioid drugs are morphine and morphine diacetate. Morphine is an opioid drug derived from the seeds of the opium plant. Morphine diacetate is in turn synthesized out of morphine and is now better known as heroin (a highly addictive street drug). Curiously, Bayer first introduced heroin as a non-addictive cough remedy in 1898 (Meldrum, 2003). Opioid drugs act on the periaqueductal gray (PAG; see Figure 1.2), which is part of the central nervous system. The PAG in turn activates enkephalin-releasing neurons that bind to mu opioid receptors, inhibiting the release of the neurotransmitter substance P, on the incoming A δ and C-fibers. The nociceptive signal is in this case inhibited before it reaches the cortical areas. In addition, opioids produce sedation and decreases emotional upset associated with pain. It also inhibits production of pain inflammation. A major disadvantage of the use of opioids is the development of tolerance, in which repeated use of a constant dose of the opioid drug results in decreased effects. Subsequently, the development of tolerance may lead to potentially drug dependence or in the worst-case addiction. Other side effects are nausea, vomiting and constipation. These opioids are therefore only used to treat severe pain in combination with weak-opioid and non-opioid drugs to minimize the use of these addictive strong-opioid drugs.

Weak-opioids drugs (e.g., codeine, tramadol or hydrocodone) are used to treat moderate pain and are semisynthetic derivatives of morphine. These weak-opioids are naturally occurring opioid receptor agonists and relieve pain in the same way as the strong opioids, however they are much less effective as their stronger relatives.

Humans also have their own anti-pain system, which is the endogenous opioid system. The attenuating effect on pain is achieved by affecting the incoming nociceptive information in the spinal cord dorsal horn. It does so by acting directly on the neurons in the central and peripheral nervous system. This effect is primarily controlled by the PAG (see Figure 1.2; Boivie & Meyerson, 1982; Baskin, Mehler, Hosobuchi, Richardson, Adams, & Flitter, 1986). The PAG causes the interneurons to release endogenous opioid neurotransmitters (e.g., enkephalin or dynorphin). Activation of opiate receptors of the interneurons produces hyperpolarization of these neurons. This hyperpolarization results in the inhibition of firing and the release of nociceptive information signals.

Non-opioid drugs include non-steroidal anti-inflammatory drugs (NSAIDs) or paracetamol. A NSAID provides painkilling, fever-reducing and anti-inflammatory effects for light or moderate pain. Aspirin and ibuprofen are commonly known examples of a NSAID. Paracetamol is slightly different to the other NSAIDs as it has only little anti-inflammatory activity. NSAIDs inhibit the production of prostaglandins, physiologically active lipid compounds, by inhibition of the enzyme cyclooxygenase (COX) at the site of injury. This inhibition decreases the formation of pain mediators in the peripheral

nervous system (Pasternak, 1993). However, other studies have shown that NSAIDs may act on the PAG (Fields, 2004).

In 1986, the World Health Organization (WHO) published a set of guidelines regarding the use of painkillers. Although these guidelines were specifically designed for the treatment of cancer pain there are now also used to treat pain in general. It describes a three-step approach of sequential use of medical drugs corresponding with the pain level as reported by the patient. Non-opioid drugs are placed on the first step of this WHO analgesic ladder followed by the weak-opioids and strong-opioids drug on the next steps. The WHO analgesic ladder was introduced to promote the use of non-opioid drugs for relieve from pain. If non-opioid drugs are insufficient, weak-opioids drugs can be given and the application of strong-opioids is only recommended when the applied drugs are insufficient.

An anaesthetic is another type of drug, not being a painkiller, which is used in certain conditions to induce anaesthesia, which is a reversible loss of sensation and is generally used to facilitate surgery. As such it differs from the aforementioned medical drugs, which relieve pain without eliminating sensations. Anaesthesia causes analgesia (loss of responses to pain), amnesia (loss of memory), immobility (loss of motor reflexes), unconsciousness (loss of consciousness) and skeletal muscle relaxation. Although the exact mechanism of general anaesthesia is still not known, it is suggested that different molecular mechanisms might underlie the different effects of anaesthesia (Antkowiak, 2001). The drug affects the central nervous system at the spinal cord, brainstem, thalamus, and cerebral cortex (Antkowiak, 2001; Barash, Cullen, Stoelting, Cahalan, & Stock, 2012). It is suggested that the effect on the thalamus and the neuronal networks that regulate its activity are most likely responsible for the temporary loss of consciousness (Franks, 2008).

1.4.2 Placebo response

The use of a placebo (in most cases a pill without any working ingredients) is probably one of the most extraordinary methods to modulate pain. The modulation that a placebo causes, a change in a symptom or condition of an individual, is known as the placebo effect or the placebo response. It is falsely believed that the placebo response is the direct result of the pill (without active ingredients) taken. It is the treatment expectations that cause the effect and not the sham drug by itself (Benedetti, Carlino, & Pollo, 2011). As such, the placebo response can be elicited by suggestions, past effects of active treatments, or cues that signal that an active medication has been given (Price, Finniss, & Benedetti, 2008). Past effects of active treatments are probably the most important factor in the placebo response. A placebo given after an actual drug is more effective than when given without the experience of the drug they are intended to substitute (Laska & Sunshine, 1973). Furthermore, the placebo effect has been shown to resemble the concept of behavioural conditioning as it induces a physiological response after a procedure of associative learning (Benedetti, Pollo, Lopiano, Lanotte, Vighetti, & Rainero, 2003).

The attenuation of pain in response to a placebo is the result of the release of endogenous opioids on a neural level (see section 1.4.1). In addition, the placebo also modulates the development of a pain experience, namely the emotional value of the pain. Indeed, the use of a placebo therapy to attenuate the experience of pain has shown to yield excellent results. This placebo effect on the experience of pain underlines the proposition that cognition is an important factor in modulating pain experience.

1.4.3 Cognitive modulation of pain

As stated in the previous paragraphs, cognition seems to play an important role in the processing of pain. Cognition itself is defined as “a general term, which includes all the mental processes by which people become aware of, and gain knowledge about, the world” (Statt, 1998). Defined in such a broad way, cognition seems to include aspects such as culture, religion, personality, fear, memory and importantly attention. Interestingly, all of these aspects have indeed been shown to modulate the experience of pain in some way (e.g., Bantick, Wise, Ploghaus, Clare, Smith, & Tracey, 2002; Rainville et al., 1997; Petrovic, Petersson, Ghatan, Stone-Elander, & Ingvar, 2000; Bushnell, Duncan, Hofbrauer, Ha, Chen, & Carrier, 1999), further motivating the link between cognition and pain.

The cognitive function known as ‘attention’ is required and employed in almost every task executed throughout the day and may therefore be considered as the most important mental process that humans apply. There seems to be a direct relation between attention and pain. Pain attracts attention, which enables a person to gather information about the cause of the pain experience. The link or correlation between pain and attention is best observed when attention is deliberately directed away from noxious stimuli. Namely, distraction away from an upcoming painful stimulus attenuates the experienced pain. For example, a demanding task can be used to consume a major part of an individual’s limited capacity for attention. This will reduce the attentional resources that can be directed to the presented painful stimulus (bottom-up attention; McCaul & Malott, 1984). In contrast, voluntary direction of attention (top-down attention) to upcoming nociceptive stimuli has shown to increase the pain experience. These results seem to suggest that the amount of attention directed towards a painful stimulus has a direct correlation with the experienced amount of pain. However, the question still remains in which way attention affects the processing of nociceptive stimuli or the development of a pain experience.

The underlying mechanisms of attention (in general, so not limited to pain processing) have been the subject of research for many years. On the one hand it is suggested that attention strengthens a relevant signal (current task, goals, conversation etc.), by increasing the allocation of resources. This results in increased performance on a task. On the other hand it is suggested that the cognitive process of attention attenuates noise, being irrelevant stimuli and goals, other conversations, etc., resulting in a similar increase in performance on a task. For example, your attention is currently focused on

this text and this increase in attention helps you comprehend the contents. The question is whether the increased comprehension of this text is the result of increased effort in focussing on this text or whether it is the result of increased effort in ignoring the blinking Outlook envelop on the computer screen in front of you, or the cars passing by outside the office.

The current models on visual attentional control for example suggest that two separate frontoparietal cortical systems are at play in directing different attention operations. The two separate systems are the dorsal and ventral attention system (Corbetta & Shulman, 2011). The dorsal attention system is suggested to be involved in the overt and covert orientation of visual attention. It represents the top-down selection of visual attention and its activity is observed bilaterally over the frontal eye fields and intraparietal sulcus (Corbetta & Shulman, 2002). The ventral attention system is involved in the orientation of visual attention in response to unexpected but behaviourally relevant stimuli (Vossel, Geng, & Fink, 2013). This system represents the bottom-up selection of visual attention. Activity representing attention orientation via the ventral attention system is primarily observed over the right hemisphere and is thought to originate from the temporoparietal junction and the ventral frontal cortex (Fox, Corbetta, Snyder, Vincent, & Raichle, 2006). The interactions between both systems produce normal behaviour. The current models on attention state that top-down (endogenous) or bottom-up (exogenous) attention is not directed to a single sensory modality, but that it may be crossmodal (Driver & Spence, 1998). Crossmodal links have been proposed to integrate various modalities (i.e., audition, vision, touch etc.; see Van der Lubbe & Postma, 2005). While the majority of studies in the past focused on audio versus visual interactions, an increasing number of studies have observed similar interactions between other pairs of sensory modalities. For example, it was tested whether nociceptive stimuli applied to a body limb (orientation via an internal somatotopic reference frame) can orient spatial attention in external space towards visual stimuli delivered close to the limb (external reference frame). Indeed, the location of a nociceptive cue modified the visual processing through a modulation of neural activity in the visual cortex (Favril, Mouraux, Sambo, & Legrain, 2014). This suggests that there exists a common frame of reference able to coordinate the mapping of the space of the body and the mapping of the external space. However, the question remains whether the orientation of spatial attention to nociceptive stimuli presented on the body is directed within an anatomically centered (internal somatotopic) frame of reference or a body-centered (external relative to the body-midline) reference frame. This question will be addressed in a study presented in Chapter 3 of this dissertation.

1.5 Paradigms to examine the role of attention on pain

The current theories explaining the interaction between attention and pain propose that pain is evolutionarily predisposed to interrupt and capture attention (Eccleston &

Crombez, 1999). To fight this bottom-up selection of attention by pain, the individual must intentionally use cognitive resources to redirect attention away from pain (top-down attention; Eccleston, 1995; Legrain, Perchet, & Garcia-Larrea, 2009). The majority of the studies on attention used visual or auditory stimuli to examine the different mechanisms of attention. By measuring the difference in stimulus processing between different conditions in which participants either attended certain stimuli or conditions in which attention was distracted from the same type of stimuli the effect of the attentional modulation on stimulus processing could be defined. Distraction away from stimuli can be achieved by presenting an attention-demanding task concurrent to the presented stimuli. With respect to pain, this form of (sustained) attention away from nociceptive stimuli has shown to indeed affect the processing of the painful stimuli. For example, the presentation of an arithmetic task affected stimulus processing of nociceptive stimuli, showing different results than when attention was directed to the nociceptive stimuli (Yamasaki, Kakigi, Watanabe, & Hoshiyama, 2000). The effect of sustained distraction using attention demanding task on the neural processing of nociceptive stimuli is further examined in Chapter 2 of this dissertation.

An alternative way to examine the underlying mechanism of attention is to intently direct attention towards the upcoming location of a stimulus or to divert attention away from the location. A commonly used task to investigate this effect of attention on stimulus processing is the Posner (pre-)cueing task. The Posner pre-cueing task or Posner paradigm assesses an individual's ability to perform an attentional shift (Posner, Snyder, & Davidson, 1980). In this task a central cue indicates the likely location of an upcoming to-be-detected target. On a large proportion of trials (usually around 75 or 80 percent) the cue will correctly indicate the target location (valid trials), however in the other trials the target will be presented at another location (invalid trials). Results from studies employing the Posner paradigm showed that knowledge of the probable forthcoming location of a visual stimulus or tactile stimulus (e.g., Spence, Pavani, & Driver, 1998) affects the subsequent processing of this stimulus. Participants detected the target faster (and more accurately) on valid trials compared to neutral (where no information was given on the likely location of the target) or invalid trials. These results seem to suggest that attention has a beneficial effect on the processing of stimuli. An important difference between this Posner paradigm and the earlier mentioned attention-distraction paradigm is that attention is to be reoriented constantly on a trial-by-trial basis (transient attention) in the Posner paradigm whereas in the attention-distraction paradigm attention is either constantly directed to the stimuli or distracted away from the stimuli with an attention demanding task (sustained attention or sustained distraction). In the later paradigms the presented painful stimuli are not within the 'attentional set' when attention is completely directed to another task. The attentional set is thought to represent a target-defining feature. For instance, when looking for an object an aspect of the visual environment that matches the attentional set, for example color, is prioritized (e.g., Olivers & Eimer,

2011; Wolfe & Horowitz, 2004). In the Posner paradigm, nociceptive stimuli that are to be distracted are within the same attentional set as the stimuli that are to be responded to. The possible effects of these differences will be further examined and addressed in this dissertation by employing sustained and transient attentional manipulations (e.g., see Chapter 4).

More insight on the opposite effect, that of pain on attention, could further clarify the relation between pain and attention. Other tasks have been proposed to test the limits of attention. In the attentional blink (AB) paradigm a stream of stimuli, generally letters or digits, is presented with a speed of approximately 10 stimuli per second. Generally, participants are able to reproduce almost all of the presented stimuli. In contrast, when only two stimuli in the stream are declared as relevant, a first target (T1) and a second target (T2), participants regularly fail to accurately report T2 when it is presented in a time window up to half a second after T1. This deficit to accurately identify T2 is labelled the 'attentional blink' (Raymond, Shapiro, & Arnell, 1992). The attentional blink indicates that there is a limit in the currently available attentional resources. This limit in attentional resources could be used to examine the link between pain and attention. As stated earlier, pain demands attention (bottom-up attention). This additional demand for attentional resources should in theory affect the attentional blink, which is investigated in a study presented in Chapter 5 of this dissertation.

1.6 Experimentally induced pain

A requirement for any study investigating the effects of attention on pain or vice versa is the presence of a (controlled) pain experience by the participants. This can be achieved by recruiting participants that are already in pain or by inducing pain to participants that are reporting to be free of pain. The first method is rather difficult to employ, as it is hard to obtain a large enough group of participants that report to have the same (subjective) pain experience. Furthermore, a drawback is the fact that the participants are in constant pain, making it difficult to vary the pain sensation or to obtain a baseline session with no pain. The second method involves the presentation of pain in pain-free participants. Beecher (1959) and Gracely (1994) outlined a number of qualities a pain stimulus should have. The stimulus should produce a distinct pain sensation, is easy to apply, has a rapid onset and offset, produces only minimal tissue damage, should have no psychological or physical health risks, and it should be possible to cancel the application of the stimulus at any time. Furthermore, the stimulus should be repeatable with minimal temporal effects, the intensity of the pain stimulus and the magnitude of the pain response should be closely correlated and the pain intensity should be repeatable and readily discriminable throughout the stimulus range (Beecher, 1959; Gracely, 1994). Different methods employing different stimulation techniques have been proposed over the last years that match the above-mentioned qualities.

1.6.1 Nociceptive stimulation methods

The primary methods used to induce experimental pain are mechanical pressure, cold pressor, thermal heat and electrocutaneous stimulation. Mechanical pressure stimulation implies the application of forceful pressure to portions of the body (Handwerker, Anton, & Reeh, 1987; Slugg, Campbell, & Meyer, 2004). The advantages of this stimulation method are the ability to target discrete tissue sites and the controllability of the stimulus intensity and stimulus duration. However, the disadvantage of this method is the moderate reliability and validity, as well as the low inter-individual stimulus control. Finally, it is difficult to control the onset and offset of the mechanical stimuli.

Other stimulation methods use temperature (heat or cold) to induce the painful sensations. The cold pressor stimulation method uses cold water to induce a painful feeling. In this method a participant emerges a limb in a cold-water bath (Mitchell, MacDonald, & Brodie, 2004). Advantages of this method are the high degree of subject control during the procedure, the high level of safety, and the rapid decrease in pain sensation following stimulus termination. Disadvantages of this method are the long inter-trial recovery time (which may take up to 10 minutes) and potential adaption to the numbing effects of cold water. The major disadvantage of this method is that the sensation induced by the cold water may be perceived as discomfort rather than pain.

Another method that involves the application of temperature to induce a painful sensation is thermal pain stimulation. This method involves the application of temperature controlled objects or radiant heat to the skin, which slowly heats up to a certain painful temperature. Advantages of this method are the high degree of stimulus control as well as the absence of mechanoreceptor stimulation. However, the slow increase and decrease in temperature makes this method of stimulation less suitable for time-critical measurement techniques (e.g., reaction times and neural responses). A more time specific method of heat stimulation involves the use of laser stimuli (Plaghki & Mouraux, 2003). Laser stimulation excites the same thermoreceptors, however much faster than with the contact thermode. Although faster, the activation time of a thermoreceptor is still approximately 40 ms (Treede, Lorenz, & Baumgartner, 2003). This delay in activation should be accounted for when analysing neural activity induced by laser stimuli. A major advantage of laser stimulation is that it selectively activates the A δ - and C-fiber nociceptors (see Figure 1.1). However, the time it takes for the thermoreceptors to return to baseline is several seconds, which is the result of slow passive cooling of the skin (Mouraux, Iannetti, Colon, Nozaradan, Legrain, & Plaghki, 2011). Moreover, repeated stimulation on the same area has the major disadvantage of potentially burning of the skin. Variation in stimulus intensity can only be achieved by increase the intensity of the laser stimulus. However, with an increase of stimulus intensity a varying number of thermoreceptors are stimulated, making it difficult to carefully compare stimulus processing between stimuli of multiple intensities as the varying number of stimulated thermoreceptors can lead to different processing of the stimuli in the brain.

Possibly the best stimulation technique is the application of electrical currents to induce pain sensation. The major advantage of an electrical stimulus is that it bypasses the receptor and directly activates the nerves. In addition, electrical stimulation can be applied to the same location on the body without potential burn injuries. Moreover, an electrical stimulus with a very short duration (1 ms) is enough to induce a painful feeling. A drawback of this stimulation method is that stimuli may be perceived as uncomfortable rather than painful. However, this observation is most likely caused by the stimulation technique used. Namely, electrical stimulation can be achieved in different ways. The first and easiest way to induce a noxious stimulus is by transcutaneous stimulation, the method in which the electrical current is presented on the skin. The activated peripheral nerve triggers various sensations as a result of the non-selective activation of the fibers in the epidermis and dermis (see Figure 1.1). Consequently not only pain-specific fibers are activated but also tactile fibers, thereby contaminating the stimulus and the subsequent activation in the brain.

Another, more efficient, technique of electrocutaneous stimulation is intracutaneous stimulation, which involves stimulation of the free-nerve ending of fibers just under the upper skin (see Figure 1.1) and was first proposed by Bromm and Meier (1984). The presented method involved drilling a small hole in the upper skin after which an electrode was placed in the epidermis. A drawback of this method is that this special preparation could only be achieved at the fingertips. To overcome this problem, Inui, Tran, Hoshiyama and Kakigi (2002) introduced a pushpin-like electrode based on the intracutaneous stimulation method proposed by Bromm and Meier (1984). The main advantage of this electrode is that it requires no hole, so it can be used at various skin sites. The designed electrode is a stainless steel concentric bipolar needle electrode consisting of a cathode needle and an anode ring. The anode is an outer ring of 1.2 mm in diameter while the needle, placed in the middle of the anode ring, service as the cathode. The needle protrudes 0.2 mm from the anode ring. The needle tip is inserted adjacent to the nerve ending of the thin myelinated A δ -fibers in the epidermis and superficial part of the dermis, while the outer ring is attached to the skin surface (see Figure 1.1) when gently pressing against the skin. Intracutaneous stimulation is shown to selectively activate the free-nerve ending of A δ -fibers when a low intensity of stimulation is used (Mouraux, Iannetti, & Plaghki, 2010). Both the transcutaneous and intracutaneous stimulation methods are independently employed in the current dissertation. Although the two stimulation techniques are not systematically compared, it was questioned whether it is possible to deduct from the electrophysiological responses whether the employed methods selectively activity pain fibers or also activity tactile fibers. The difference between the two stimulation methods is further discussed in Chapter 3. In addition, it was questioned what the possible implication of the selected site of stimulation is in combination with the employed electroencephalography technique to measure the processing of the pain stimuli.

A common method to modulate the intensity of the stimulus is by increasing the stimulus current. With increasing stimulus currents, the stimulus will be perceived as more intense, but the number of stimulated fibers also increases, similar to the earlier mentioned laser stimulation technique. This change in the number of stimulated fibers between intensities makes it difficult to compare stimulus processing between stimuli of multiple intensities. Furthermore, selective activation of A δ -fibers can only be achieved when using low stimulus intensities (Mouraux et al., 2010). An alternative way to modulate the stimulus intensity is to deliver multiple low intensity stimulus pulses in short succession. For example, a train of five pulses will be perceived as more painful than a train of two pulses of the same stimulus current. The same number of nociceptive fibers will be stimulated with increasing number of pulses. In this case, an increase in brain activity in response to a higher intensity stimulus is related to the intensity of the stimulus and not related to a possible increasing number of stimulated fibers. This makes it possible to compare the responses to different intensities of stimuli. Furthermore, it should be noted that when the pulses are presented with an inter stimulus interval of 5 ms the stimulus is perceived as one continuous stimulus even though it is made up out of several pulses. The stimulus interval of 5 ms between pulses lies outside the refractory period of the receptors (Van der Heide, Buitenweg, Marani & Rutten, 2009; Mouraux, Marot & Legrain, 2014). It was questioned whether this method indeed results in significant differences in pain ratings between different lengths of pulse trains. Furthermore, it may be questioned whether the presentation of large numbers of stimuli results in habituation to the presented stimuli and whether or not this habituation is dependent on the employed attentional manipulations. These questions will be addressed in our studies presented in Chapter 2 and 3 of this dissertation.

1.6.2 Assessment of the pain experience

As mentioned earlier, pain is the product of nociceptive information influenced by an individual's genetic composition, current psychological status, sociocultural influences and prior events. Furthermore, the subjective rating of pain can only be registered when someone is conscious, as it requires input from the person himself or herself. Therefore, making a subjective assessment of pain is very difficult (McCaffrey & Beebe, 1989). Some methods have been proposed over the last years to assess or measure the subjective experience of pain. These methods include questionnaires, colour scales, numerical rating scales, visual analogue scales and verbal graphical rating scales. The three most commonly used pain-rating scales are the Visual Analogue Scale (VAS), Numerical Rating Scale (NRS) and the Verbal Rating Scale (VRS). All three pain-rating scales are based on the same principle and were demonstrated to be valid and reliable (Williamson & Hoggart, 2005). The VAS measure is actually a form of cross-modality matching in which line length is the response continuum. Participants describe their pain level by placing a mark on a 10 cm line with 'no pain' and 'unbearable pain' as endpoints. The NRS is an 11,

21 or 101-point scale (a higher point scale is chosen when higher precision is needed) where the end points are the extremes of no pain and unbearable pain in resemblance to the VAS. With an increasing number of points on the scale, the sensitivity of the pain intensity ratings increases (Williamson & Hoggart, 2005). The VRS contains a list of adjectives (no pain; mild pain; moderate pain; and severe or intense pain) used to indicate increasing pain intensities. It should be noted that the VAS, NRS and VRS are only one-dimensional assessments of pain. This means that no distinction can be made between the objective and subjective aspects of the pain experience. VAS ratings are able to give a general overview of the intensity and unpleasantness of the different nociceptive stimuli. In contrast, it is impossible to assess any differences in nociceptive stimuli processing with the VAS as it only reports the subjective experience. Namely, the processing of the stimuli can be modulated by attention while the experienced pain remains constant.

1.6.3 Assessment of nociceptive processing

The processing of sensory information is an important step with respect to the final production of the experience of pain. As reported, a number of brain areas are involved in the processing of sensory information (see section 1.2.2). An average human brain contains up to 86 billion strongly interconnected neurons (Herculano-Houzel, 2009). Each neuron is an electrically excitable cell that processes and transmits information by electrical and chemical signalling. A number of techniques are available to measure the activity of these neurons.

The most commonly employed techniques to measure the activity are functional magnetic resonance imaging (fMRI), magnetoencephalography (MEG) and electroencephalography (EEG). fMRI is a neuroimaging procedure for measuring brain activity by detecting changes in blood flow (hemodynamic response) related to energy use by brain cells (i.e., blood-oxygen-level dependent (BOLD) contrast). The main advantage of fMRI is the high spatial resolution, however the temporal resolution is low (precision of seconds due to the slow haemoglobin response), so it cannot produce evidence about the timing of cognitive processes (Chen, Davis, Pulvermüller, & Hauk, 2013). In addition, the running costs of fMRI measurements are very high (building, machine, operators etc.).

EEG is a non-invasive method, with electrodes placed on the scalp, to record the electrical activity of the neurons in the brain. EEG measures the voltage fluctuations resulting from activity within the neurons of the brain. The electric potential generated by a single neuron is far too small to be detected by an electrode. Therefore the recorded EEG activity always reflects the summation of the synchronous activity of thousands or millions of neurons that have similar spatial orientation (Speckmann & Elger, 1999). EEG has a high (millisecond) temporal resolution (Sharon, Hämäläinen, Tootell, Halgren, & Belliveau, 2007), but the spatial resolution of EEG is low (2-3cm, see Burle, Spieser, Roger, Casini, Hasbroucq, & Vidala, 2015). However, current analysing techniques and

increasing number of electrodes (128 or 256 electrodes) make it possible to perform source analyses on EEG data ($< 1\text{cm}$, see Im, Gururajan, Zhang, Chen, & He, 2007). Most importantly, EEG is shown to be a very cost-effective, easy-to-use brain imaging method (Michel & Murray, 2012), which makes it the most frequently used method to record brain activity.

MEG maps brain activity by recording magnetic fields produced by the neurons, using very sensitive superconducting magnetometers. MEG provides timing as well as spatial information about brain activity. Magnetic fields are less distorted than electric fields by the skull and scalp (Hämäläinen, Hari, Ilmoniemi, Knuutila, & Lounasmaa, 1993). The average running costs of MEG are lower than that of fMRI. However, large structural requirements (complete magnetic shielding) are also necessary in order to use MEG equipment. Furthermore, only groups of neurons that are orientated tangentially to the scalp surface (positioned in the sulci of the cortex) project measurable portions of their magnetic fields outside of the head. MEG is unable to record the activity in the gyri of the cortex, as these sections are not tangentially to the scalp surface.

In general, thousands of simultaneously processes are ongoing in the brain at any given moment, which means that the brain response to a single stimulus is not visible in the EEG recording in response to that single trial. The signal elicited by the stimulus is overpowered by the noise elicited by all other processes. The signal-to-noise ratio can be enhanced by presenting a stimulus multiple times and subsequently averaging the evoked activity as the stimulus evoked activity has an almost fixed time-delay to a stimulus, while other processes are not fixed to that stimulus. The background noise is then averaged out, as it is random, whereas the stimulus onset locked activity is not. The computed waveform of the brain activity in response to the external stimulus is called an event-related potential (ERP; Coles & Rugg, 1996). An ERP consists of successive positive- and negative- going deflections called components. These components have been related to certain processes in the brain. In relation to painful (electrocutaneous) stimuli the following components can be observed. The N1 component is an early deflection in the ERP in response to the stimulus peaking between 100 ms and 200 ms, being mostly maximal at the electrodes over the somatosensory cortex. The SI or SII contralateral to the stimulated body part is the major source of this component and this component is therefore thought to represent an early stage of somatosensory processing (Desmedt & Robertson, 1977; García-Larrea, Frot, & Valeriani, 2003; Thees, Blankenburg, Taskin, Curio, & Villringer, 2003; Valentini, Hu, Chakrabarti, Hu, Aglioti, & Iannetti, 2012; Van der Lubbe, Buitenweg, Boschker, Gerdes, & Jongsma, 2012). At a later latency, around 300 ms after stimulus presentation, a positive deflection is observed (P3a) that is maximal at the scalp vertex. This component appears to be generated in the ACC (Bromm & Chen, 1995) and is generally thought to reflect an orienting response of attention towards a stimulus (Legrain, Guérit, Bruyer, & Plaghki, 2002, 2003; Van der Lubbe et al., 2012; Polich, 2007). However, until recently it was still a matter of debate

whether the late positive deflection should be understood as a P3a component reflecting an orienting response of attention or as a P2 component reflecting other functions related to the processing of nociceptive stimuli. This debate is further discussed in the study presented in Chapter 2. The effects of attention on stimulus processing can be analyzed by presenting the same stimuli in different attentional conditions. If attention affects the nociceptive stimulus processing this would become visible as differences on the components of the measured ERPs. If attention affects the early N1 component than this would suggest that attention also affects the processing of pain at an early stage (nociceptive processing) and not only through modulation of the ACC, which is also linked to other cognitive processes including attention.

The effect of attentional manipulations on the direction of attention can be observed in the EEG as well. For example, the covert direction of attention either to the left or right is observed to result in differences in hemispheric activation depending on the side to which attention is directed. The orientation of attention to the left side of space causes contralateral activation in the right hemisphere and vice versa. This lateralized activation in response to the directional cues can be evaluated using event related lateralizations (ERLs; Wascher & Wauschkuhn, 1996; Van der Lubbe, Wauschkuhn, Wascher, Niehoff, Kömpf, & Verleger, 2000). An ERL is a difference wave extracted from neural activity using a double subtraction technique. The activity recorded at an electrode ipsilateral to the attended side is subtracted from the activity recorded at the contralateral electrode and subsequently averaged over multiple trials. The same procedure is used on trials in which attention is directed to the opposite side (Van der Lubbe & Utzerath, 2013). The ERL is therefore a stimulus locked recording of the orientation of attention. The computed ERL typically reveals three components that are suggested to represent different stages in attentional orienting. The first stage is the selection and interpretation of the presented cue (see Van Velzen & Eimer, 2003). Activity related to this stage is commonly observed around 200–400 ms after cue onset and has a contralateral negativity with a maximum above occipitoparietal sites and is consequently denoted as the early directing attention negativity (EDAN). The second stage is observed over anterior sites around 400 ms after cue onset. It is named the anterior directing attention negativity (ADAN) and is most likely either the reflection of premotor cortex activity, frontal eye fields activity or possible inhibition of eye movements. The late directing attention positivity (LDAP) is the final component and is suggested to represent spatial selection processing based on a visual-based reference frame of space. It is observed as positive activity above posterior sites around 500–700 ms after cue onset (Hopf & Mangun, 2000; Gherri, Van Velzen, & Eimer, 2007). A close examination of the phase preceding the presentation of a nociceptive stimuli provides more information required to answer our previously stated questions on the employed reference frames to direct spatial attention to a location on the body (e.g., see Chapter 3), in addition to our question related to the possible differences between the employed sustained and transient attentional manipulations (e.g., see Chapter 4).

Recently, an additional analysis technique, the lateralized power spectra (LPS), was proposed to analyse the orientation of attention. This method is suggested to have some advantages over the traditional ERL analyses. Namely, a weakness of the ERL procedure is that possible relevant information can be deliberately cancelled out due to the method used to compute ERLs (stimulus locked analysis). The computation of ERLs requires a sufficient number of trials to cancel out noise. However, the onset of the activity related to the orientation of attention in response to a cue varies over trials and individual participants. Consequently, if the variation in onset of attentional processes is too large the relevant activity is cancelled out. The LPS method enables the analysis of ongoing activity instead of stimulus locked activity. The method is based on the fact that groups of neurons synchronize their firing patterns based on feedback connections between the neurons, which result in oscillatory activity. Oscillations in the alpha frequency band for example have been related to attentional processes. Alpha activity refers to neural oscillations in the frequency range of 8 to 13 Hz. These oscillations are the result of synchronous and coherent electrical activity of neurons and predominantly originate from occipital sites. Klimesch, Sauseng and Hanslmayr (2007) suggested that alpha activity is involved in inhibition of task-irrelevant processes leading to an enhanced signal-to-noise ratio in neural resources allocated to stimuli-relevant processes. Lateralized ipsilateral increases in alpha power suggest that the ipsilateral hemisphere is inhibited and that the processing of stimuli at the contralateral hemisphere is facilitated. A variant of alpha activity (same frequency band) is also found on the somatosensory domain and is known as mu activity. In tactile discrimination tasks mu activity was decreased in the somatosensory cortex contralateral to the attended hand, but increased ipsilaterally (Haegens, Händel, & Jensen, 2011; Anderson & Ding, 2011). The LPS technique indexes the lateralized activity based on wavelet analyses of the raw EEG. In this index the power within a specific frequency band is determined for the hemispheres ipsilateral and contralateral to the direction of a cue. The ipsi-contralateral difference in power for the left and right cue is scaled by the sum of activation in both hemispheres. This calculation is performed for both cue directions after which an average is calculated (Van der Lubbe & Utzerath, 2013).

Oscillations at lower or higher frequencies than the alpha band have also been categorized and have different names and are believed to represent different functions. Oscillations with a range up to 4 Hz are termed delta. Delta oscillations are important for large-scale cortical integration and for attentional and syntactic language processes (for a review, see Sauseng & Klimesch, 2008). Theta activities are neural oscillations in the frequency range of 4 to 8. Theta oscillations seem to be important for a variety of cognitive functions involving (virtual) navigation and memory processes. Beta oscillations, ranging from 13 to 20 Hz, are closely linked to motor behavior and are generally attenuated during active or imagined movements (Pfurtscheller & Lopes Da Silva, 1999; Brinkman, Stolk, Dijkerman, de Lange, & Toni, 2014). Activity in the beta range has also been suggested to play an important role during attention or higher cognitive functions (e.g.,

Sauseng & Klimesch, 2008). Further examination of these oscillations might shed more light on the role of attention on the processing of pain.

1.7 Overview of this dissertation

As presented in this introduction, pain is important with respect to escape related actions and behaviours. In order to achieve these goals, it demands attention and directs attention to the affected location on the body. Although there is an agreement on the mechanisms of nociception, the role of attention on the processing of pain remains unclear. The main aim of this dissertation was to further examine the supposedly strong interconnectedness between pain and attention. More specifically the underlying mechanisms that explain how attention affects pain were examined. This concerns the level at which attention affects nociception, and the varying roles of attention in the case of different attentional manipulations (Chapter 2 to 4). Secondly, the question was raised under what task conditions pain stimuli induce exogenous orienting effects (Chapter 2 to 5). Thirdly, the orientation of attention towards nociceptive stimuli may differ between various attention manipulations. In addition, the orientation of attention may operate within different spatial reference frames, so the question was what reference frame (anatomically centered or an external body-centered) is actually dominant in the case of nociception (Chapter 3).

In addition, the research was focused on the relation between the pain experience and objective measures of nociceptive processing (Chapter 2 to 5). An important question here is whether measuring electrophysiological responses might possibly lead to a more objective estimate of a pain experience.

Subsequently, I will focus on the employed methods to answer the different proposed questions in this dissertation. Related to these employed methods the crucial role of the employed stimulation site was further examined (Chapter 2) as well as the respective roles of tactile and nociceptive fibers in the various experiments (Chapter 2 to 5).

The answers to the aforementioned questions based on the different empirical chapters will be given and discussed in Chapter 6. In addition, practical implications and possible directions for future research are stated in this final chapter.

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Chapter 2

Distraction reduces both early and late electrocutaneous stimulus evoked potentials

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Abstract

Previous electroencephalography studies revealed mixed effects of sustained distraction on early negative and later positive event related potential components evoked by electrocutaneous stimuli. In our study we further examined the influence of sustained distraction to clarify these discrepancies. Electrocutaneous stimuli of three intensities were delivered in pulse trains to the forearm either while participants attended the stimuli or while they performed a mental-arithmetic or a word-association distraction task. The amplitudes of the N1 and the late P2/P3a components were attenuated during both distraction tasks. These results seem to resolve the debate concerning the attentional modulation of the N1 component. Furthermore, we observed that the amplitude of the late P2/P3a component was strongly affected by stimulus change, in line with the opinion that this component is actually a P3a orienting response. Our study additionally revealed that habituation effects were reflected in lower intensity ratings and reduced amplitudes of the N1 and P3a components. The latter effects were independent of the type of task, which suggests that habituation is unaffected by attention.

2.1 Introduction

Research has shown that distraction results in lower pain ratings to acute experimental pain in healthy subjects, with more demanding distraction tasks causing even greater pain attenuation (Veldhuijzen, Kenemans, de Bruin, Olivier, & Volkerts, 2006). A reduction in subjective pain ratings has additionally been observed while carrying out cognitive distraction tasks during administration of cold pressor pain (Frankenstein, Richter, McIntyre, & Rémy, 2001; Hodes, Rowland, Lightfoot, & Cleeland, 1990), painful heat stimuli (García-Larrea, Peyron, Laurent, & Mauguière, 1997; Rémy, Frankenstein, Mincic, Tomanek, & Stroman, 2003), or electrocutaneous stimuli (Yamasaki, Kakigi, Watanabe, & Hoshiyama, 2000). From these observations, the question may arise whether these subjective reports are somehow reflected in physiological measures reflecting the processing of stimuli perceived as painful. This question may be answered by employing neuroimaging methods like electroencephalography (EEG), magnetoencephalography (MEG), and functional magnetic resonance imaging (fMRI).

Studies employing these methods highlighted that cold pressor, heat, and electrocutaneous stimuli elicit responses in the primary and secondary somatosensory cortices (SI and SII), the insula, and the anterior cingulate cortex (ACC; García-Larrea, Frot, & Valeriani, 2003; Treede, Kenshalo, Gracely, & Jones, 1999). In the EEG, these responses are visible as deflections in event-related potentials (ERPs). The N1 component is an early deflection in the ERP in response to electrocutaneous stimulation peaking between 100 ms and 140 ms, being mostly maximal at the C5 or C6 electrode. This component is thought to represent an early stage of somatosensory processing (Desmedt & Robertson, 1977). Several studies employing EEG source analyses suggest that the SI contralateral to the stimulated body part is the major source of this component (García-Larrea et al., 2003; Thees, Blankenburg, Taskin, Curio, & Villringer, 2003; Valentini et al., 2012; Van der Lubbe, Buitenweg, Boschker, Gerdes, & Jongsma, 2012). At a later latency, around 250 ms after stimulus presentation, a positive deflection is observed (P2/P3a) that is maximal at the scalp vertex (Cz electrode). This component appears to be generated in the ACC (Bromm & Chen, 1995) and is generally thought to reflect an orienting response of attention toward the stimuli (Dowman, 2004b; Dowman, Darcey, Barkan, Thadani, & Roberts, 2007; Legrain, Guérit, Bruyer, & Plaghki, 2002, 2003), although it also has been argued to reflect pain-specific activation (Dowman, 2004c). Whether this component should be considered as a pain-specific P2 component or as a P3a orienting response is still a matter of debate (see Legrain, Perchet, & García-Larrea, 2009; Lorenz & García-Larrea, 2003) and will be addressed later on in this section.

Yamasaki et al. (2000) conducted a combined EEG/MEG study to examine the effects of distraction on the processing of painful electrical stimulation. Participants received painful electrocutaneous stimuli of a single intensity at the right index finger while carrying out an attention task and two sustained distraction tasks: a calculation and

a memorization task. During the attention task, participants were required to fixate on a centrally positioned fixation point while attending the electrocutaneous stimuli. During the distraction tasks, participants had to focus on 25 random two-digit numbers, which were arranged in a 5 x 5 grid and were projected on a screen. In the calculation task, the five numbers on each line had to be added up and reported. In the memorization task, all numbers had to be memorized and to be reported at the end of the session. At the end of each session, participants were asked to score the perceived pain intensity of the stimuli presented in the last session on a visual analog scale (VAS). In line with the aforementioned findings, these scores showed decreased pain intensity ratings in both distraction tasks relative to the attention task. The ERP results revealed that the peak-to-peak difference between the N1 and P2 components at the vertex was attenuated due to distraction but no clear attenuation effects were present for the separate N1 or P2 components.

In a quite comparable paradigm, Dowman (2004a) examined the influence of sustained distraction on ERPs. Electrocutaneous stimuli of three intensities were delivered in random order to the sural nerve of the ankle. The intensity of these stimuli was manipulated by increasing the stimulus current. In the attention task, participants were instructed to attend to all electrocutaneous stimuli and rate their perceived intensity on a VAS. In the distraction task participants had to mentally count backwards from a three-digit number by steps of three. The N1 and P2 components were quantified at an electrode situated 2 cm posterior to the vertex (near CPz). In contrast to the aforementioned results by Yamasaki et al. (2000), Dowman (2004a) revealed enlarged amplitudes of the N1 component during the distraction task, whereas in accordance with the findings of Yamasaki et al. (2000), the amplitudes of the P2 component were attenuated due to distraction.

Dowman (2004a) noticed a discrepancy between his results and those of studies employing laser stimuli, which showed attenuation of the N1 component due to sustained distraction (Beydoun, Morrow, Shen, & Casey, 1993; García-Larrea et al., 1997; Siedenberg & Treede, 1996). Dowman (2004a) reasoned that electrocutaneous stimuli might induce more activity by the caudal ACC in comparison with laser stimuli, which could result in different scalp topographies. Regional cerebral blood flow (rCBF) studies have shown that various subregions of the caudal ACC display increased activity with distraction, whereas others show decreased activity (Bantick et al., 2002; Frankenstein et al., 2001). According to Dowman, electrocutaneous stimuli might have activated the subregion that shows a distraction-related increase in activity, whereas laser stimuli might activate the subregion that exhibits a distraction-related decrease. This explanation, however, does not provide an account for the discrepancy with the findings of Yamasaki et al. (2000). The studies of Dowman (2004a) and Yamasaki et al. (2000) are indeed highly comparable, but there appear to be some subtle differences in the procedures employed, which may be responsible for the observed discrepancy. According to our opinion, one

key difference concerns the locations at which the electrocutaneous stimuli were applied. Specifically, the ankle was stimulated in Dowman's study, whereas Yamasaki et al. (2000) stimulated on the fingertip. This difference in stimulation may be responsible for the discrepant findings in these studies. Penfield and Boldrey (1937) reported that stimuli delivered to different body parts are processed in different parts of the somatosensory cortex due to the specific somatotopic organization of this cortex. The representation of the ankle lies medial to the midline of the brain within the longitudinal fissure, whereas the representation of the fingertip is situated at a more lateral inferior location (Kandel, Schwartz, & Jessell, 2000). A likely consequence is that stimulation of the ankle results in a different topography on the scalp because of the vertical orientation (on the sagittal plane) of the area representing the ankle in the longitudinal fissure, thereby possibly accounting for the discrepancies between the studies of Dowman (2004a) and Yamasaki et al. (2000).

As indicated above, another debate in the literature concerns the issue whether the positive deflection in the ERP peaking around 250 ms after stimulation should be understood as a P2 or as a P3a component. These components are believed to represent different processes. For example, Dowman (2004c) argued that the P2, thought to originate from the ACC, indexes a stimulus evaluation process where sensory input is compared to an environmental template maintained by working memory. The P3a component is generally accepted to reflect an orienting response, which is thought to originate from ACC (Polich, 2007). Although these definitions of the P2 and P3a components seem to concern different processes, it should be realized that the presence of an orienting response implicitly assumes a kind of a comparison between an actual state and a previous state. The common source of both components is another indication that these components might reflect the same underlying process. Several studies additionally showed that the P2/P3a component is actually modulated by attentional manipulations (Van der Lubbe et al., 2012; Yamasaki et al., 2000). Furthermore, Legrain et al. (2003) employed a sustained selective attention task and observed that the amplitude of the P2/P3a component was enlarged for rare nociceptive stimuli, which together with the previous finding fits with an attentional interpretation. Although the P3a interpretation is generally favored, the issue whether the positive deflection should be understood as a P2 or P3a component remains undecided (see Legrain et al., 2009). As indicated above, another debate in the literature concerns the issue whether the positive deflection in the ERP peaking around 250 ms after stimulation should be understood as a P2 or as a P3a component. These components are believed to represent different processes. For example, Dowman (2004c) argued that the P2, thought to originate from the ACC, indexes a stimulus evaluation process where sensory input is compared to an environmental template maintained by working memory. The P3a component is generally accepted to reflect an orienting response, which is thought to originate from ACC (Polich, 2007). Although these definitions of the P2 and P3a components seem to concern different processes, it

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The aim of the present study was to clarify the effects of sustained distraction on the processing of electrocutaneous stimuli. A major issue concerned the discrepancy in results of the N1 component between the studies of Dowman (2004a) and Yamasaki et al. (2000). An experiment was carried out resembling the experiment employed by Dowman (2004a). One attention task and a mental-arithmetic task were to be performed by our participants. We included an additional word-association distraction task to check for the generalizability across different distraction tasks. Electrocutaneous stimuli of three intensities were delivered at the median nerve of the left forearm. This location was chosen because forearm stimulation was expected to produce more pronounced lateralized activation in EEG recordings due to the aforementioned somatotopic organization of the somatosensory cortices. This pronounced lateralized activation facilitates a comparison of ERPs for attended and unattended stimuli. An additional benefit is that it is easier to attach stimulation electrodes to the forearm than to the ankle or fingertip. Importantly, in our study the intensity of the stimuli was manipulated by varying the number of pulses instead of increasing stimulus current (see also Van der Heide, Buitenweg, Marani, & Rutten, 2009; Van der Lubbe et al., 2012). The major advantage of the latter method is that the same fibers will be employed for the different intensities as increasing the number of pulses only leads to an increase in the generation of action potentials along these fibers. In contrast, increasing the stimulus current of a single electrical pulse will enlarge the area of activated fibers, which due to the variable local distribution of tactile and nociceptive fibers causes activation in an increased but unknown proportion of involved fibers (Van der Heide et al., 2009). Apart from our attentional effects on the early and late ERP components, we also focused on the effect of changes in stimulus intensities between succeeding trials. A well-known characteristic of the P3a component (see e.g., Polich, 2007) concerns its sequential dependency. Namely, the P3a component attenuates in the case of stimulus repetition as compared to stimulus alternation. As a consequence, focusing on sequential effects of the P2/P3a component might provide extra support for the view that this component should be considered as a P3a component rather than as a pain-specific P2 component. If the positive deflection is a P3a, we would expect

strong sequential dependencies, with increased amplitudes in the case of an intensity change. Finally, we examined whether habituation effects, which are likely present in our perceived pain ratings, are accompanied by changes in our ERP components, and additionally, we checked whether these potential effects are modulated by attention.

2.2 Methods

Participants

Eighteen healthy right-handed students (7 males and 11 females, age: 19-29 years) participated in the experiment, which lasted for approximately 2.5 hr. They received €15 for their participation. Every participant was given a detailed explanation of the procedure and signed a written informed consent before participating. The Medical Ethical Committee of the Roessingh Rehabilitation Center approved the experimental procedures (Project No. 08.04.7.2). Two participants (two males) were excluded after EEG analysis due to too many artifacts (due to excessive eye movements) in their EEG recordings.

Stimuli and Procedure

A custom-built stimulator borrowed from the Electronic Research Group of the Radboud University in Nijmegen was used to deliver the electrocutaneous stimuli. Two stimulation electrodes were taped, 2 cm apart, over the median nerve at the left forearm. Pulse train lengths varied from single, three, to five (2 ms rectangular) pulses, with fixed stimulus current intensity matching individual participants' thresholds. Stimuli represented low, medium, and high intensity stimuli, respectively. The interpulse interval (IPI) between two subsequent pulses in the pulse train was 5 ms. Each pulse was presented well outside the refractory period controlling for possible temporal summation due to the increased number of pulses.

Participants were asked to rate the intensity of the presented electrocutaneous stimuli on different moments during the experiment (see Task section). A paper version of the VAS was used in the pretest and participants were asked to rate the sensation of each stimulus on the 0-10 scale verbally. A digital version of the VAS was used during the experiment. Participants were asked to rate the stimulus intensities on a 0–10 scale using the left and right arrows on a keyboard. Zero on the VAS matched to no feeling at all, whereas 10 matched to extreme painful (on both scales).

In a pretest we assessed the stimulus current intensities matching the participants' individual sensation threshold and pain threshold. These thresholds were identified by increasing the intensity of a five-pulse stimulus with steps of 0.1 mA starting at 0. The sensation threshold was defined as the first intensity that participants were able to detect (mean threshold = 0.4 mA $\pm$ SD = 0.1). With increasing current intensities, the quality of the stimulus changes from a sense of being touched to a more prickling sensation. The

latter sensation corresponds with the pain threshold (mean threshold = $0.9 \text{ mA} \pm \text{SD} = 0.4$). This pretest was subsequently repeated with stimuli consisting of three pulses. This time, only the pain threshold (VAS rating of 5) was determined. The intensity of the stimulus (mean threshold = $1.3 \text{ mA} \pm \text{SD} 0.5$) used during the experiment was set at this individual pain threshold. This initial subjective intensity for a three-pulse stimulus equalled a VAS rating of 5.

Task

Before the start of the experiment, a short explanation of the purpose of the study and the use of the VAS was presented on the participant's screen. Stimuli were delivered to the participants while engaged in three different tasks; an attention task, a mental-arithmetic distraction task, and a word-association distraction task. Three experimental sessions, each consisting of three task blocks, were presented with a 5-min break between each session. The order of the task blocks was counterbalanced across participants in the first session and this sequence was repeated in the other two sessions. During each task block, 15 stimuli for each pulse train length were presented (45 stimuli in total), which were semi-randomly applied. In all tasks, the interstimulus interval between two stimuli varied semi-randomly between 4,500 ms and 6,500 ms in steps of 500 ms.

In both distraction tasks, participants fixated a white fixation cross displayed on the screen during the entire task. In the mental-arithmetic task, participants were instructed to count backwards in steps of 3 from 810, 736, and 983 (in the three subsequent sessions of the task). The final number they arrived at was recorded by an experimenter at the end of each block of trials. A mean of 107 ($\text{SD} = 54$) deduction steps were performed by the participants in the mental-arithmetic tasks. In the word-association task, participants were instructed to generate as many words as possible (a minimum of 30) within a certain word category (animals, singers, and athletes) without speaking aloud. The experimenter checked whether sufficient words were generated at the end of each block. All participants performed adequately on this distraction task in all three sessions.

In the attention task, participants were instructed to rate each individual stimulus. Participants were instructed to look at the fixation cross during the task. At 1,000 ms after stimulus onset, a VAS appeared on the screen for a maximum duration of 3,000 ms and the participants rated each individual stimulus based on the experienced sensation.

At the end of each task block, a VAS was presented, and participants were instructed to mark the globally experienced sensation of the stimuli in the preceding task. These sensation ratings were used to control for possible hypervigilance, which could occur due to repeated stimulation. Participants received the instructions on the general VAS rating before the start of the experimental sessions. The instruction included the notion that the VAS ratings were solely for controlling purposes during the experiment and not for analysis purposes. This was done to ensure that the general VAS ratings would not interfere with the distraction task instructions, where they were instructed to attend

the distraction task. Stimulus intensity rating was followed by a 30-s break. Stimulus presentation, response registration and production of external triggers were controlled by E-Prime Software (version 2.0).

Recording

The EEG was recorded from 61 standard channels (extended 10-20 system), using Ag/AgCl electrodes mounted on an electrocap (EasyCap GmbH, Herrsching-Breitbrunn, Germany). All electrode impedances were reduced until below 10 k Ω . A ground electrode was placed on the forehead. The vertical and horizontal electrooculograms (EOG) were measured with bipolar Ag/AgCl electrodes located on the outer canthi of the eyes and from above and below the left eye. Signals passed through a QuickAmp amplifier (Brain Products GmbH, Munich, Germany) and were recorded online against an average reference at a sample rate of 500 Hz. Online filtering with a 200 Hz low-pass filter and a notch filter of 50 Hz was applied.

Data analysis

Stimulus intensity ratings assessed in the attention tasks with the VAS were analyzed with ANOVAs with stimulus intensity and session as within-subject factors. The differences between single-pulse, three-pulse, and five-pulse stimuli and first, second, and third session were assessed with the appropriate contrast analysis.

EEG was analyzed using Brain Vision Analyzer (version 1.05.005, Brain Products GmbH). A time window around each electrocutaneous stimulus from -100 to 500 ms was selected. The baseline was set from -100 to 0 ms before stimulus onset. For each task and session, ERPs were computed for all electrodes by averaging EEG for trials without artifacts. Maximum/minimum allowed amplitudes were ± 250 , 200, 150, and 100 μ V for prefrontal, frontal, central, and parietal electrodes, respectively. Different criteria were used to avoid exclusion of EEG data because of EOG artifacts, which induce larger amplitudes at frontal than at parietal sites. In addition, ocular correction (Gratton, Coles, & Donchin, 1983) was applied to the ERPs.

Next, appropriate time windows and electrodes for analyses of the N1 and P2/P3a components were selected based on results of earlier studies and inspection of the grand means (see Figure 2.2). We analyzed the following components: N1: 120-140 ms on C6, and P2/P3a: 235-285 ms on Cz. Obtained averages (across trials without eye movements and EEG artifacts) per individual were subjected to repeated-measures ANOVAs ($3 \times 3 \times 3$) for each component individually with the factors task (attention, mental-arithmetic, and word-association), stimulus intensity (single pulse, three pulse, and five pulse), and session (first, second, and third session). Additional contrast analyses were carried out to specify observed significant effects. To show and analyze the sequential dependency of the late positive component, we analyzed the amplitude of the P2/P3a component following intensity changes and repeated stimulus intensity. The P2/P3a component amplitude

elicited by single-pulse, three-pulse, and five-pulse stimuli following single-pulse, three-pulse, or five-pulse trials were compared using repeated-measures ANOVAs with the preceding stimulus intensity as the main factor. The Greenhouse-Geisser ϵ correction was applied to the repeated-measures ANOVAs to correct for violations of the sphericity assumption whenever appropriate.

2.3 Results

Behavioral data

ANOVAs on the intensity ratings during the attention task estimated with the VAS (see Figure 2.1) with the factors stimulus intensity and session revealed a significant main effect of stimulus intensity, $F(2,30) = 77.2$, $p < 0.001$. Participants rated single-pulse stimuli significantly lower than threepulse stimuli, $F(1,15) = 69.9$, $p < 0.001$, while three-pulse stimuli received lower ratings than five-pulse stimuli, $F(1,15) = 54.9$, $p < 0.001$. A decrease in stimulus intensity sensation was observed over time, $F(2,30) = 16.5$, $p < 0.001$. Lower stimulus intensity ratings were observed in the second session as compared to the first session, $F(1,15) = 17.0$, $p = 0.001$. The decrease in intensity ratings between the second and third session approached the level of significance, $F(1,15) = 4.5$, $p = 0.051$.

Figure 2.1. Mean stimulus intensity ratings for single-pulse, three-pulse, and five-pulse stimuli obtained with a VAS in the attention task in the first, second, and third session. Error bars represent standard errors of the mean.

EEG data

Grand-average ERPs for the three tasks, the three stimulus intensities, and the three sessions are presented in Figure 2.2. The electrocutaneous stimuli elicited a negative component (N1) contralateral to the stimulation side with a peak latency between 120

ms and 140 ms and a positive central component (P2/P3a) with a peak latency between 235 ms and 285 ms. Topographical maps as a function of task, stimulus intensity, and session are displayed in Figure 2.3 and Figure 2.4. Inspection of the topographical maps of both the N1 and P2/P3a components shows increased activation with higher stimulus intensities, increased activation in the attention task compared to the two distraction tasks. Finally, a decrease in activation can be observed between the three sessions.

Figure 2.2. The ERPs showing the N1 (C6 electrode) and P2/P3a (Cz electrode) components with the corresponding windows used for analysis. In Panel (A), ERPs are presented as a function of task (attention, mental arithmetic, and word association), in Panel (B) ERPs are presented as a function of the stimulus intensity (single pulse, three pulse, and five pulse), and in Panel (C) ERPs are presented as a function of session (first, second, and third session).

The N1 component. A significant main effect of task was observed, $F(2,28) = 13.7$, $p < 0.001$, suggesting that the amplitude of the N1 component was more negative for the attention task than for the mental-arithmetic or word-association task (see Table 2.1 for an overview of mean amplitudes). Separate contrast analyses (see Table 2.2) confirmed

Figure 2.3. Topographic maps (scaling -4 to $4 \mu\text{V}$) displaying spherical spline interpolated averaged activity in the N1 component time window as a function of task (attention, mental arithmetic, and word association) in Panel (A), intensity (single pulse, three pulse, and five pulse) in Panel (B), and session (first, second, and third session) in Panel (C). Principal component analysis determined with BESA (version 5.2.4.48, MEGIS Software GmbH) on the N1 time window revealed one component explaining 94.1-96.4% of the total variation, suggesting that activity within this time window is mainly due to a single underlying source.

Figure 2.4. Topographic maps (scaling -8 to $8 \mu\text{V}$) displaying spherical spline interpolated averaged activity in the P2/P3a component time window as a function of task (attention, mental arithmetic, and word association) in Panel (A), intensity (single pulse, three pulse, and five pulse) in Panel (B), and session (first, second, and third session) in Panel (C).

task than the average of the two distraction tasks. An increase in stimulus intensity was accompanied with increased N1 component amplitude, $F(2,28) = 10.3$, $\eta^2 = 0.73$, $p = 0.002$. Specifically, a significant increase in N1 component amplitude was observed between single-pulse and three-pulse stimuli, but no difference was observed between the three-pulse and the five-pulse stimuli (see Table 2.2).

Table 2.1. Overview of the mean amplitudes (μV) of the N1 component (C6 electrode; 120-140 ms) and P2/P3a component (Cz electrode; 235-285 ms) as a function of task (attention, mental-arithmetic, and word-association), intensity (single pulse, three pulse and five pulse) and session (session 1, session 2 and session 3).

	N1 component (μV)	P2/P3a component (μV)
Task		
Attention	-3.0	6.1
Mental-arithmetic	-2.3	4.4
Word-association	-2.1	4.2
Intensity		
Single pulse	-1.9	3.4
Three pulse	-2.8	5.2
Five pulse	-2.8	6.3
Session		
Session 1	-3.2	6.0
Session 2	-2.4	4.9
Session 3	-1.9	3.9

The amplitude of the N1 component additionally decreased as time progressed, $F(2,28) = 19.0$, $p < 0.001$. A significant attenuation in the amplitude of the N1 component was observed between the first and second session, but not between the second and third session (see Table 2.2). No interaction effects were found between all task, intensity, and session combinations, $F < 1.9$, $p > 0.11$.

The P2/P3a component. A significant main effect of task was observed, $F(2,28) = 17.6$, $p < 0.001$, indicating that the P2/P3a component was larger in the attention task than in the distraction tasks, whereas no significant difference was observed between the two distraction tasks. The amplitude of the P2/P3a component increased when stimulus intensity increased, $F(2,28) = 56.9$, $p < 0.001$. Significant differences were found (see Table 2.2) between single-pulse and three-pulse stimuli and between three-pulse and five-pulse stimuli.

Amplitude of the P2/P3a component decreased over time, $F(2,28) = 16.1$, $p < 0.001$. The P2/P3a component became smaller from the first to the second session, as well as

from the second to the third session (see Table 2.2). No interaction effects were found between all task, intensity, and session combinations, $F < 1.1$, $p > 0.384$.

Table 2.2. Summary of additional planned contrasts carried out to specify observed significant main effects in ANOVA results.

	N1 component			P2/P3a component		
	df	F	p	df	F	p
Task						
Attention vs mental-arithmetic and word-association	(1,15)	17.6	0.001	(1,15)	24.5	<0.001
Mental-arithmetic vs word-association	(1,15)	2.0	0.183	(1,15)	0.5	0.483
Intensity						
Single pulse vs three pulse	(1,15)	12.7	0.003	(1,15)	54.2	<0.001
Three pulse vs five pulse	(1,15)	0.0	0.849	(1,15)	27.3	<0.001
Session						
Session 1 vs session 2	(1,15)	18.9	0.001	(1,15)	9.1	0.009
Session 2 vs session 3	(1,15)	1.9	0.074	(1,15)	12.9	0.003

Figure 2.5. ERPs of five-pulse stimuli trials showing the P2/P3a (Cz electrode) component with the corresponding window used for analysis presented as a function of the stimulus intensity (single pulse, three pulse, and five pulse) in the preceding trial.

The amplitude of the P2/P3a component elicited by five-pulse stimuli following trials with either single-pulse, three-pulse, or five-pulse stimuli was analyzed to determine whether the P2/P3a component was affected by the stimulus intensity in the preceding

trial. The results show (see Figure 2.5) that this was the case, $F(2,30) = 6.2$, $p = 0.006$. The P2/P3a component amplitude elicited by a five-pulse stimulus was enlarged when the preceding trial contained a single-pulse stimulus, $F(1,15) = 7.7$, $p = 0.014$, or a three-pulse stimulus, $F(1,15) = 7.5$, $p = 0.015$, compared to when a five-pulse stimulus was presented in the preceding trial. This effect was not observed for either single-pulse stimulus trials following three-pulse or five-pulse stimulus trials, $F < 0.4$, $p > 0.547$, as well as three-pulse stimulus trials following single-pulse or five-pulse stimulus trials, $F < 0.07$, $p > 0.792$, compared to when a stimulus of the same intensity was presented in the preceding trial.

2.4 Discussion

Previous EEG studies in which the effects of sustained distraction on cortical processing of electrocutaneous stimuli were explored revealed conflicting results. In a study by Yamasaki et al. (2000) sustained distraction caused a decrease in the peak-to-peak amplitude difference between the early negative N1 component and the late positive P2/P3a component at the vertex. In contrast with these results, Dowman (2004a) showed that distraction resulted in an enlargement of the N1 component whereas the amplitude of the P2/P3a component decreased. This discrepancy in results between Yamasaki et al. (2000) and Dowman (2004a) raised the need for a further examination of the influence of sustained attentional distraction on the processing of electrocutaneous stimuli.

In our study, participants carried out three tasks. In the attention task, they actively attended and rated electrocutaneous stimuli and in the two distraction tasks they either had to perform a mental-arithmetic or a word-association task. Our results clearly demonstrate that sustained distraction has an attenuating effect on the amplitudes of both the N1 and the P2/P3a components relative to the task in which attention was directed at the electrocutaneous stimuli. Thees et al. (2003) suggested in their combined EEG-fMRI study that activity in the primary and secondary somatosensory cortices is reflected by the N1 component (see also Valentini et al., 2012; Van der Lubbe et al., 2012). Our N1 component was maximal over the contralateral somatosensory cortex (electrode C6), which corresponds with an origin in somatosensory cortices. Therefore, it may be argued that the observed attenuation of the N1 component during distraction probably reflects reduced somatosensory processing of the stimulus in these task conditions.

Our results roughly accord with the pattern of results reported by Yamasaki et al. (2000); sustained distraction leads to an attenuation of cortical processing of electrocutaneous stimuli. However, in our study we could demonstrate a reduction of both the N1 and P2/P3a components due to distraction rather than a change in the peak-to-peak (N1-P2/P3a) amplitudes. Obviously, our results are in contrast with the findings reported by Dowman (2004a), who reported an enlarged N1 component due to sustained distraction. This discrepancy in results seems most likely due to the different locations

used for electrocutaneous stimulation, which will result in different scalp topographies (see Treede, Kief, Hölzer, & Bromm, 1988).

The P2/P3a component was most prominent at the vertex (electrode Cz) and results of several other studies suggest that this component is likely to be generated by the ACC (Crottaz-Herbette & Menon, 2006; Thees et al., 2003; Van der Lubbe et al., 2012). Attenuation of the P2/P3a component, as observed during the two distraction tasks, is in line with studies using both electrocutaneous as well as laser-induced nociceptive stimuli. Studies involving electrocutaneous stimuli like Dowman (2004a) and Yamasaki et al. (2000) showed attenuation of the P2/P3a component due to distraction. Alternatively, Beydoun et al. (1993), García-Larrea et al. (1997), and Siedenberg and Treede (1996) used laser stimuli in their studies, but observed an attenuation of the P2/P3a component due to distraction as well, although they denoted this deflection the P350 or P400 (based on the latencies). The difference in latency of the P2/P3a component as observed in studies using laser stimuli and that in our study, including those of Dowman (2004a) and Yamasaki et al. (2000), is most likely caused by the different stimulation methods. Laser stimuli selectively stimulate the slower nociceptive A δ -fibers, whereas the electrocutaneous stimulation method used in our study stimulates both the slower nociceptive Ad fibers as well as the faster A β fibers. Furthermore, while electrocutaneous stimuli directly stimulate the nerve fibers, laser stimulation excites thermoreceptors, which have an activation time of approximately 40 ms (Treede, Lorenz, & Baumgärtner, 2003). A combination of the instant activation of the nerve fibers by electrocutaneous stimulation and the contribution of the faster A β fibers probably causes the P2/P3a deflection to occur earlier.

As noted in the Introduction section, there is a debate whether the positive deflection in the ERPs, observed around 250 ms after electrocutaneous stimulation, should be understood as a P2 or a P3a component (see Dowman, 2004c). Several arguments have been raised to solve this debate. As indicated in our Introduction section, one argument concerns the common sources (i.e., ACC) obtained for these components (Dowman, 2004a; Legrain et al., 2003), which fits with the idea that they reflect a single underlying process (see also Lenz et al., 1998). Another argument concerns the observation that this P2/P3a component is sensitive to attention manipulations (Van der Lubbe et al., 2012; Yamasaki et al., 2000), which additionally fits with an enlargement of this component with rare nociceptive stimuli (Legrain et al., 2003). To these arguments, we can add our observation of a strong sequential dependency of the P2/P3a component. We could demonstrate that the P2/ P3a component in the case of a five-pulse stimulus was enhanced when preceded by a single-pulse or a three-pulse stimulus as compared to a five-pulse stimulus. This observation, an enlargement of the P2/P3a component due to a deviant and salient stimulus, suggests that this component reflects an orienting response (Friedman, Cycowicz, & Gaeta, 2001; Polich, 2003). Therefore, we suggest that this component should be understood as a P3a component. Furthermore, we conclude that the decreased P3a component in our distraction tasks should either be interpreted

as a reduced orienting response toward to-be-ignored electrocutaneous stimuli, or alternatively as an increased orienting response toward attended electrocutaneous stimuli, or as a combination of these effects.

Finally, we examined whether the habituation effect, likely to be reflected in our VAS scores, is accompanied by changes in our ERP components. Indeed, intensity ratings obtained in the blocks with the task instruction to attend the stimuli showed a decrease over time, being lower in the second session as compared to the first session. A further attenuation of the intensity ratings between the second and third session approached the level of significance. This decrease in intensity ratings over time was accompanied by a reduction in the amplitudes of both the N1 and the P3a components. These effects seem unlikely to be due to sensory refractoriness of the nociceptors or nociceptive fibers due to pulse train stimulation, because an IPI of 5 ms between subsequent pulses used to produce differences in the intensity of stimuli is well outside the refractory period of these nociceptors or fibers (Van der Heide et al., 2009). The observed attenuation of ERP components was present in all three tasks and followed nearly the same pattern over time. Although we cannot fully exclude the possibility that the observed attenuation is an effect of general fatigue of the participants, our interpretation on the attenuation observed over time on the intensity ratings and the N1 and P3a components is that they are the effects of habituation. Furthermore, the fact that the decrease over time in our study was independent from the type of task indicates that habituation is independent from attention.

In conclusion, our results extend the earlier observed effects of sustained distraction on electrocutaneous stimulus processing, and additionally, they seem to resolve two issues. First, on the basis of the reduced amplitude of the N1 component in our distraction tasks it may be concluded that cortical activity, probably arising from somatosensory areas, is indeed reduced for unattended as compared to attended stimuli. Secondly, the observed sequential effects of stimulus intensity on the P2/P3a component strongly favor an interpretation of this component as a P3a orienting response.

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Chapter 3

Endogenous spatial attention directed to transcutaneous and intracutaneous nociceptive stimuli on the forearms occurs within an external body-centered reference frame

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Abstract

The present study examined whether the direction of endogenous attention to locations on the body in anticipation of painful stimulation occurs within an internal anatomical reference frame or within an external body-centered reference frame. In two experiments, transcutaneous (Exp. 1) and intracutaneous nociceptive stimuli (Exp. 2) were presented to either the left or right forearm, while participants placed their hands on a table in front of them in a normal position (left hand on the left side and vice versa) or in a crossed-hands position (left hand on the right side and vice versa). A directional cue with a validity of 80% instructed participants to attend to either the left or the right location on each trial. Crossing the hands results in a conflict of reference frames enabling to determine the type of employed reference frame. Analyses of the electroencephalogram (EEG) during the cue-stimulus interval (using event-related lateralizations and lateralized power spectra) showed that crossing the hands did not lead to a reversal of neural activity over central sites (neither the anterior directing attention negativity nor mu power). Furthermore, a late direction attention-related positivity and increased ipsilateral alpha power over occipito-parietal sites were observed in both conditions. Crossing the hands influenced the processing of the subsequently presented nociceptive stimuli as no effect of cue validity was observed on the amplitudes of the P3a component on crossed hands trials. In conclusion, our results suggest that endogenous spatial attention to nociceptive stimuli primarily occurs within an external body-centered reference frame.

3.1 Introduction

Healthy humans hold a number of important automated actions and behavioral mechanisms to ensure our survival. The ability to sense and process pain enables us humans to cope with potential life-threatening events. In such situations, the sensation of pain triggers the orientation of attention (i.e., exogenous orienting; Eccleston & Crombez, 1999), which facilitates the selection of appropriate actions to adequately deal with the potential life-threatening situation. Up to the present day, the mechanisms underlying the orientation of attention to a location on the body in anticipation of or in response to a painful event occurring at that location remain largely unexplained.

The voluntary direction of spatial attention (i.e., endogenous orienting) to a certain location on the body may in principle be carried out within multiple spatial reference frames, which depend on the reference point taken. This can be a somatotopically-centered (anatomically) internally based reference frame or an external body-centered (head-centered, rhomb-centered, eye-fixation-centered, or hand-centered) reference frame. The anatomical reference frame encodes the location of a stimulus according to an internal somatotopic spatial map of the body. In this view the anatomical (location) codes are independent of the position of the body part (e.g., the hand) in external space. Encoding of the location within an external for example body-centered reference frame is guided by the location of that body part relative to a reference point in external space (the body in this case), which often depends on a visual representation of external space and the location of the body part in that space. The question remains according to what reference frame attention is directed to nociceptive stimuli presented on the body. This could either be an anatomically centered (internal) reference frame, a body-centered (external) reference frame or a combination of the two. A combination of both reference frames may be preferred as earlier studies revealed that a stimulus applied to a body limb modifies processing of a visual stimulus delivered closely to that limb (Favril, Mouraux, Sambo, & Legrain, 2014). The latter observation suggests that there exists a so-called crossmodal spatial map, which integrates tactile/nociceptive spatial processing and external visually based processing. Similar crossmodal links have been proposed to integrate various modalities (i.e., visual, auditory, tactile etc.; see Driver & Spence, 1998; Van der Lubbe & Postma, 2005; Van der Lubbe, Van Mierlo & Postma, 2010). A better understanding of the orientation of attention in response to painful stimuli could be a starting point for the development of new and more effective behavioral therapies for patients suffering from (chronic) pain.

In order to experimentally determine and demonstrate by means of which reference frame (internal or external) endogenous attention is guided, the influence of the individual reference frames needs to be separated. This separation can be achieved by instructing participants to covertly direct their attention to a location at which they have placed their hands. Whenever the hands are placed in a normal position (left hand on the left side and

vice versa for the right) the guidance of covert attention via either of the reference frames will correspond. However, when the hands are crossed over the body midline (the left hand is now placed on the right side and vice versa) a conflict between the two reference frames will be induced. Namely, when attention is guided by an internal or somatotopic reference frame, this change in hand position should lead to a change in activity in the hemispheres, as the neural activity representing the direction of attention to the body part is independent of the location of the hand in space. In contrast, when attention is directed via an external reference frame, direction of attention to the left would result in activity in the hemisphere irrespective of the hand position. Thus, if activity stays the same in normal and crossed hands positions this supports the involvement of an external reference, while an inversion of activity in the crossed hands position would support the involvement of an internal reference frame.

A suitable task to study endogenous orienting and examine the involvement of different spatial reference frames is a variant of the Posner paradigm (Posner, Snyder, & Davidson, 1980; Van der Lubbe, Neggers, Verleger, & Kenemans, 2006). In this paradigm, a centrally presented visual cue is often used to indicate the location (left or right) to which attention has to be directed in anticipation of a relevant stimulus, which enables to study the orienting phase. In the case of delivery of nociceptive stimuli to the hands, using a normal posture or a crossed hands posture should allow to determine the involvement of an internal or an external reference frame. When the direction of attention occurs primarily within an internal reference frame a reversal of hemispheric activity should be observed relative to the normal posture condition (e.g., see Gherri & Forster, 2012), as then hand-related (and possibly attention-related) neural activity has an ipsilateral focus (relative to the attended location). Absence of a reversal of activity in the crossed hands would support the involvement of an external reference frame.

The neural activity reflecting the direction of endogenous spatial attention in the orienting phase can be examined by calculating event related lateralizations (ERL) on the basis of direction-dependent event related potentials (ERPs), which can be derived from the electroencephalogram (EEG). The advantage of ERLs is that they display the neural activity that solely depends on the direction of attention. ERLs can be computed by determining contra-ipsilateral difference waves for left and right relevant sides, and subsequently average them (a so-called double subtraction technique applied to symmetrical electrode sites, which was introduced by Wascher & Wauschkuhn, 1996). ERLs recorded in the orienting phase generally display a number of components that are thought to reflect different stages of attentional orienting. An early contralateral negativity over occipito-parietal sites observed around 200-400 ms after cue onset, the early directing attention negativity (EDAN), is thought to reflect the selection and interpretation of the lateral relevant part of the cue (see Van Velzen & Eimer, 2003). The later anterior directing attention negativity (ADAN) is often observed over anterior sites at around 400 ms after cue onset, and is suggested to reflect the control of spatial

attention that affects subsequent posterior processes (e.g., see Grent-‘t-Jong & Woldorff, 2007; for an alternative view, see Van der Lubbe et al., 2006). Finally, a late directing attention positivity (LDAP) is generally observed over posterior sites around 500-700 ms after cue onset, which is thought to reflect spatial selection processing based on a body-centered reference frame (Hopf & Mangun, 2000; Gherri, Van Velzen, & Eimer, 2007).

In a recent study with tactile stimuli (Gherri and Forster, 2012), participants were instructed to covertly attend to the hand placed on the side indicated by the visual cue and to respond whenever a target tactile stimulus was presented at the cued hand. Non-target stimuli (both at the cued and the uncued hand) had to be ignored. On half of the trials the hands were to be placed in a crossed position, which was varied between blocks. ERLs were computed to examine the orientation of attention. Results revealed an LDAP over posterior sites contralateral to the cued side in space, regardless of the hand position. An ADAN was observed over fronto-central electrodes between 300 and 500 ms post-cue. This component was also unaffected by the hand position. Hence, based on these results the covert shifts of attention were exclusively guided by the external reference frame. Later in the cue-stimulus interval (700-900 ms time-interval) an enhanced negativity was observed over central sites, which reversed in polarity on crossed hands trials. Thus, the component was observed contralateral to the relevant hand and not contralateral to the cued side of space, which suggests that it reflects a process that takes place within an internal reference frame.

The ERL method is based on evoked activity (activity is time-locked to a certain event), which implies that individual differences and especially intra-individual (trial-to-trial) differences are cancelled out (e.g., see Van der Lubbe, Bundt, & Abrahamse, 2014). Recently, Van der Lubbe & Utzerath (2013) introduced an alternative method, which enables to assess lateralized activity that is not strictly time-locked to a specific event. In this method, the lateralized power of the EEG is determined for different frequency bands (i.e., lateralized power spectra[LPS]) by means of a double subtraction technique. Activity in the alpha frequency band, ranging from 8-13 Hz, is thought to reflect inhibition of task-irrelevant processes, which may lead to an enhanced signal-to-noise ratio. The often observed ipsilateral increase in alpha power suggests that processing of the irrelevant as compared to the relevant field is suppressed. Alpha activity predominantly originates from occipital sites (Klimesch, Sauseng & Hanslmayr, 2007) and is therefore primarily associated with (visuo-)spatial processes. An increase in posterior ipsilateral alpha activity over occipital sites independent from hand position would suggest that attention is directed along an external body-centered reference frame. Above central sites (overlying primary motor and somatosensory cortex), lateralized activity can be observed within the same frequency band, which is generally denoted as “mu” activity. Mu power also decreases in the case of cortical involvement, with movement or just an intention to move (e.g., Pfurtscheller, Neuper, Andrew & Edlinger, 1997). If attention affects somatotopic activity then a reversal of activity (both ERLs and lateralized mu

power) should be observed in the case of a crossed hands position relative to a position with normal posture (see, Eimer, Forster, & Van Velzen, 2003; Eimer, Van Velzen, & Driver, 2002; Gherri & Forster, 2012). In contrast, if attentional orienting occurs within an external reference frame, then no effect of hand position should be observed on ERL components or lateralized alpha or mu power.

Several earlier studies examined the orienting phase while awaiting tactile stimuli (see, Eimer et al., 2002, 2003; Gherri et al., 2007; Gherri & Forster, 2012), however, it may be questioned whether a similar strategy is employed while anticipating nociceptive stimuli. First, nociceptive stimuli are likely to have a larger impact on attentional orienting due to their crucial role in signaling potential life-threatening damage to the body (Eccleston & Crombez, 1999). As a consequence, attentional orienting towards these stimuli may preferentially occur within a somatotopic internal reference frame, as specific body parts have to be protected. Secondly, the anatomical and neural processing of tactile and nociceptive stimuli is far from identical. Specifically, tactile stimuli are processed along A β -fibers with a speed of 30 to 70 m/s (Millan, 1999; Manzano, Giuliano, & Nobrega, 2008). Nociceptive stimuli, however, are processed along much slower pain specific (nociceptive) fibers (A δ - and C-fibers) with a speed of 2 to 30 m/s (Millan, 1999; Manzano et al., 2008). Nociceptive fibers cross to the contralateral side directly after entering the dorsal root ganglion cells in the spinal cord, while tactile fibers initially stay on the ipsilateral side. Both paths join at the level of the medulla and project to the ventral posterior medial nucleus of the thalamus, thereafter they reach the primary somatosensory cortex (e.g., see Almeida, Roizenblatt, & Tufik, 2004). Given these different processing routes, the different arrival times in primary somatosensory cortex, and the aforementioned functional differences it may very well be the case that attentional modulation differs between tactile and nociceptive stimuli.

In two experiments, we employed a variant of the Posner paradigm to examine the influence of endogenous orienting on the processing of transcutaneous (Experiment 1) and intracutaneous stimuli (Experiment 2). We focused both on the orienting phase and on the subsequent processing of the anticipated stimuli. The employed stimulation technique in these experiments determines which fibers (tactile or pain specific) are activated. Transcutaneous stimulation has been shown to activate tactile fibers (A β -fibers) besides pain specific fibers (A δ -fibers and C-fibers), whereas intracutaneous stimuli selectively activate the A δ -fibers (Mouraux, Iannetti, & Plaghki, 2010; Steenbergen, Buitenweg, Trojan, Van der Heide, Van den Heuvel, Flor et al., 2012). The neural processing in response to the presented transcutaneous (Experiment 1) and intracutaneous stimuli (Experiment 2) are examined by computing ERPs relative to the onset of these stimuli.

Earlier studies employing tactile stimuli and crossed hands manipulations reported that the amplitude of the N1 component was delayed and attenuated under crossed hands conditions, which was suggested to be the result of a mismatch between the anatomical and body-centered reference frames (e.g., see Eimer, Cockburn, Smedley

& Driver, 2001). Other studies employing attention manipulations to examine the effect of attention on stimulus processing revealed a cue validity effect showing larger amplitudes of the N1 components whenever attention was directed at the location of the stimulus, while increased amplitudes of the P3a component were observed in response to unattended stimuli (attentional reorienting response; Blom, Wiering, & Van der Lubbe, 2012). If attention fully operates within an internal reference frame, then no interaction between hand position and cue validity should be observed. In contrast, an absence of a cue validity effect on crossed hands trials would indicate that attention operates within an external reference frame.

Experiment 1

3.2 Methods

Participants

Sixteen healthy right-handed students (9 males and 7 females, age: 20–25 years) participated in this experiment, which lasted approximately three hours. Handedness was assessed with the Annett Handedness Inventory (Annett, 1970). All participants had normal or corrected-to-normal vision and were free of neurological and psychiatric illness by self-report. Every participant received a detailed explanation of the procedure and signed a written informed consent before participating. They received €18 for their participation. The medical ethical committee of the Roessingh Rehabilitation Center approved the experimental procedures used in this experiment (project no. 08.04.7.2).

Stimuli and Procedure

Two DS5 constant current stimulators (Digitimer, Welwyn Garden City, UK) were used to deliver the electrocutaneous stimuli, one stimulator for each stimulation side. Two stimulation electrodes were taped, 2 cm apart, over the median nerves at the left and right forearms.

Stimuli of two intensity levels were used with a fixed intensity of the stimulus current that matched the individual participant's thresholds (see below). The low intensity stimuli consisted of a volley of two 1 ms rectangular pulses and the high intensity stimuli consisted of a volley of five 1 ms rectangular pulses. The interpulse interval between two subsequent pulses in the pulse train was 5 ms, which lies well outside the neuronal refractory period. This was done to control for possible temporal summation of pulses in a longer train (Van der Heide, Buitenweg, Marani, & Rutten, 2009).

A pretest was used to assess the stimulus current intensities matching the participant's individual sensation threshold, pain threshold, and pain tolerance level. Thresholds were identified by increasing the current of a five-pulse stimulus with steps of 0.1 mA starting from zero. Participants were instructed to report the first stimulus that they were able to

detect (sensation threshold, $M = 0.4$ mA; SE 0.08). With increasing current amplitudes, the character of the stimulus changes from a small pinprick sensation to a painful prickling sensation (pain threshold, $M = 1.2$ mA; SE 0.3). Increasing the intensity of the current even further causes the sensation to become unpleasant, corresponding to the pain tolerance level ($M = 2.0$ mA; SE 0.5). The amplitude of the stimulus current used during the experiment was set at this last threshold level.

Four stimulus-rating sessions were presented to the participant during the experiment. The sessions were presented at the end of each block (see below). These sensation ratings were used to control for possible hypervigilance or habituation, which could occur due to repeated stimulation. During each session one two-pulse stimulus and one five-pulse stimulus was presented to the participant at the left and right arm in a random order. The participants were asked to rate each stimulus separately on a digital Visual Analogue Scale (VAS), which was displayed on the screen 1000 ms after stimulus onset. Participants were asked to rate the stimulus intensities on a 0–10 scale using the left and right arrows on a keyboard. Zero on the VAS matched to ‘no feeling at all’ whereas 10 matched to ‘extremely painful’. The rating sessions after the four blocks were followed by a 2-minute break. The hands of the participant were always in the uncrossed position during the stimulus-rating sessions.

Design and Procedure

The experiment started with a short explanation of the purpose of the task, which was presented on the participant’s screen. The task started after the thresholds pretest and a short practice block containing 16 trials. Subsequently, a total of four blocks, each containing 100 trials, were presented to the participant. A white fixation cross was displayed throughout a trial. Twelve hundred ms after trial onset the cross was replaced by a visual directional cue for 400 ms. The directional cue was composed of a red triangle and a blue triangle both pointing outwards (< >). The cue signaled the likely target side of an upcoming stimulus by the direction of the red or the blue triangle. The order of the relevant color (either the first and the second block red and the third and the fourth blocks blue or vice versa) was counterbalanced between participants. The relevant side of the rhomb pointed with equal probability to the left or the right side. On 80% of the trials the direction of the cue was correct (validly cued trials) and on the other 20% of the trials the direction of the cue was incorrect (invalidly cued trials). At 600 ms after offset of the rhomb a low or a high intensity stimulus was delivered at the participant’s left or right forearm. Half of the stimuli were of low intensity (two-pulse stimuli) and the other half of the stimuli were of a high intensity (five-pulse stimuli). Participants were instructed to report if the delivered stimulus had a low or a high intensity by pressing either the left or right foot pedal with respectively their left or right foot. Responses were instructed to be as fast and accurately as possible after stimulus onset. The white fixation cross subsequently turned grey as an indication that a response was made. Only during the first sixteen

practice trials the fixation cross would turn green or red informing the participant about the correctness of their responses. No information on the performance on individual trials was given to participants in the four test blocks. However, a general performance indication was given to the participant after each block of trials. The required response side to low and high intensity stimuli was counterbalanced between participants. A trial ended 4000 ms after the onset of the nociceptive stimulus. In two blocks (the second and fourth) participants were instructed to cross their hands and to lay them on the same location on the table. Participants started with the uncrossed hands condition as a start with crossed hands was thought to be less natural and might lead to performance issues. A possible disadvantage is that this design might induce order effects. The distance between the left and right hands was about 30 cm in both conditions. Stimulus presentation, response registration and production of external triggers were controlled by E-Prime Software (version 2.0).

Recordings

EEG was recorded from 61 standard channels (extended 10-20 system), using passive Ag/AgCl electrodes mounted on an electrocap (EasyCap GmbH, Herrsching-Breitbrunn, Germany). All electrode impedances were reduced until below 10 k Ω . The ground electrode was placed on the forehead. The vertical and horizontal electrooculogram (EOG) were measured with bipolar Ag/AgCl electrodes located on the outer canthi of the eyes and from above and below the left eye. Signals passed through a QuickAmp amplifier (Brain Products GmbH, Munich, Germany) and were recorded online against an average reference at a sample rate of 500 Hz. Online filtering with a 200 Hz low pass filter and a notch filter of 50 Hz was applied throughout the recording session.

Data Analysis

Stimulus intensity ratings assessed with the VAS were analyzed with a repeated measures ANOVA with Stimulus Intensity (two-pulse vs. five-pulse), Stimulation side (left vs. right) and Session (rating-session 1 to 4) as within-subject factors. The differences between two-pulse and five-pulse stimuli, stimulation side and time were further assessed with contrast analyses.

Responses faster than 100ms were considered as anticipations and were omitted from the behavioral analyses. Outliers (RT > 3 SD above the individual mean) were also removed from the behavioral data. On average nine trials (2.2%) per participant were excluded from the analysis.

The recorded EEG was analyzed using Vision Analyzer (Version 2.02.5859; Brain Products GmbH). First, a time window around the onset of each directional cue from -100 to 2000 ms was selected. The mean amplitude from -100 to 0 ms before cue onset served as a baseline. Trials with vertical and horizontal eye movements exceeding $\pm 60\mu\text{V}$ during the orienting phase were excluded. ICA (independent component analysis) ocular

correction was applied to correct the EEG for remaining eye movement-related activity.

Cue-stimulus interval

For analyses of the cue-stimulus interval a time window around the onset of each directional cue from -100 to 1000 ms was selected. Trials with artifacts were excluded with maximum/minimum allowed amplitudes of $\pm 150 \mu\text{V}$. ERLs were computed for trials in which attention was directed to the left location for the uncrossed and crossed hands condition. We analyzed activity in uncrossed and crossed hands trials for the electrode pairs C5/C6, FC5/FC6 and PO7/PO8 in twenty subsequent 40 ms time windows between 200 and 1000 ms after cue onset. The high number of statistical tests could result in a type I error. To reduce this chance, effects were considered significant only when two or more consecutive intervals showed an effect. In that case the critical p-value can be determined as $\sqrt[3]{(0.05/((\text{nr. time windows} - 1) * \text{nr. electrodes}))}$, which here amounts to 0.0296. Therefore, we decided to use a significance criterion of 0.02 (for comparable procedures, see Talsma, Wijers, Klaver, & Mulder, 2001; Van der Lubbe et al., 2014).

The LPS were computed for artifact-free trials in which attention was directed to the left or right for the uncrossed and crossed hands conditions. We first extracted the power of the lower and upper alpha bands by performing a wavelet analysis on the raw EEG. A complex Morlet wavelet (c5) was chosen with Gabor normalization. The following frequency bands were specified: alpha-low ($\alpha 1$: 7.2–10.7Hz), and alpha-up ($\alpha 2$: 9.4–14.0Hz). Individual averages of these estimates were computed for both normal and crossed hands conditions per side of the relevant condition. Next, normalized lateralization indices ($([\text{ipsilateral}-\text{contralateral}]/[\text{ipsilateral}+\text{contralateral}])$) were calculated for the different frequency bands, both for the left and right relevant side. These power indices are computed for symmetrical electrode pairs. Furthermore, an average can be computed across the indices for both relevant sides, thereby constructing the LPS (see Van der Lubbe & Utzerath, 2013). A positive deflection from zero may indicate ipsilateral as compared to contralateral inhibition, while a negative deflection would imply an opposite effect. We restricted the LPS analyses to the same electrode pairs as for the ERL analyses (C5/C6, FC5/FC6 and PO7/PO8), and examined the same twenty subsequent 40 ms time windows between 200 and 1000 ms after cue onset. Now, the critical p-value amounts to 0.0209 as two bands are involved. We decided to apply the same significance criterion (0.02) as for the ERLs.

Transcutaneous stimulus processing

A time window around each electrocutaneous stimulus from -100 to 900 ms was selected to analyze processing of the transcutaneous stimuli. The mean amplitude from -100 to 0 ms before stimulus onset served as a baseline. Individual channels with artifacts were excluded with maximum/minimum allowed amplitudes of $\pm 150 \mu\text{V}$. Next,

appropriate time windows and electrodes for analyses of the N1 and P3a components were selected based on inspection of the grand means and results of earlier studies (e.g., Blom et al., 2012; Van der Lubbe, Buitenweg, Boschker, Gerdes, & Jongsma, 2012). We analyzed the following components: N1: 150–170 ms on C5 and C6, and P3a: five 40 ms-time windows between 200–400 ms on Cz. Obtained averages (across trials without eye movements and EEG artifacts) per individual were subjected to repeated measures ANOVAs with the factors Stimulation Side (left vs. right), Stimulus Intensity (two-pulse vs. five-pulse), Cue Validity (valid vs. invalid), and Hand Position (uncrossed vs. crossed hands). For the analysis of the amplitude of the N1 component the factor Electrode (either ipsilateral vs. contralateral to the stimulated hand) was used instead of the factor Stimulus side. For the analysis of the amplitude of P3a component the factor Time (five 40 ms-time windows) was added. The Greenhouse-Geisser ϵ correction was applied to the repeated measures ANOVA to correct for violations of the sphericity assumption whenever appropriate.

3.3 Results

Behavioral data

The VAS scores (see left panel of Figure 3.1) obtained during the rating session indicated that five-pulse stimuli were judged as more painful than two-pulse stimuli (5.7 vs 2.6; $F(1,15) = 58.2$, $p < 0.001$). No significant change in intensity rating was observed over time ($F(3,45) = 2.5$, $p = 0.069$) and there was no difference in the perceived intensity between stimuli presented to the left or the right forearms ($F(1,15) = 0.3$, $p = 0.625$).

The overall accuracy of responses was 89.1 (SE: 1.6)%. More specifically, response accuracy on uncrossed hands trials was 88.6 (1.5)%, and 89.6 (1.9)% on crossed hands trials, which did not differ from each other, ($F(1,15) = 0.8$, $p = 0.501$). Stimulation side ($F(1,15) = 1.0$, $p = 0.330$), cue validity ($F(1,15) = 0.0$, $p = 0.904$) and intensity ($F(1,15) = 1.8$, $p = 0.202$) all had no effect on response accuracy. In addition, no interactions between any of the factors were observed ($F < 3.5$, $p = 0.079$).

The mean RT for correctly responded stimuli preceded by a valid cue was with 844 ms significantly faster ($F(1,15) = 25.4$, $p < 0.001$) than the mean RT for invalidly cued stimuli (912 ms; see Figure 3.1). Furthermore, the RT to stimuli on uncrossed hands trials was with 896 ms slower than the RT to stimuli on crossed hands trials (860 ms; $F(1,15) = 16.2$, $p = 0.001$). In addition, responses made to stimuli presented to the left forearm (865 ms) were faster than responses to stimuli presented to the right forearm (891 ms; $F(1,15) = 8.4$, $p = 0.011$). The intensity of the stimuli had no effect on RT ($F(1,15) = 2.5$, $p = 0.138$). Finally, an interaction was observed between the factors hand position and cue validity ($F(1,15) = 5.1$, $p = 0.039$). Responses to invalidly cued stimuli were faster when the hands were crossed compared to when the hands were uncrossed, whereas no differences were observed between the hand positions for validly cued stimuli.

No other interactions were observed ($F < 3.0$, $p > 0.105$).

Figure 3.1. In the left panel, we displayed the mean stimulus intensity ratings for two-pulse and five-pulse stimuli delivered at the left and right arm obtained with a visual analog scale (VAS) in the first, second, third, and fourth session of Experiment 1. Mean RTs for validly and invalidly cued two-pulse and five-pulse stimuli in the uncrossed and crossed condition are displayed in the right panel. In both panels, error bars represent standard errors of the mean.

EEG data

Attentional orienting

ERL data. ERL data were statistically evaluated by determining the average value for each individual and relevant condition in 40-ms intervals from 200 to 1000 ms after cue onset for the selected electrode pairs. These analyses revealed three different effects (see Figure 3.2). The observed activity from 320–600 ms on the FC5/FC6 electrode pair probably represents an ADAN. A significant deviation from zero was observed on the C5/C6 electrode pair from 320–440 ms. A pronounced LDAP was observed over occipito-parietal sites (PO7/PO8 electrode pair) from 560–640 ms. No EDAN seems present in the ERLs. Importantly, no differences were observed between the ERLs on uncrossed and crossed hands trials (no two consecutive time windows in which the critical value was of 0.02 was met).

Table 3.1. A summary of the effects observed on the ERLs. Effects are described in terms of contra-ipsilateral differences. EDAN = early directing attention negativity. ADAN = anterior directing attention negativity. LDAP = late directing attention positivity.

Window (ms)	Maxima	Deflection	$F(1,14)$	$p <$	ERL component
320–600	FC5/FC6	Negative	8.7 – 25.4	0.000 – 0.010	ADAN
320–440	C5/C6	Negative	8.1 – 18.0	0.001 – 0.012	
560–640	PO7/PO8	Positive	9.2 – 11.6	0.004 – 0.009	LDAP
720–800	FC5/FC6	Negative	12.3 – 12.6	0.003 – 0.003

Figure 3.2. Grand average event related lateralizations (ERLs) as observed during the cue-stimulus interval at frontal, central and occipito-parietal sites. Significant deviations from zero are indicated in light grey boxes. Topographical maps (right hemisphere, scaling -1 to 1 μV) displaying the ipsi-contralateral difference map of the ERLs in 40 ms windows from 320 to 600 ms and 720 to 800 ms after cue onset on uncrossed hands trials and crossed hands trials.

LPS data. LPS data were statistically evaluated by determining the average value for each individual and relevant condition in 40-ms intervals from 200 to 1000 ms after cue onset for the selected electrode pairs. Increased ipsilateral occipito-parietal power (PO7/PO8 electrode pair) was observed in the lower $\alpha 1$ band (see Figure 3.3) from 440–560 ms ($F(1,14) > 7.6$, $p < 0.015$). A similar focus was observed for the upper $\alpha 2$ band from 480–560 ms ($F(1,14) > 8.8$, $p < 0.010$). An opposite effect was observed over frontal sites (FC5/FC6 electrode pair) on the upper $\alpha 2$ band from 920–1000 ms showing an increase contralateral power (negative deflection; $F(1,14) > 7.6$, $p < 0.015$).

A difference in alpha power was observed in the upper $\alpha 2$ band over frontal sites (FC5/FC6 electrode pair) from 720–800 ms ($t(15) > 7.1$, $p < 0.018$). Increased ipsilateral power was observed on crossed hands trials, while an opposite effect (increase in contralateral power) was observed on uncrossed hands trials (see Figure 3.3).

Table 3.2. A summary of the results for the LPS analysis. Table shows the time windows and electrode pair in which the alpha power in the two alpha bands significantly deviated from zero. All effects are described in terms of ipsi-contralateral differences.

Window (ms)	Maxima	Deflection	$\underline{F}(1,14)$	$p <$
440–560	PO7/PO8	Positive	7.9 – 11.0	0.005 – 0.013
480–560	PO7/PO8	Positive	8.8 – 10.5	0.005 – 0.010
920–1000	FC5/FC6	Negative	7.5 – 8.9	0.009 – 0.015

Figure 3.3. The lateralized power spectra for the lower α_1 band (left) and upper α_2 band (right). Positive values mean increased ipsilateral relative to contralateral power. Light grey boxes indicate significant deviation from zero. Significant differences between the uncrossed and crossed hands power spectra are indicated by dark grey boxes. Topographical maps (right hemisphere reflecting ipsi-contralateral power difference, scaling -0.050 to 0.050 μV) of the lower α_1 band and upper α_2 band in 40 ms windows (top: uncrossed hands trials, lower: crossed hands trials). Positive values in the right hemisphere reflect increased ipsilateral as compared to contralateral power.

ERPs of transcutaneous stimulus processing

Inspection of the topographical maps revealed that the N1 component was maximal at the C5 or C6 electrode contralateral to the stimulated forearm (see Figure 3.4). The P3a component showed (see Figure 3.5) a maximum at the vertex (electrode Cz). Furthermore, the topographical maps of both the N1 and P3a components display increased activity when five-pulse stimuli were presented compared to when two-pulse stimuli were presented. Finally, the P3a component was larger in response to invalidly cued stimuli as compared to validly cued stimuli.

N1 component. The amplitude of the N1 component was significantly larger (Hand Position; $F(1,15) = 13.3$, $p = 0.002$) on uncrossed hands trials than on crossed hands trials (-1.8 versus $-1.3 \mu V$). Furthermore, the amplitude of the N1 component was larger at the contralateral than at the ipsilateral electrode (Electrode; -2.7 versus $-0.5 \mu V$; $F(1,15) = 27.3$, $p = 0.006$). The amplitude of the N1 component was larger in response to five-pulse as compared to two-pulse stimuli (Stimulus Intensity; 1.7 versus $-1.4 \mu V$; $F(1,15) = 5.0$, $p = 0.041$). Cue Validity had no effect on the amplitude of the N1 component ($F(1,15) = 0.5$, $p = 0.496$), but an interaction was observed between Electrode and Cue Validity ($F(1,15) = 5.4$, $p = 0.034$). On the contralateral electrode larger amplitudes of the N1 component were observed in response to invalidly cued stimuli compared to validly cued stimuli (-2.8 versus $-2.5 \mu V$), while on the ipsilateral electrode the amplitude of the N1 component was $-0.7 \mu V$ in response to validly cued stimuli and $-0.3 \mu V$ in response to invalidly cued stimuli.

Figure 3.4. ERPs showing the N1 (C5/C6 electrode contralateral and ipsilateral to the stimulated hand) component in response to the presented stimuli. The grey time window highlights the N1 component and the analysed time windows (150 - 170 ms). Topographical maps of the N1 component (scaling -4 to $4 \mu V$) in response to valid cued high intensity stimuli in the time window 150 - 170 ms after stimulus onset (top: uncrossed hands trials, lower: crossed hands trials, left: stimuli presented to the left forearm, right: stimuli presented to the right forearm).

P3a component. Larger amplitudes of the P3a component were observed on uncrossed hands trials compared to crossed hands trials (Hand Position; 4.9 versus 3.7 μV ; $F(1,15) = 17.9$, $p = 0.001$). Furthermore, the amplitude of the P3a component was significantly lower when a two-pulse stimulus was presented as compared to the presentation of a five-pulse stimulus (Stimulus Intensity; 3.7 versus 4.9 μV ; $F(1,15) = 28.3$, $p < 0.001$). The P3a component was enlarged for invalidly cued as compared to validly cued stimuli (Cue Validity; 4.6 versus 4.0 μV ; $F(1,15) = 5.4$, $p = 0.035$). Furthermore, significant changes in the amplitude of the P3a component were observed between the different time windows (Time; $F(4,60) = 16.8$, $\eta^2 = 0.44$, $p < 0.001$). In contrast, no differences in the amplitude of the P3a component were observed between stimuli presented to the left or right forearm (Stimulation Side; 4.2 versus 4.4 μV ; $F(1,15) = 1.6$, $p = 0.225$).

Figure 3.5. ERPs (left) showing the activity recorded at Cz electrode in response to the presented stimuli. The grey time window highlights the P3a component and the analyzed time windows. Topographical maps of the P3a component (right, scaling -7 to 7 μV) in response to high intensity stimuli presented to the left side in the time window 200 - 400 ms after stimulus onset (top: uncrossed hands trials, lower: crossed hands trials, left: validly cued, right: invalidly cued).

An interaction was observed between the factors Time and Hand Position ($F(4,60) = 5.3$, $\eta^2 = 0.43$, $p = 0.015$). This interaction seems to be the consequence of the later onset of the P3a component on crossed hands trials as compared to uncrossed hands trials. Additionally, an interaction was observed between the factors Stimulus Intensity and Cue Validity ($F(1,15) = 9.0$, $p = 0.009$). A larger difference in amplitude between validly and invalidly cued stimuli was observed on two-pulse stimuli trials as compared to five-pulse stimuli trials on uncrossed hands trials ($F(1,15) = 5.1$, $p = 0.040$; crossed hands ($F(1,15) = 1.1$, $p = 0.315$). An additional interaction was observed between the factors Hand Position and Cue Validity ($F(1,15) = 17.8$, $p = 0.001$). Invalidly cued stimuli resulted in a larger amplitude of the P3a component compared to the validly cue stimuli in uncrossed hands trials (5.4 versus 4.4 μV ; $F(1,15) = 16.5$, $p = 0.001$), while no such effect was observed on the crossed hands trials (3.7 versus 3.8 μV ; $F(1,15) = 0.2$, $p = 0.675$). However, we observed an interaction between Time and Cue Validity on crossed hands trials ($F(4,60) = 5.1$, $p = 0.001$), as well as an interaction between Time, Cue Validity and Intensity ($F(4,60) = 2.6$, $p = 0.045$). A marginally larger amplitude of the P3a component was observed in response to invalid cued stimuli compared to validly

cued stimuli in the fourth (3.3 versus 2.9 μV) and fifth (1.9 versus 1.3 μV) time window.

3.4 Discussion

In this first experiment we investigated whether attentional orienting towards a location on the body in anticipation of or in response to a painful event occurs with an external (body-based) or internal (somatotopic) spatial reference frame. The stimuli were presented to the left or right hand while the hands were placed in a normal position or crossed over the body midline.

ERL and LPS analyses for the orienting phase revealed the presence of the ADAN and LDAP (ERL method) in addition to frontal and occipito-parietal effects on alpha power (LPS method). First of all, the ADAN, observed over central sites, was not reversed on crossed hands trials compared to uncrossed hands trials, which was expected to occur whenever attention was directed via an internal anatomical reference frame. The LDAP component (occipito-parietal sites) representing spatial selection processing based on a body-centered reference frame was observed in both conditions and was not reversed on crossed hands trials. The LPS analyses revealed a pronounced increase in alpha activity over ipsilateral occipito-parietal sites on uncrossed and crossed hands trials. This observation in combination with the results on the LDAP suggests that attention to transcutaneous stimuli is primarily based on an external body-centered reference frame (see also Eimer et al., 2002, 2003).

However, a difference in neural activity between uncrossed and crossed hands trials was revealed by the LPS analyses. An increase in alpha power was observed over frontal sites around 720 ms after cue onset on crossed hands trials, whereas no such effect was observed on uncrossed hands trials. This observation could represent additional effort in directing attention to the cued location within the body-centered reference frame caused by the induced mismatch in reference frames by the crossed hands manipulation. No lateralized activity representing the EDAN was observed in the ERLs, which is normally thought to represent selection and interpretation of the presented cue (Van Velzen & Eimer, 2003). The absence of the EDAN may suggest that the activity associated with the selection and interpretation of the cue was not clearly lateralized in this experiment and therefore not visible in the ERL analyses.

Analyses of the neural activity in response to the presented transcutaneous stimuli revealed the presence of N1 and P3a components, which are commonly observed in response to tactile or nociceptive stimulation. Interestingly, the commonly observed effect of cue validity on the amplitude of the P3a component was absent on crossed hands trials. This seems to suggest that the reorienting effect is by some means cancelled whenever the reference frames are in conflict. In addition, an overall attenuation of the amplitudes of these components was observed on crossed hands trials compared to uncrossed hands trials, which could have been the result of the followed experimental procedure. Namely,

crossed hands trials were always presented in the second and the fourth block of this experiment. This could have led to habituation to the presented stimuli (e.g., see Blom et al., 2012). Slower RTs were observed on crossed hands trials as compared to uncrossed hands trials, which may reflect practice effects. Notwithstanding this confounding, the implications of the earlier attentional effects observed in the cue-stimulus interval still stand, as endogenous attentional orienting in that interval should be independent of any practice effects.

A second experiment was carried out wherein the order of uncrossed and crossed hands blocks was counterbalanced. In addition, an intracutaneous instead of a transcutaneous stimulation technique was employed. The employed stimuli in Experiment 1 likely activated not only pain specific fibers (A δ -fibers and C-fibers), but also tactile fibers (A β -fibers). This could imply that the observed effects might not reflect pain-specific effects. Intracutaneous stimuli are delivered right under the skin (epidermis), which is thought to selectively activate A δ -fibers (Mouraux et al., 2010; Steenbergen et al., 2012). We expected that the N1 component would be delayed in this second experiment because of the reduced processing speed along nociceptive fibers.

Experiment 2

3.5 Methods

Participants

Sixteen healthy students (6 males and 10 females, age: 19–27 years) participated in this experiment, which lasted approximately three hours. Fifteen participants were right-handed, whereas one participant was ambidextrous. The other procedures employed in the second experiment were the same as in Experiment 1 unless otherwise indicated. The Medical Ethical Committee of Medisch Spectrum Twente, Enschede, The Netherlands, approved the employed experimental procedures (NL31474.044.11/P11-11).

Stimuli and Procedure

Nociceptive intracutaneous electrical stimuli were generated by two DS5 constant current stimulators (Digitimer, Welwyn Garden City, UK). Bipolar concentric electrodes (Inui, Tran, Hoshiyama, & Kakigi, 2002) were positioned over the median nerves at the left and the right forearm to deliver the stimuli. These bipolar concentric electrodes use a short needle, which slightly penetrates the epidermis to selectively activate the A δ -fibers (see Mouraux et al., 2010).

A pretest was used to assess the stimulus current intensities matching the participant's individual sensation threshold ($M = 0.3$ mA; SE 0.03), pain threshold ($M = 0.9$ mA; SE 0.3), and pain tolerance level ($M = 1.2$ mA; SE 0.2). The amplitude of the stimulus current used during the experiment was set at this last threshold level.

Five stimulus-rating sessions were used during the experiment. The first session was presented before the first block and the other sessions were presented after each of the four blocks. In Experiment 1, no rating session was used before the start of the experiment. Furthermore, during each session 2 two-pulse stimuli and 2 five-pulse stimuli were presented to the participant at the left and right arm in a random order instead of a single stimulus. The hands of the participant were always in the uncrossed position during the stimulus-rating sessions.

Task

The overall procedure was the same as in Experiment 1. except that an additional VAS stimulus-rating session was presented before the experiment. A total of four blocks, each containing 100 trials, were presented to the participants. Now the order of the uncrossed and crossed hands blocks was counterbalanced across participants. Again, on 80% of the trials the direction of the cue was correct (validly cued trials) and on the other 20% of the trials the direction of the cue was incorrect (invalidly cued trials). Half of the stimuli were of low intensity (two-pulse stimuli) and the other half of the stimuli were of a high intensity (five-pulse stimuli). Responses were instructed to be as fast and accurately as possible after stimulus onset.

Recording and data analysis

EEG recording and analysis was identical to Experiment 1. Eight trials (2%) per participant on average were now excluded from the analyses. Appropriate time windows and electrodes for analyses of the N1 and P3a components were selected based on inspection of the grand means. The N1 component seems present from 165 to 185 ms on C5 and C6, and the P3a component seems present from 200 to 400 ms on Cz. The P3a component was analyzed with five 40 ms-time windows for the aforementioned time interval.

3.6 Results

Behavioral data

Analyses of the VAS scores (see Figure 3.6) revealed that five-pulse stimuli were judged as more painful than two-pulse stimuli (4.6 vs 2.8; $F(1,15) = 43.8$, $p < 0.001$). The scores also revealed that the intensity ratings attenuated over time ($F(4,60) = 13.4$, $\eta^2 = 0.49$, $p < 0.001$). Namely, lower stimulus intensity ratings were observed after the first block (session 2) as compared to the start of the experiment (session 1), $F(1,15) = 10.6$, $p = 0.005$. A significant decrease in stimulus intensity ratings was also observed between the fourth and the fifth rating session ($F(1,15) = 9.8$, $p = 0.007$). No differences were observed in the stimulus intensity ratings between stimuli applied to either the left or to the right forearm ($F(1,15) = 0.4$, $p = 0.518$).

Figure 3.6. In the left panel, the mean stimulus intensity ratings for two-pulse and five-pulse stimuli delivered at the left and right arm obtained with a visual analog scale (VAS) in the first (before start of block 1), second, third, fourth and fifth session of Experiment 2 is displayed. Mean RTs for validly and invalidly cued two-pulse and five-pulse stimuli in the uncrossed and crossed condition are displayed in the right panel. In both panels, error bars represent standard errors of the mean.

The overall accuracy of the responses was 79.4 (SE: 2.1)%, with an accuracy of 79.8 (2.4)% on uncrossed hands trials and of 78.9 (2.1)% on crossed hands trials ($F(1,15) = 0.1$, $p = 0.796$). Side of stimulation ($F(1,15) = 0.2$, $p = 0.659$) and cue validity ($F(1,15) = 0.3$, $p = 0.604$) had no effect on response accuracy. In contrast, the accuracy of the responses to five-pulse stimuli was with 69.3 (3.0)% significantly lower than with the two-pulse stimuli, which was 89.0 (2.1)% ($F(1,15) = 45.0$, $p < 0.001$).

RTs (see Figure 3.6) for validly cued stimuli (939 ms) were faster than for invalidly cued stimuli (1002 ms), ($F(1,15) = 7.7$, $p = 0.014$). No difference in RT was observed between uncrossed (951 ms) and crossed hands trials (989 ms; $F(1,15) = 1.9$, $p = 0.193$). Furthermore, stimulus intensity had no effect on RT ($F(1,15) = 0.5$, $p = 0.488$). Additionally, no effect of side of stimulation was observed ($F(1,15) = 1.9$, $p = 0.192$). Finally, no interaction was observed between the factors hand position and cue validity ($F(1,15) = 0.0$, $p = 0.940$). In addition, no significant interactions were observed between any of the other factors ($F < 4.0$, $p > 0.065$).

EEG data

Attentional orienting

ERL data. ERL analyzes revealed the presence of an EDAN over occipito-parietal sites (PO7/PO8 electrode pair) from 200 to 360 ms (see Table 3.3). An ADAN was observed over frontal sites (FC5/FC6 electrode pair) from 240 to 960 ms (-2.2 – -5.4), which extended over central sites (C5/C6 electrode pair) from 320-520 ms. Visual inspection of the grand average waveforms shows a positivity around 560 to 640 ms over

occipito-parietal sites (PO7/PO8 electrode pair), which represents an LDAP. However, this positive lateralization was only significant for one time window (560 to 600 ms; $F(1,14) = 6.8$, $p = 0.020$) and therefore did not meet the two consecutive time windows criteria. Furthermore, no differences in ERLs were observed between uncrossed hands trials and crossed hands trials (no two consecutive time windows in which the critical value was of 0.02 was met).

Figure 3.7. Grand average event related lateralizations (ERLs) as observed during the cue-stimulus interval at frontal, central and occipito-parietal sites. Significant deviations from zero are indicated in light grey boxes. Topographical maps (right hemisphere, scaling -1 to 1 µV) displaying the ipsi-contralateral difference map of the ERLs in 40 ms.

LPS data. Increased ipsilateral occipito-parietal power (PO7/PO8 electrode pair) was observed for the lower $\alpha 1$ band from 360–600 ms ($F > 6.9$, $p < 0.0019$) and for the upper $\alpha 2$ band from 360–680 ms ($F > 6.5$, $p < 0.022$). An increase in ipsilateral activity over central sites (C5/C6 electrode pair) was observed for the lower $\alpha 1$ band from 240–600 ms ($F > 7.4$, $p < 0.016$) and on the upper $\alpha 2$ band from 360–560 ($F > 8.2$, $p < 0.012$). Finally, increased ipsilateral central power (C5/C6 electrode pair) was observed for the lower $\alpha 1$ band from 920–1000 ms ($F > 7.9$, $p < 0.013$).

A difference in alpha activity between uncrossed and crossed hands trials was observed

from 360–440 ms on the lower $\alpha 1$ band over central sites (C5/C6 electrode pair). A larger ipsilateral increase in alpha activity was observed on crossed hands trials compared to uncrossed hands trials ($F > 9.5$, $p < 0.008$).

Table 3.3. Summary of effects observed on the ERLs. Effects are described in terms of contra-ipsilateral differences, which in the displayed topographies are projected on the left hemisphere. EDAN = early directing attention negativity. ADAN = anterior directing attention negativity. LDAP = late directing attention positivity.

Window (ms)	Maxima	Deflection	$F(1,14)$	$p <$	ERL component
200–360	PO7/PO8	Negative	7.8 – 20.8	0.000 – 0.014	EDAN
240–960	FC5/FC6	Negative	6.6 – 47.7	0.000 – 0.016	ADAN
320–520	C5/C6	Negative	10.6 – 28.8	0.000 – 0.005	

Table 3.4. A summary of the results for the LPS analysis. Table shows the time windows and electrode pair in which the alpha power in the two alpha bands significantly deviated from zero. All effects are described in terms of ipsi-contralateral differences.

Window (ms)	Band	Maxima	Deflection	$F(1,14)$	$p <$
240–600	$\alpha 1$	C5/C6	Increase	7.4 – 29.0	0.000 – 0.016
360–560	$\alpha 2$	C5/C6	Increase	8.2 – 12.9	0.003 – 0.012
360–600	$\alpha 1$	PO7/PO8	Increase	6.9 – 17.6	0.001 – 0.019
360–640	$\alpha 2$	PO7/PO8	Increase	10.3 – 19.4	0.001 – 0.006
920–1000	$\alpha 1$	C5/C6	Increase	7.9 – 8.5	0.011 – 0.013

ERPs of intracutaneous stimulus processing

Inspection of the topographical maps showed that the N1 component was maximal at the C5 or C6 electrode contralateral to the stimulated forearm (see Figure 3.9). On average, the N1 component peaked later in Experiment 2 ($t(30) = -5.2$, $p < 0.001$; $M = 176$ ms, $SE = 1.8$) than in Experiment 1 ($M = 162$ ms, $SE = 2.0$). The P3a component was maximal at the vertex (electrode Cz; see Figure 3.10).

N1 component. The amplitude of the N1 component (see Figure 3.9) was larger for five-pulse than for two-pulse stimuli (Stimulus Intensity: -1.7 versus -1.4 μV ; $F(1,15) = 8.7$, $p = 0.010$) and was also larger at the contralateral than at the ipsilateral electrode (Electrode: -2.5 versus -0.7 μV ; $F(1,15) = 29.6$, $p < 0.001$). No effects were observed for the factor Cue Validity ($F(1,15) = 0.1$, $p = 0.738$) and Hand Position ($F(1,15) = 0.5$, $p = 0.509$). In addition, no interactions were observed ($F(1,15) < 4.3$, $p > 0.055$).

Figure 3.8. The lateralized power spectra for the lower α_1 band (left) and upper α_2 band (right). Positive values mean increased ipsilateral relative to contralateral power. Light grey boxes indicate significant deviation from zero. Dark grey boxes indicate the significant differences between the uncrossed and crossed hands trials power spectra. The topographical maps (right hemisphere reflecting ipsi-contralateral power difference, scaling -0.050 to $0.050 \mu\text{V}$) of the lower α_1 band and upper α_2 band in 40 ms windows (top: uncrossed hands trials, lower: crossed hands trials). Positive values in the right hemisphere reflect increased ipsilateral as compared to contralateral power.

P3a component. The amplitude of the P3a component (see Figure 3.10) was significantly larger for five-pulse stimuli as compared to two-pulse stimuli (Stimulus Intensity; 3.7 versus $2.4 \mu\text{V}$; $F(1,15) = 23.2$, $p < 0.001$). Furthermore, larger amplitudes of the P3a component ($F(1,15) = 7.5$, $p = 0.015$) were observed in response to invalidly cued stimuli as compared to validly cued stimuli (Cue Validity; 3.4 versus $2.7 \mu\text{V}$). No difference was observed for the P3a component amplitude between the uncrossed hands ($3.1 \mu\text{V}$) and crossed hands ($3.0 \mu\text{V}$) trials (Hand Position; $F(1,15) = 0.3$, $p = 0.585$). Furthermore, no differences were observed between the two sides of stimulation (Stimulation Side; 3.1 versus $2.9 \mu\text{V}$; $F(1,15) = 1.9$, $p = 0.184$). The amplitude of the P3a component changed between the subsequent time windows from $2.9 \mu\text{V}$ in the first time window (200 to 240 ms), 3.6 in the third time window (280 to 320 ms), to $2.4 \mu\text{V}$ in the time window from 360 to 400 ms (Time; $F(4,60) = 3.4$, $\xi = 0.59$, $p = 0.037$). An

interaction was observed between the factors Time and Cue Validity ($F(4,60) = 4.3$, $\epsilon = 0.42$, $p = 0.029$), showing a decrease in amplitude of the P3a component in response to validly cued stimuli in time window from 320 to 360 ms and the final time window from 360 to 400 ms. Furthermore, an interaction effect between Time and Hand Position was observed ($F(4,60) = 2.9$, $\epsilon = 0.72$, $p = 0.048$). Separate analyses of the uncrossed and crossed hands trials revealed that an effect of time was only observed in the uncrossed hands trials ($F(4,60) = 4.7$, $\epsilon = 0.57$, $p = 0.013$). The amplitude of the P3a component changed between the subsequent time windows from $3.0 \mu\text{V}$ in the first time window from 200 to 40 ms, to $3.8 \mu\text{V}$ in the third time window from 280 to 320 ms, to $2.13 \mu\text{V}$ in the last time window from 360 to 400 ms. No effect of Time was observed in the crossed hands trials ($F(4,60) = 1.9$, $\epsilon = 0.59$, $p = 0.151$).

Figure 3.9. Grand average ERPs (left) showing the N1 component (contralateral and ipsilateral) in response to the presented intracutaneous stimuli. The grey time window highlights the N1 component and the analyzed time window. Topographical maps of the N1 component (right, scaling -4 to $4 \mu\text{V}$) in response to valid cued high intensity stimuli in the time window 165 - 185 ms after stimulus onset (top: uncrossed hands trials, lower: crossed hands trials, left: stimuli presented to the left forearm, right: stimuli presented to the right forearm).

The separate analyses also revealed a difference in effects on the factor Cue Validity between conditions. Namely, a larger amplitude of the P3a component was observed in response to invalidly cued stimuli compared to validly cued stimuli on uncrossed hands trials (3.6 versus $2.6 \mu\text{V}$; $F(1,15) = 8.8$, $p = 0.009$), while no validity effect was observed on the crossed hands trials (2.7 versus $3.2 \mu\text{V}$; $F(1,15) = 2.8$, $p = 0.112$).

3.7 Discussion

In this experiment intracutaneous stimulation was employed, which selectively activates pain specific fibers (the slower conducting A δ -fibers and C-fibers). It was

Figure 3.10. ERPs (left) showing the activity recorded at Cz electrode in response to the presented stimuli. The grey time window highlights the P3a component and the analyzed time windows. Topographical maps of the P3a component (right, scaling -7 to 7 μ V) in response to high intensity stimuli presented to the left side in the time window 200 – 400 ms after stimulus onset (top: uncrossed hands trials, lower: crossed hands trials, left: validly cued, right: invalidly cued).

questioned whether this change in type of stimulation would result in other observations. Detailed analyses of ERPs from Experiment 1 and 2 revealed an earlier peak latency of the N1 component in Experiment 1 as compared to Experiment 2 (162 versus 176 ms after stimulus onset). This observation suggests that the transcutaneous stimulation technique activates the faster conducting tactile A β -fibers were activated in addition to the slower conducting pain specific A δ -fibers and C-fibers, while in line with the hypotheses the employed intracutaneous stimulation technique in this second experiment indeed specifically activated the slower conducting pain specific A δ -fibers and C-fibers.

ERL analyses of the neural activity recorded in cue-stimulus interval revealed the presence of an ADAN. Again, as in Experiment 1, the ADAN was not inverted on crossed hands trials compared to uncrossed hands trials. Now, an EDAN was observed in the ERL analyses, which is thought to represent the selection and interpretation of the presented cue (Van Velzen & Eimer, 2003). Furthermore, a positivity was observed over occipito-parietal representing an LDAP in both conditions. The LPS analyses revealed increased ipsilateral alpha power over posterior sites in the LDAP time window irrespective of the hand position. Furthermore, increased ipsilateral mu power was observed over central sites with higher activity on crossed hands trials compared to uncrossed hands trials, however no reversal of this activity was observed. This absence suggests that the increase in mu power most likely represents increased effort in selecting the location of the relevant hand on crossed hands trials instead of the direction of attention within the anatomical frame of reference. These observations again suggest that endogenous orientation of attention is primarily based on the body-centered frame of reference irrespective of whether the stimuli are intracutaneous or transcutaneous presented.

Analyses of the neural activity recorded in response to the intracutaneous stimuli revealed that the amplitudes of the P3a component was only affected by validity of the cue on uncrossed hands trials. Increased amplitudes of the P3a component in response to unattended stimuli compared to attended stimuli are suggested to represent the orienting

response of attention from the unattended stimuli (Van der Lubbe et al., 2012). The absence of a cue validity effect on crossed hands trials may indicate that attention is directed via external reference frame instead of the internal reference frame.

Analysis of the behavioral data revealed a lower accuracy of the responses compared to the first experiment. Detailed analyses revealed a low accuracy in response to the presented five-pulse stimuli. The observation of faster RTs in response to validly cued stimuli compared to invalidly cued stimuli suggests that attention was, as instructed, covertly directed to the cued locations based on the visual cues. Sensation ratings decreased over time, which is likely the result of the commonly observed habituation to the presented nociceptive stimuli during an experiment (e.g., Blom et al., 2012). Subsequently, the contrast between high intensity stimuli and the low intensity stimuli decreased during the experiment. As a result, participants may have adopted a more conservative strategy in which they classified the high intensity five-pulse stimuli as low intensity two-pulse stimuli.

3.8 General discussion

The aim of the present study was to examine according to what reference frame attention is directed to nociceptive stimuli presented on the body. In general, pain triggers the direction of attention (exogenous) to an affected body part, which in turn facilitates the selection of specific actions to cope with the potential life-threatening situation. The mechanisms behind this orientation of attention to a location on the body in anticipation of a painful event were further examined in this study. In detail, it was questioned whether attention in anticipation of a to be presented painful stimuli on the body is directed to the stimulus location via an internal anatomical reference frame or via an external (based on external spatial codes in relation to the body) reference frame or perhaps a combination of both reference frames.

Two experiments were reported, in which participants were instructed to direct their attention to the likely upcoming location at which either transcutaneous stimuli (Exp. 1) or intracutaneous stimuli (Exp. 2) were presented. Transcutaneous stimulation is known to activate tactile fibers (faster conducting A β -fibers) besides pain specific fibers (the slower conducting A δ -fibers and C-fibers), while intracutaneous stimulation thought to selectively activate the pain specific fibers. The left and right hand were placed either in a normal position on a table in front of the participant or on the same locations but then with their arms crossed (left hand on the right side and vice versa). The latter manipulation was employed to induce a conflict between the two reference frames, in order to determine the reference frame employed for orienting attention. Namely, if attention is oriented via the external reference frame crossing the arms would not lead to a reversal of lateralized components in the neural activity as the location of upcoming remains the same irrespective of the hand placed at that location. However, if attention is

oriented via the internal reference frame then the manipulation should lead to a reversal of lateralized activity.

The results obtained in the analyses of the neural activity in the cue-stimulus interval, representing the endogenous orientation of attention to the likely upcoming location at which a stimulus is presented, suggest that attention is primarily oriented via the external body-centered reference frame. The observed LDAP component in the lateralized EEG, reflecting the spatial selection process (see Gherri et al., 2007; Hopf & Mangun, 2000), and the increased power in the alpha band over occipito-parietal sites irrespective of hand position suggest that the orientation of attention is likely based on an external representation of the body. The absence of a reversal of the ADAN and mu-power over fronto-central sites on crossed hands trials further strengthens the view that endogenous attention towards a location on the body in anticipation of a painful stimulus is primarily based on the external body-centered reference frame.

Our results on the mechanism of the direction of attention to painful stimuli extend our knowledge on attentional orienting to events occurring on our body. The current knowledge on this topic was primarily based on experiments employing tactile stimuli. For example, Gherri and Forster (2012) employed a similar experiment using tactile stimuli. They observed an LDAP over posterior sites contralateral to the cue side of space regardless of the hand position in addition to an unaffected ADAN over fronto-central electrodes between 300 and 500 ms post-cue. Covert shifts of attention were exclusively guided by the external reference frame. Later in the cue-stimulus interval (700-900 ms time-interval) an enhanced negativity was observed over central sites, which was reversed in polarity in the crossed hands position. The component was observed contralateral to the relevant hand and not to the cued side of space, which suggests that it was guided by the anatomical frame of reference. Such a late component over central sites was not observed in our study. An increase in ipsilateral mu power was observed over central sites (C5/C6 electrode pair) in the ADAN time window with higher activity on crossed hands trials compared to uncrossed hands trials, however the activity was not reversed. This increase in mu power may represent increased effort in selecting the location of the relevant hand on crossed hands trials and not the direction of attention within the anatomical frame of reference.

In addition, we examined the neural processing in response to the presented stimuli. We hypothesized that if attention fully operates via the internal reference frame, then no effect of hand position should be observed. In Experiment 1, the amplitudes of the N1 and P3a components were attenuated in response to crossed hands trials as compared to uncrossed hands trials. This observation is more likely the result of the order in which the trials (uncrossed and crossed) were presented in Experiment 1 than the result of the induced conflict. The results from Experiment 2, in which the blocks were counterbalanced, confirms this suggestion, as the general attenuation in amplitudes of the N1 and P3a components between conditions was absent. The commonly observed

intensity modulation between low and high intensity stimuli was absent on crossed hands trials (regardless of cue validity) in Experiment 2. Interestingly, no effects of cue validity were observed in our experiments on the N1 components. This in contrast to earlier studies employing attentional manipulations to examine the processing of nociceptive stimuli all observed an attenuation of the amplitude of the N1 component in response to unattended stimuli (e.g. Blom et al., 2012; Van der Lubbe, Blom, De Kleine & Bohlmeijer., 2017; Van der Lubbe et al., 2012). The most likely explanation for the observed discrepancies between our results and that of earlier studies (e.g. Van der Lubbe et al., 2017; Van der Lubbe et al., 2012) is the difference in employed task instructions. That is, all of the presented stimuli in the current experiments were task-relevant as a response was demanded in response to both validly and invalidly cued stimuli, whereas in other studies responses were only made to stimuli presented at the attended hand (Van der Lubbe et al., 2012; Van der Lubbe et al., 2017). Attenuation of early stimulus processing in the SI or SII is only achieved when stimuli are completely unattended, either by employing an additional attention demanding task or when they are really task-irrelevant.

In addition, separate analyses of the uncrossed and crossed hands trials revealed an absence of a validity effect on the amplitude of the P3a component on crossed hands trials. In general, the P3a component is suggested to represent the neural response linked to orienting and involuntary shifts to changes in the environment or novelty stimuli (Polich & Criado, 2006; Polich, 2007). In relation to nociceptive stimuli, the reorientation of (spatial) attention to a nociceptive stimulus has been shown to result in increased amplitudes of the P3a component (e.g. Blom et al., 2012). Visual inspection of the ERPs revealed a later onset of the P3a component on invalid cued stimuli compared to validly cued stimuli on crossed hands trials, which is in line with the observed interaction between time and condition. It suggests that attention is either not directed to the cued location or directed to a lesser extent resulting in the presence of residual attention to the unattended hand. These observations suggest that the endogenous direction of attention not fully operates via the internal reference frame (see also Shore, Spry, & Spence, 2002; Yamamoto & Katazawa, 2001; Eimer et al., 2003).

In conclusion, the results from our experiments show that the covert orientation of endogenous spatial attention to nociceptive stimuli presented on the body primarily occurs within a body-centered reference frame, meaning that attention is directed to the location on the body in relation to the external space and not via the internal representation of the body.

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Chapter 4

Comparing the effects of sustained and transient spatial attention on the orienting towards and the processing of electrical nociceptive stimuli

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Abstract

The objective of the current study was to examine whether sustained versus transient spatial attention differentially affect the processing of electrical nociceptive stimuli. An endogenous variant of the Posner paradigm was employed in which cued nociceptive stimuli of a relevant intensity (two-pulse or five-pulse) on the left or right forearm required a foot pedal press. The cued side varied from trial to trial in the transient attention condition, while it remained constant during a block of trials in the sustained attention condition. Apart from behavioral measures, EEG activity was used to examine the orienting phase preceding the nociceptive stimuli by focusing on lateralized activity. ERPs were computed to examine the influence of spatial attention on the processing of the nociceptive stimuli. Behavioral results revealed no increased efficiency of spatial attention in the sustained spatial attention condition. Increased ipsilateral centro-parietal alpha power was observed in the transient attention condition, while increased ipsilateral centro-parietal beta power was found in the sustained attention condition. Support for increased efficiency of spatial attention in the sustained attention condition was obtained for the N180 (i.e., N1) and the P540 component, but no additional influence was observed for the early N130 and the P340 (i.e., P3a). In conclusion, spatial attention seems to be more efficient in the case of sustained spatial attention, however, this increased efficiency does not imply an effect at an earlier processing stage related to the N130. In addition, the call for attention by uncued nociceptive stimuli is present in both sustained and transient spatial attention conditions.

4.1 Introduction

A functional perspective on pain implies that its purpose is not to induce unpleasant feelings, but to signal the body of a potential or actual physical threat, and to induce appropriate behaviors (e.g., see Legrain, Iannetti, Plaghki, & Mouraux, 2011). All sensory modalities may induce warning signals, which automatically trigger an attentional response (i.e., they induce exogenous orienting). However, the nociceptive system (the peripheral and central nervous system involved with signaling potential tissue damage) seems to be specialized in this function. This especially becomes clear when patients suffer from congenital analgesia to pain (i.e., when they cannot feel pain, see Peddareddygari, Oberoi, & Grewal, 2014 and the General Introduction) as they systematically develop serious injuries that often lead to a premature death. Thus, pain and attention appear to be largely intertwined (see also Eccleston & Crombez, 1999). This supposed interconnectedness between attention and pain may have further implications. For example, the processing of nociceptive stimuli may directly activate structures known to be involved with attentional orienting like the anterior cingulate cortex (ACC) and the insular cortex. This prediction has been confirmed by several neuroimaging studies (Mouraux & Iannetti, 2009; Mouraux, Diukova, Lee, Wise, & Iannetti, 2011; Seeley, Menon, Schatzberg, Keller, Glover, Kenna et al., 2007). It also implies that attentional manipulations like distraction or focused attention instructions will largely affect the cortical processing of stimuli that activate the nociceptive system (e.g., see Blom, Wiering & Van der Lubbe, 2012; Van der Lubbe, Buitenweg, Boschker, Gerdes, & Jongsma, 2012). On the other hand, varying the task relevance of nociceptive stimuli is also likely to have an impact. When stimuli belong to the so-called attentional set (the mental set of stimulus features that participants use to identify task-relevant stimuli), evoked activity may be stronger than when stimuli are to be ignored. This aspect may explain discrepancies between the results of Blom et al. (2012) and Van der Lubbe et al. (2012) regarding the P2/P3a (or P260) event-related potential (ERP) component that can be derived from the electroencephalogram (EEG; see discussion). In the current study, the main interest was whether it matters if attention is continuously and unpredictably shifted from side to side (i.e., transient spatial attention to a spatial location on the left or right) as compared to when attention is consistently directed at one side (i.e., sustained spatial attention). This issue will be addressed by using an endogenous variant of the Posner cuing paradigm (Posner, Snyder, & Davidson, 1980) and by focusing on the orienting phase preceding nociceptive stimuli, and by examining the processing of the nociceptive stimuli themselves. By computing event related potentials to the nociceptive stimuli, we may track the cortical processing of these stimuli from primary (SI) and secondary somatosensory cortex (SII) up to ACC (e.g., see Van der Lubbe et al., 2012). Furthermore, by focusing on attention-direction-dependent EEG activity in the orienting phase (cue-stimulus), we may determine whether there are differences between sustained and transient spatial orienting conditions. This will not

only be examined by determining so-called event-related lateralizations (ERLs), which can be derived from ERPs (e.g., see Van der Lubbe, Neggers, Verleger, & Kenemans, 2006), but also by computing lateralized power differences in relevant frequency bands with the LPS (lateralized power spectra) index (see Van der Lubbe & Utzerath, 2013; Van der Lubbe, Bundt, & Abrahamse, 2014), as the latter index seems to be more sensitive.

Eimer and Forster (2003) compared the effects of sustained and transient spatial attention on the processing of mechanical tactile stimuli. Participants were instructed to detect target stimuli presented at an attended location on the body. In the sustained spatial attention condition, participants continuously attended to either their left or right hand during a block of trials. In the transient spatial attention condition, participants had to switch attention in an unpredictable way from one hand to the other, which was signaled by a central visual cue. Cues were only employed in the latter condition. ERPs revealed an enhanced N140 component and later negativity for attended as compared to unattended stimuli in both the sustained and the transient spatial attention conditions. However, an earlier increased contralateral negativity, around the N80, was only observed in the case of sustained spatial attention. This finding led Eimer and Forster (2003) to suggest that sustained spatial attention can modulate processing within SI while effects of transient spatial attention concern SII and later stages. Based on these findings with mechanical tactile stimuli, the question may be raised whether the processing of nociceptive stimuli is possibly affected in a similar way.

In a recent study, the influence of transient spatial attention on the processing of intracutaneous electrical stimuli presented to the index fingers of the left and right hands was examined (Van der Lubbe, et al., 2012). Stimulus intensity was manipulated by using either a single pulse, or five subsequent pulses with short interstimulus intervals. This method has the important advantage that the same fibers are recruited, as an increased number of pulses should only increase the amount of generated action potentials (see Van der Heide, Buitengeweg, Marani, & Rutten, 2009). Furthermore, by comparing attentional effects with the effect of stimulus intensity, it could additionally be established whether the attentional effect can be considered as gain modulation (e.g., see Moran & Desimone, 1985). Results revealed that the N100 and the N150 components were enhanced for attended as compared to unattended stimuli. An opposite effect, a decrease in amplitude for attended stimuli, was observed for the later P260 (or P3a) component. The latter effect was interpreted as “a call for attention” by the up to that moment ignored stimulus (i.e., an orienting effect; see Polich, 2007). Results of source analyses with BESA software indicated that the early attentional effects on the N100 and the N150 components may be related to increased activity within SII, while the attentional effect on the P260 component was ascribed to increased activity in ACC for unattended stimuli. In contrast with these attentional effects, all ERP components (N100, N150, P260) were enlarged for more intense (five pulse) stimuli. Examination of the estimated source activities suggests that attentional effects were rather diffuse while the effect of stimulus intensity

already seemed to invoke SI. However, due to the employed stimulation technique, both nociceptive (A δ) and tactile (A β) fibers were activated, therefore, it could not be concluded that observed effects concern nociception. Recent studies indicate that a specific type of stimulation electrodes, bipolar needles developed by Inui, Tran, Hoshiyama and Kakigi (2002), selectively activate nociceptive fibers (see Mouraux, Iannetti, & Plaghki, 2010). Thus, the question may be raised whether transient spatial attention effects as previously observed are also present when electrical stimuli selectively activate nociceptive fibers. Furthermore, these effects may be stronger in the case of a sustained than in the case of a transient spatial attention manipulation.

Apart from comparing effects of transient and sustained spatial attention on nociceptive processing, it seems also quite relevant to examine the orienting phase itself. Various attention-direction-dependent ERP components (or ERLs) have been observed while participants were awaiting visual, tactile, and auditory stimuli on the left or the right (e.g., Eimer, Van Velzen, & Driver, 2002; Hopf & Mangun, 2000; Van der Lubbe et al., 2006). Seiss, Gherri, Eardley and Eimer (2007) examined whether the so-called anterior directing attention negativity (ADAN) and the posterior late directing attention positivity (LDAP) may be considered as multimodal (or even supramodal) components. Orienting seems to be multimodal when it doesn't matter whether the to-be-attended stimulus on the left or right is auditory, visual, or tactile. In earlier studies of Green, Teder-Sälejärvi and McDonald (2005) and Green and McDonald (2006) no ADAN was observed when auditory cues were employed that preceded visual or auditory targets, which might imply that the ADAN is not multimodal. Seiss et al. (2007), however, observed both the ADAN and the LDAP in the orienting phase when auditory cues indicated the side of auditory imperative stimuli, in line with the idea that these two ERL components are multimodal. Another earlier component, the early directing attention negativity (EDAN), however, probably reflects selection of the relevant part of the visual cue that signals the to-be-attended side (Van Velzen & Eimer, 2003) and therefore seems not very informative about the orienting phase. Results of several other studies question the multimodal nature of the ADAN and LDAP components. For example, Eimer, Cockburn, Smedley and Driver (2001) showed a polarity reversal in the case of a crossed arms condition, which suggests that the ADAN is related to somatosensory space rather than to external visual space. Moreover, the LDAP was not observed for blind people, which suggest that this component is related to external (visual) space (Van Velzen, Eardley, Forster, & Eimer, 2006). In a study of Forster, Sambo and Pavone (2009) tactile imperative stimuli were presented on the hands, and conditions were examined with bilateral visual cues (close to the hands) and tactile cues preceding the imperative stimuli. The switching pattern of the cues indicated the side to be attended. The ADAN was observed in both conditions, but was more widespread and longer lasting with tactile cues than with visual cues. No LDAP was observed. These findings support the idea that the ADAN and the LDAP are not reflections of a multimodal or even supramodal orienting mechanism. A possible

problem, however, is that some effects may not show up with the ERL method due to individual and especially intra-individual (trial-to-trial) fluctuations. This variability may also depend on the type of cue that is employed as an arrow pointing to the left or right may be easier to interpret than the pitch of a tone that signals whether you have to attend to the left or the right.

Recently, Van der Lubbe and Utzerath (2013) introduced a method that may circumvent this problem. They related the computation of lateralized attention-direction dependent activity with ERPs to so-called lateralized power spectra (LPS) that can be derived from the raw EEG. The general idea of the LPS method is to determine an ipsi-contralateral power difference for a specific frequency band and to scale this difference by the sum of the power at both ipsi- and contralateral electrodes (for a comparable procedure, see Thut, Nietzel, Brandt, & Pascal-Leone, 2006). This procedure can be applied to various frequency bands. Application of this method suggests that the LDAP may be a reflection of lateralized power changes in the theta (θ), alpha (α) and even the beta (β) band. Furthermore, Van der Lubbe and Utzerath (2013) suggested that the ADAN may not always be visible due to individual differences, as application of the LPS method showed relevant lateralized activity in the θ and β bands while no ADAN was observed. Thus, earlier support for a unimodal interpretation of the ADAN and the LDAP may be due to differences in variability between the relevant conditions.

In the present study, a comparison was made between effects of sustained and transient spatial attention conditions on lateralized EEG activity, and effects of sustained and transient spatial attention on the subsequent processing of electrical nociceptive stimuli as reflected in ERPs. The nociceptive stimuli were presented on the left and right forearms. In both conditions, the to-be-attended side was indicated by a visual cue (a rhomb consisting of two triangles of different colors, where one color and therefore one side was defined as relevant). In the transient spatial attention condition, the cued side varied from trial to trial, whereas in the sustained spatial attention condition, the cued side was kept constant over trials. We manipulated stimulus intensity by varying the number of pulses. Only one intensity was defined as relevant for each participant. They were all instructed to press a foot pedal when the relevant intensity occurred at the cued side.

We expected to observe different lateralized ERP components in the orienting phase, which may be related to lateralized activity in specific frequency bands as determined with the LPS method. However, the LPS method may also reveal new information that is not reflected in lateralized ERP components. Lateralized activity might be more pronounced in the case of sustained than in the case of transient spatial attention. Furthermore, effects of spatial attention like observed in the study of Van der Lubbe et al. (2012) on different ERP components, but now after electrical nociceptive stimuli, were predicted to be stronger in the case of sustained than in the case of transient spatial attention, in line with the earlier observations by Eimer and Foster (2003).

4.2 Methods

Participants

Seventeen healthy students (14 females and 3 males, age range: 20–34 years) participated in the experiment in exchange for free participation in a mindfulness training that would occur at a later moment in time. The experiment lasted about three hours. All participants had normal or corrected-to-normal vision and reported to be free of neurological and psychiatric disorders. Sixteen participants were right-handed and one participant was left-handed, which was assessed with the Annett Handedness Inventory (Annett, 1970). Every participant received a detailed explanation of the procedure and signed a written informed consent before participating. The Medical Ethical Committee of Medisch Spectrum Twente approved the employed experimental procedures (NL31474.044.11/P11-11). Two participants were excluded from the analyses due to technical and procedural errors. This left 15 participants (13 female, 2 males; $M_{\text{age}} = 24.5$ years, all right-handed) for the analyses. The current data are part of a larger dataset in which the effects of mindfulness training on nociceptive stimuli processing were examined. Only data from a first session before the training (i.e., the control group) are reported. None of the participants had been involved in an experiment involving nociceptive stimulation before.

Stimuli and Procedure

Two Digitimer DS5 constant current stimulators (Digitimer, Welwyn Garden City, UK) were used to present the electrical stimuli, one for each stimulation side. Bipolar concentric electrodes (Inui et al., 2002) were placed over the median nerves of the left and right forearms. These electrodes selectively activate A δ -fibers located in the epidermis through a tiny needle that is inserted right under the skin.

During the experiment, stimuli of two intensity levels were used with a fixed stimulus current that matched the individual pain tolerance threshold of each participant (see above). The low intensity stimuli consisted of a volley of two 1 ms rectangular pulses and the high intensity stimuli consisted of a volley of five 1 ms rectangular pulses. To control for possible temporal summation of pulses an interpulse interval between two subsequent pulses in the pulse train of 5 ms was chosen, which lies well outside the refractory period (Van der Heide et al., 2009).

The individual sensation threshold, the pain threshold, and the pain tolerance threshold were obtained in a pretest by increasing the amplitude of a five-pulse stimulus with steps of 0.1 mA starting from zero. Participants were instructed to report the first stimulus that they were able to detect (the sensation threshold: 0.3 mA $\pm$ SE 0.02). With an increasing amplitude, the character of the stimulus changed from a sense of being touched to a more prickling sensation (the pain threshold: 0.8 mA $\pm$ 0.1). Finally, participants reported when a stimulus became annoying (the pain tolerance threshold: 1.2 mA $\pm$ 0.2). The amplitude used during the experiment was set at the individual pain

tolerance threshold. The subjective intensity ratings of the employed electrical stimuli were measured at five moments during the experiment. Participant received two two-pulse stimuli and two five-pulse stimuli to each forearm in a random order in each rating-session. Participants were instructed to rate the stimulus intensity of each stimulus on a 0-10 visual analogue scale (VAS) by using the left and right arrows on a keyboard. The value “0” matched with ‘no feeling at all’ whereas “10” matched with ‘extremely painful’.

Design and Procedure

Before the start of the experiment, a brief explanation of its purpose was presented on the screen. The experiment started after the pretest (see below), and consisted of four blocks, each containing 96 trials. Rating sessions (see above) were presented at the start, and after each block. A short block containing 16 practice trials was presented before the start of the third block.

In the sustained attention blocks (block 1 and 3 or block 2 and 4, counterbalanced) the relevant color was presented the first half of the block to the left and the second half of the block to the right or vice versa (counterbalanced). In the transient attention blocks (block 2 and 4 or block 1 and 3) the side of the relevant color varied randomly from trial to trial. In each block, there were four equally likely events, namely a nociceptive stimulus of two-pulse or five-pulse, being presented on the left or the right forearm. Each possible event occurred 24 times.

Each trial started with a white fixation cross ($0.48^\circ \times 0.48^\circ$) displayed in the center of a CRT screen. After 1200 ms, the fixation cross was replaced by a rhomb (the visual cue; $3.62^\circ \times 1.91^\circ$) for 400 ms. The rhomb consisted of a red and a green triangle (< >). One of the triangles signaled the to be attended side, which depended on the relevant cue color in that specific block of trials. In two successive blocks, red was the relevant color, and in two other blocks green was the relevant color. The order of the relevant colors was counterbalanced.

One thousand ms after onset of the visual cue, a two-pulse (low intensity) or a five-pulse (high intensity) nociceptive stimulus was delivered at the participant’s left or right forearm. The intensity and stimulation side varied randomly from trial to trial. The relevant stimulus intensity (two-pulse or five-pulse) was fixed, and varied between participants (see below). Foot pedal presses had to be made when the relevant stimulus intensity occurred on the to-be-attended side. The white fixation cross turned grey to indicate that a response was made. Each trial ended 4,000 ms after onset of the nociceptive stimulus. Feedback on performance was given on practice trials and an overall performance indication was given after each block of trials. Stimulus presentation, response registration and production of external triggers were controlled by E-Prime Software (version 2.0).

Recordings

EEG was recorded from 61 standard channel positions (extended 10-20 system), using

Ag/AgCl electrodes mounted on an electrocap (EasyCap GmbH, Herrsching-Breitbrunn, Germany). All electrode impedances were kept below 10 k Ω . The ground electrode was placed on the forehead. The vertical and horizontal electrooculogram (vEOG and hEOG) were measured with bipolar Ag/AgCl electrodes located on the outer canthi of the eyes and from above and below the left eye. Signals passed through a 72 channel QuickAmp amplifier (Brain Products GmbH, Munich, Germany) and were recorded online with an in-built average reference at a sample rate of 500 Hz. Online filtering with a 200 Hz low pass filter and a notch filter of 50 Hz was applied.

Data Analysis

Behavioral data

Hit rates and false alarm rates were determined and were subsequently used to compute signal detection theory measures: sensitivity (d') and response bias ($\ln\beta$) (e.g., see Macmillan & Creelman, 2005). A repeated measures ANOVA was performed on both measures with the within-subjects factor Attention Condition (sustained or transient), and the between-subjects factor Group (relevant intensity: low or high). We also analyzed reaction times (RT) for correct target detection responses with the same factors.

Stimulus intensity ratings assessed with the VAS were analyzed with a repeated measures ANOVA with Stimulus Intensity (two-pulse vs. five-pulse), Stimulation Side (left vs. right) and Block (0 [before the first experimental block] - 4 [after the final experimental block]) as within-subject factors, and Group as between-subjects factor.

EEG data

EEG was analyzed using Brain Vision Analyzer (Version 2.0.2.5859; Brain Products GmbH, Munich, Germany). First, relevant segments were extracted from the continuously measured EEG, from 2200 ms before until 1500 ms after the onset of the nociceptive electrical stimuli (which equals from 1200 ms before until 2500 ms after the cue). A baseline was set from -1130 till 1030 ms before the nociceptive stimuli, shortly before presenting the cue. Next, trials were removed in which eye movements ($> 100 \mu\text{V}$) were made in the direction of the hands for the time interval from -1000 until 200 ms after onset of the nociceptive stimuli. Trials with major artefacts were removed (gradient criterion: $100 \mu\text{V}/\text{ms}$; min-max criterion: $\pm 250 \mu\text{V}$; low activity criterion: $0.1 \mu\text{V}$ per 50 ms). Subsequently, Independent Component Analysis (ICA ocular correction) was applied to exclude components that have no cortical origin (e.g., EOG, electromyographic, electrocardiographic). Next two separate analyses were performed, one for the orienting phase (from -1000 to 2000 ms relative to cue onset, both ERL and LPS), and one for the nociceptive stimuli (from -100 to 1500 ms relative to onset of the nociceptive stimuli; ERPs).

For the orienting phase, trials were checked for remaining small artefacts (min-

max criterion: $\pm 150 \mu\text{V}$), which left on average 90.1% of the trials. A baseline was set from -100 to 0 ms relative to cue onset. Next, two analyses were performed. In the ERL analysis, we determined ERPs for left and right relevant sides for both attention conditions and subsequently performed a double subtraction technique to estimate contra-ipsilateral difference waves (e.g., see Van der Lubbe et al., 2006). Average amplitudes were computed per individual for 50 ms time windows starting from 200 ms after cue onset until onset of the nociceptive stimulus. A first statistical analysis was carried out for ten selected electrode pairs (F4/3 [frontal]; FC4/3 [fronto-central], C4/3 [central], C6/5 [lateral central], CP4/3 [centro-parietal], CP6/5 [lateral centro-parietal], P4/3 [parietal], P8/7 [occipito-temporal], PO4/3 [occipito-parietal], PO8/7 [occipital]) to see whether there were any deviations from zero. The critical p-value for this analysis was determined by the same procedure as employed in Van der Lubbe et al. (2014). With ten electrode pairs, fifteen successive time windows, and two conditions, this implies that a critical p-value of 0.013 had to be overstepped for at least two successive time windows. Subsequently, a comparison was made between the transient and the sustained attention conditions including the factor Group for those time windows and sites that showed most pronounced effects.

For the LPS analysis, we followed a comparable procedure as described in Van der Lubbe et al. (2014). We extracted the power of different frequency bands, by carrying out a wavelet analysis (complex Morlet with Gabor normalization, $c = 5$) on the raw EEG. We extracted the lower $\alpha 1$ (7.2-10.7 Hz) and the higher $\alpha 2$ (9.4-14.0 Hz) bands, and the lower $\beta 1$ (12.2-18.4 Hz) and the higher $\beta 2$ (16.0-24.0 Hz) bands. Individual averages for left and right relevant sides for the transient and sustained attention conditions were computed. Next, normalized lateralization indices ($[\text{ipsilateral}-\text{contralateral}]/[\text{ipsilateral}+\text{contralateral}]$) were computed for the two frequency bands for the relevant conditions. An average was computed across both relevant sides for the two attention conditions per frequency band, which results in the LPS. Subsequently, the data were evaluated per frequency band in the same way as for the ERLs, with an adjusted critical p-value for two successive time windows of 0.006, as now four frequency bands were examined. Subsequently, a comparison was made between the Transient and the Sustained Attention conditions including the factor Group for those time windows, sites, and frequency bands that seemed most relevant.

For the analyses performed to evaluate the processing of the nociceptive stimuli, we also checked for remaining small artefacts, which left on average 90.3% of the trials. A new baseline from -100 to 0 ms relative to the onset of the nociceptive stimuli was set. Subsequently, ERPs were computed for all relevant conditions (cued/uncued, two-pulse/five-pulse stimuli, left/right side, transient/sustained attention condition). Appropriate time windows and electrodes were selected based on our earlier study in combination with an inspection of the grand average waveforms. We expected to observe the same components as in Van der Lubbe et al. (2012), the N100, N150, P260, and P500,

but all with a delay as we now employed electrodes that selectively activate A δ -fibers. Furthermore, we expected a slightly different topography as stimuli were presented on the forearms instead of the fingers. After estimating the peaks of the various components, average amplitudes in time windows of 20 ms were determined for the earliest negative components, while these amplitudes were computed within 40 ms time windows for the later positive components. Greenhouse-Geisser ϵ correction of the degrees of freedom was applied whenever appropriate.

4.3 Results

Behavioral data

Analyses on d' showed that participants were well able to discriminate between the relevant and the irrelevant stimulus intensities. Statistical analyses revealed no difference in sensitivity between the sustained (2.47, [95% confidence interval: 2.27 – 2.68]) and the transient (2.26 [1.96 – 2.56]) attention conditions; $F(1,13) = 2.6$, $p = 0.132$. Furthermore, no effect of Group (low: 2.43 [2.12 – 2.74]; high: 2.30 [2.01 – 2.60]) was observed; $F(1,13) = 0.42$, $p = 0.53$.

Analyses on $\ln\beta$ showed no bias in responding between the sustained (1.28 [0.74 – 1.82]) and transient (1.32 [0.81 – 1.83]) attention conditions; $F(1,13) = 0.11$, $p = 0.743$. A trend towards a main effect of Group, $F(1,13) = 3.7$, $p = 0.076$; $\eta p^2 = 0.22$, was visible. $\ln\beta$ tended to be lower for the participants who had to detect the low intensity (two-pulse) stimuli (0.85 [0.10 – 1.59]) as compared with participants that had to detect the high intensity (five-pulse) stimuli (1.75 [1.06 – 2.45]). This result might indicate that participants in the high intensity group were (or became) more conservative than in the low intensity group.

RT of the correct target detection responses did not differ between the sustained (908 ms [826 – 991 ms]) and transient (900 ms [815 – 985 ms]) attention conditions; $F(1,13) = 0.6$, $p = 0.457$. There was also no effect of Group; $F(1,13) = 0.7$, $p = 0.413$.

Analyses on the VAS scores revealed that five-pulse stimuli were judged as more painful than two-pulse stimuli (two-pulse: 3.3 [2.7 – 4.0]; five-pulse: 5.0 [4.6 – 5.4]; $F(1,13) = 91.3$, $p < 0.001$; $\eta p^2 = 0.88$). Furthermore, a main effect of Block was observed ($F(4,52) = 18.8$, $\epsilon = 0.58$, $p < 0.001$; $\eta p^2 = 0.59$). Linear contrast analyses revealed that intensity ratings decreased over time ($F(1,13) = 39.7$, $p < 0.001$) from 5.1 [4.6 – 5.5] before Block 1, to 3.6 [2.9 – 4.3] after Block 4. Finally, the intensity of two-pulse and five-pulse stimuli were perceived as more painful on the right (4.4 [3.8 – 5.0]) than on the left arm (3.9 [3.5 – 4.4]); $F(1,13) = 6.4$, $p = 0.025$, $\eta p^2 = 0.33$).

EEG data

To explore whether there are differences in the allocation of attention in sustained and transient attention conditions we first examined the orienting phase. This was done

with ERLs (Figure 4.1), and also with LPS for the lower and higher alpha and beta bands (Figure 4.2). The subsequent influence of sustained and transient spatial attention on the processing of the nociceptive stimuli was examined with ERPs (Figure 4.3, 4.4 and 4.5).

Table 4.1. An overview of effects observed with event related lateralizations (ERLs) during the orienting phase in the sustained and transient spatial attention conditions. Effects were considered significant when the critical p-value of 0.013 was crossed for at least two successive time windows. The lower and upper boundaries of the estimated p-values are presented in the rightmost column. A missing lower boundary means that the smallest p-value was lower than 0.001.

Attention Condition	Electrode pair	Time windows	Contra-ipsilateral polarity	$\underline{t}(14)$ $< p <$
Sustained	PO8/7	200-450 ms	negative	$0.001 < p < 0.007$
	P8/7	250-450 ms	negative	$0.001 < p < 0.011$
	FC4/3	300-450 ms	negative	$p < 0.012$
	F4/3	350-450 ms	negative	$0.003 < p < 0.009$
	PO8/7	550-700 ms	positive	$0.001 < p < 0.008$
	PO4/3	550-650 ms	positive	$0.001 < p < 0.003$
	P4/3	550-650 ms	positive	$0.001 < p < 0.003$
	PO8/7	900-1000 ms	positive	$0.001 < p < 0.008$
	PO4/3	900-1000 ms	positive	$0.005 < p < 0.012$
Transient	PO8/7	200-450 ms	negative	$p < 0.007$
	PO4/3	200-300 ms	negative	$p < 0.001$
	P8/7	200-300 ms	negative	$0.001 < p < 0.005$
	P8/7	350-450 ms	negative	$0.002 < p < 0.004$
	C6/5	200-550 ms	negative	$0.002 < p < 0.012$
	F4/3	300-500 ms	negative	$0.002 < p < 0.012$
	FC4/3	300-550 ms	negative	$p < 0.003$
	PO4/3	550-650 ms	positive	$0.006 < p < 0.009$
	PO4/3	700-850 ms	positive	$0.008 < p < 0.013$
	PO8/7	600-1000 ms	positive	$p < 0.006$
	P4/3	600-850 ms	positive	$p < 0.005$
	P4/3	900-1000 ms	positive	$0.006 < p < 0.011$

Attentional orienting

ERL data. An overview of the statistical results per Attention Condition is given in Table 4.1. In the sustained attention condition we initially (from 200-450 ms) observed significant deviations from zero above frontal, fronto-central, but especially above occipito-temporal, and occipital sites (see Table 4.1). This concerned increased contralateral negativity (see Figure 4.1). From 550 to 700 ms, an opposite effect

(contralateral positivity; the LDAP) was visible, being most marked above occipital sites. At the end of the orienting interval, this contralateral positivity returned, which stayed maximal above occipital and occipito-parietal sites.

Figure 4.1. Topographies (scaling -2 to 2 μ V) of the event-related lateralizations (ERLs) during the orienting phase in the sustained (upper panel) and transient spatial attention conditions (lower panel). The contra-ipsilateral difference is projected on the right hemisphere, while the ipsi-contralateral difference is projected on the left hemisphere. Topographies were determined for 50 ms intervals from 200 ms after cue onset until onset of the nociceptive stimulus. The topographies were based on interpolation by spherical splines (4th order).

In the transient attention condition we also observed an initial frontal, fronto-central, central, and occipital contralateral negativity. This pattern reversed to contralateral positivity above occipital and parietal sites from about 600 ms, which remained until the end of the orienting interval.

In both conditions, maximal deviations were observed above occipital sites. Inspection of our grand average data in Figure 4.1 suggests that there might be some subtle differences between the two attention conditions on these sites from 300 to 350 ms, from 550 to 650 ms, and from 950 to 1000 ms. For the 300 to 350 ms time window, no significant differences of Attention Condition and/or Group were observed although a small tendency seems present towards more contralateral negativity in the sustained than in the transient attention condition, $F(1,13) = 3.3$, $p = 0.092$, $\eta_p^2 = 0.20$. No differences

were observed from 550 to 650 ms, and also not from 950 to 1000 ms.

Figure 4.2. Topographies of the lateralized power spectra (LPS) for the lower and upper α (above) and β (below) bands (α_1 , α_2 , β_1 , β_2) during the orienting phase in the sustained (left panel) and transient spatial attention conditions (right panel, scaling -0.075 to 0.075 μV). The ipsi-contralateral difference is here projected on the right hemisphere, while the contra-ipsilateral difference is projected on the left hemisphere. Computed values are based on the ipsi-contralateral differences in power in the respective frequency bands determined by wavelet analyses, scaled by the sum of the ipsilateral and contralateral power. Topographies were determined for 50 ms intervals from 200 ms after cue onset until onset of the nociceptive stimulus. The topographies were based on interpolation by spherical splines (4th order).

Table 4.2. An overview of effects observed with lateralized power spectra (LPS) during the orienting phase in the sustained and transient spatial attention conditions. Effects were considered significant when the critical p-value of 0.006 was crossed for at least two successive time windows. The lower and upper boundaries of the estimated p-values are presented in the rightmost column. A missing lower boundary means that the smallest p-value was lower than 0.0001.

Attention condition	Electrode pair	Band	Time window	ipsi > contra or contra > ipsi	t(14) <p <
Sustained	C4/3	$\alpha 1$	450-550 ms	ipsi > contra	0.0049 < p < 0.0051
	PO8/7	$\alpha 1$	500-600 ms	ipsi > contra	0.0036 < p < 0.0037
	PO8/7	$\alpha 2$	350-550 ms	ipsi > contra	0.0008 < p < 0.0033
	C4/3	$\alpha 2$	350-550 ms	ipsi > contra	0.0010 < p < 0.0031
	C6/5	$\alpha 2$	650-800 ms	ipsi > contra	0.0018 < p < 0.0031
	C4/3	$\alpha 2$	700-800 ms	ipsi > contra	0.0035 < p < 0.0041
	C4/3	$\beta 1$	700-950 ms	ipsi > contra	0.0002 < p < 0.0032
	CP4/3	$\beta 1$	700-850 ms	ipsi > contra	0.0002 < p < 0.0051
	PO8/7	$\beta 1$	750-850 ms	contra > ipsi	0.0017 < p < 0.0022
	C4/3	$\beta 2$	700-800 ms	ipsi > contra	0.0002 < p < 0.0004
	CP4/3	$\beta 2$	700-800 ms	ipsi > contra	p < 0.0002
	PO8/7	$\beta 2$	750-850 ms	contra > ipsi	0.0007 < p < 0.0012
Transient	CP6/5	$\alpha 1$	450-550 ms	ipsi > contra	0.0009 < p < 0.0050
	P8/7	$\alpha 1$	800-900 ms	ipsi > contra	0.0009 < p < 0.0039
	CP6/5	$\alpha 2$	750-1000 ms	ipsi > contra	0.0005 < p < 0.0053
	PO8/7	$\alpha 2$	450-550 ms	ipsi > contra	0.0026 < p < 0.0034
	CP4/3	$\alpha 2$	850-950 ms	ipsi > contra	0.0035 < p < 0.0039
	CP6/5	$\beta 2$	550-650 ms	ipsi > contra	0.0015 < p < 0.0021
	C4/3	$\beta 2$	650-750 ms	ipsi > contra	0.0003 < p < 0.0015
	CP6/5	$\beta 2$	800-900 ms	ipsi > contra	0.0009 < p < 0.0013

LPS data. An overview of the statistical results per Attention Condition is given in Table 4.2. In the sustained attention condition, lateralized power was observed in all examined frequency bands (see Figure 4.2). In the $\alpha 1$ band we observed enlarged ipsilateral vs. contralateral power above occipital and central sites (see Figure 4.2), being most pronounced at around 500 to 550 ms after cue onset. In the $\alpha 2$ band a comparable effect was observed that started earlier and extended to more lateral central sites up to 800 ms after cue onset, while an opposite (non-significant) pattern (but see below) was now visible above occipito-parietal sites. In the $\beta 1$ band (see Figure 4.2) effects occurred in later time intervals. On central sites, increased ipsilateral vs. contralateral power was visible from 700 to 950 ms, while this effect was significant for a slightly shorter duration above centro-parietal sites. Simultaneously, an opposite pattern (decreased ipsilateral power)

was visible above occipital sites. In the $\beta 2$ band we also observed increased ipsilateral power above central and centro-parietal sites from 700 to 800 ms after cue onset while an opposite effect was present above occipital sites.

In the transient attention condition, we observed increased ipsilateral power in the $\alpha 1$ band above centro-parietal sites from 450 to 550 ms, which moved to occipito-temporal sites from 800 to 900 ms after cue onset. In the higher $\alpha 2$ band, an early posterior focus (450-550 ms) displaying increased ipsilateral power moved to lateral centro-parietal sites, which remained present until target onset. No effects were visible in the lower $\beta 1$ band, while early and later increased ipsilateral power in the $\beta 2$ band was observed above central, and lateral centro-parietal sites.

Inspection of the grand averages of both attention conditions suggests that late lateral centro-parietal ipsilateral enhanced $\alpha 2$ power might be more specific for the transient attention condition (see Figure 4.2), while late centro-parietal ipsilateral enhanced $\beta 1$ and especially $\beta 2$ power might be more specific for the sustained attention condition (see Figure 4.2). For the $\alpha 2$ band we indeed observed increased ipsilateral power in the transient relative to the sustained attention condition from 800 until 950 ms, $F(1,13) > 5.3$, $p < 0.038$, $\eta^2_p > 0.29$. No significant conditional differences were present for the $\beta 1$ band, while increased ipsilateral power for the sustained attention condition was present in the $\beta 2$ band from 700 to 800 ms, $F(1,13) > 7.0$, $p < 0.020$, $\eta^2_p > 0.34$.

ERPs after nociceptive stimulation

Inspection of the topographical maps and the ERPs (see Figure 4.3) indicated that a lateralized central negativity (N130) with a maximum at T7 (or T8) was followed by a more bilateral but still lateralized central negativity (N180) that had its maximum at C5 (or C6). Subsequently, a central P340 was followed by a more centro-parietal P560. To reduce the number of factors, we collapsed data across left and right stimuli and computed new averages with contralateral activity projected on the left hemisphere, and ipsilateral activity projected on the right hemisphere. ERPs at relevant electrodes are presented in Figure 4.4 (N130, N180) and in Figure 4.5 (P340, P560).

The N130. Statistical analyses were performed with the factors Electrode (T7 = contralateral, T8 = ipsilateral), Cue (cued, uncued), Stimulus Intensity (two-pulse, five-pulse), and Attention Condition (sustained, transient) as within-subjects factors, and Group (low, high) as between-subjects factor. A main effect of Electrode was observed, $F(1,13) = 26.8$, $p < 0.001$, $\eta^2_p = 0.67$, revealing more negative amplitudes at contralateral than at ipsilateral electrodes (-2.3 [$-1.2 - -3.3$] vs. -0.7 μV [$-0.2 - -1.3$]). A main effect of Stimulus Intensity was observed, $F(1,13) = 14.3$, $p < 0.003$, $\eta^2_p = 0.52$, and this effect also interacted with Electrode, $F(1,13) = 12.6$, $p < 0.005$, $\eta^2_p = 0.49$. The effect of Stimulus Intensity was present on contralateral (two-pulse: -1.8 [$-0.8 - -2.8$]; five-pulse -2.8 μV [$-1.6 - -3.9$]) but not on ipsilateral electrodes (-0.6 [$0.0 - -1.3$] vs. -0.8 μV [$-0.4 - -1.3$]).

Figure 4.3. Topographies of the ERP components observed after the electrical nociceptive stimuli (scaling N130 and N180 -3 to 3 μ V, P340 and P560 -10 to 10 μ V). Data were collapsed across left and right stimuli, and new averages were computed with contralateral activity projected on the left hemisphere and ipsilateral activity projected on the right hemisphere. Data are displayed for the five-pulse and two-pulse stimuli, as a function of cue (cued vs. uncued) for the sustained (left panel) and the transient spatial attention conditions (right panel).

A main effect of Cue was observed, $F(1,13) = 11.2$, $p < 0.006$, $\eta^2_p = 0.46$, with larger amplitudes for cued than for uncued stimuli (-1.7 [-0.9 – -2.6] vs. -1.3 μ V [-0.6 – -2.0]). The effect of Cue did not interact with Attention Condition ($p > 0.4$). Finally, an interaction was observed between Stimulus Intensity, Attention Condition, and Group, $F(1,13) = 6.7$, $p = 0.022$, $\eta^2_p = 0.34$. However, separate analyses per group, revealed no interaction between the relevant factors (Stimulus Intensity, Attention Condition).

The N180. Analyses were performed with the same factors as above, but now C5 (contralateral) and C6 (ipsilateral) were used as levels for the factor Electrode. A main effect of Electrode was observed, $F(1,13) = 25.2$, $p < 0.001$, $\eta^2_p = 0.66$, revealing more negative amplitudes at contralateral than at ipsilateral electrodes (-2.9 [-2.1 – -3.7] vs. -1.3 μ V [-0.7 – -1.8]). A main effect of Stimulus Intensity was observed, $F(1,13) = 5.8$, $p = 0.031$, $\eta^2_p = 0.31$ (-2.0 [-1.4 – -2.5] vs. -2.2 μ V [-1.6 – -2.8]), but in contrast with

the N130, this effect no longer interacted with Electrode ($p > 0.10$). An interaction was observed between Stimulus Intensity and Attention Condition, $F(1,13) = 6.3$, $p = 0.026$, $\eta^2_p = 0.33$. This effect additionally depended on Group, $F(1,13) = 14.6$, $p = 0.002$, $\eta^2_p = 0.53$. Therefore, separate analyses were performed per group.

For the low intensity group, we observed an interaction between Stimulus Intensity and Attention Condition, $F(1,6) = 10.2$, $p = 0.019$, $\eta^2_p = 0.63$. In the sustained attention condition, no effect of stimulus intensity seems present (two-pulse: -2.3 [$-1.4 - -3.2$]; five-pulse: -2.1 [$-1.1 - -3.1$]), while in the transient attention condition, this effect is present (two-pulse: -2.4 [$-1.6 - -3.2$]; five-pulse: -3.1 [$-1.9 - -4.2$]). For the high intensity group, no interaction between Stimulus Intensity and Attention Condition was observed, $F(1,7) = 3.2$, $p = 0.12$, $\eta^2_p = 0.32$.

We additionally observed an interaction between Stimulus Intensity, Attention Condition, and Cue, $F(1,13) = 6.5$, $p = 0.024$, $\eta^2_p = 0.33$. A separate analysis for two-pulse stimuli revealed no effects involving the factors Attention Condition, and Cue ($p > 0.21$). A separate analysis for five-pulse stimuli showed an interaction between Attention Condition and Cue, $F(1,13) = 6.9$, $p = 0.021$, $\eta^2_p = 0.35$. A slightly reduced negativity was visible for uncued relative to cued stimuli in the sustained attention condition (cued: -2.2 [$-1.6 - -2.9$]; uncued: -1.7 [$-1.1 - -2.4$]), while no such effect was present in the transient attention condition (-2.4 [$-1.6 - -3.1$]; -2.4 [$-1.6 - -3.3$]).

Figure 4.4. ERPs observed after the electrical nociceptive stimuli above contralateral (C5, T7) and ipsilateral (C6, T8) sites. Data were collapsed across left and right stimuli, and new averages were computed with contralateral activity projected on the left hemisphere and ipsilateral activity projected on the right hemisphere. A comparison was made between five-pulse and two-pulse stimuli that occurred on cued vs. uncued locations.

The P340. Analyses were performed with Electrode (Cz, Pz), Cue (cued, uncued), Stimulus Intensity (two-pulse, five-pulse), and Attention Condition (sustained, transient) as within-subjects factors, and Group (low, high) as between-subjects factor. A main effect of Electrode was observed, $F(1,13) = 52.2$, $p < 0.001$, $\eta^2_p = 0.80$, revealing more positive amplitudes at Cz than at Pz (7.9 [6.2 – 9.6] vs. 3.7 μV [2.4 – 5.0]). Additionally, a main effect of Stimulus Intensity was observed, $F(1,13) = 47.1$, $p < 0.001$, $\eta^2_p = 0.78$, revealing more positive amplitudes for five-pulse than for two-pulse stimuli (6.8 [5.2 – 8.4] vs. 4.9 μV [3.6 – 6.1]). We also found an interaction between Stimulus Intensity and Electrode, $F(1,13) = 9.4$, $p < 0.01$, $\eta^2_p = 0.42$, which seems due to the more pronounced effect of Stimulus Intensity at the Cz (9.1 [7.1 – 11.0] vs. 6.8 μV [5.3 – 8.3]) than at the Pz electrode (4.5 [2.9 – 6.0] vs. 2.9 μV [1.8 – 4.1]).

A main effect of Cue was obtained, $F(1,13) = 8.6$, $p = 0.012$, $\eta^2_p = 0.40$, revealing more positive amplitudes after uncued than after cued stimuli (uncued: 6.4 [4.9 – 8.0] vs. cued: 5.2 μV [3.8 – 6.6]). However, this effect again differed per electrode, $F(1,13) = 29.1$, $p < 0.001$, $\eta^2_p = 0.69$, and was present at Cz (9.2 μV [7.2 – 11.1] vs. 6.7 [5.0 – 8.3]) but not at Pz (3.7 μV [2.3 – 5.1] vs. 3.7 [2.2 – 5.1]).

Figure 4.5. ERPs observed after the electrical nociceptive stimuli above Cz and Pz, displayed separately for the high intensity group (left panels) and the low intensity group (right panels). A comparison was made between five-pulse and two-pulse stimuli that occurred on cued vs. uncued locations.

The P560. Analyses were performed with the same factors as the P340. A main effect of Stimulus Intensity was observed, $F(1,13) = 24.5$, $p < 0.001$, $\eta^2_p = 0.65$, which was due to more positivity for five-pulse than for two-pulse stimuli (4.7 μV [3.9 – 5.5] vs. 3.4 [2.7 – 4.2]). An interaction between Cue and Electrode was observed, $F(1,13) = 34.4$, p

< 0.001 , $\eta^2_p = 0.73$, between Stimulus Intensity, Cue, and Group, $F(1,13) = 17.6$, $p < 0.002$, $\eta^2_p = 0.58$, between Electrode, Stimulus Intensity, and Group, $F(1,13) = 38.9$, $p < 0.002$, $\eta^2_p = 0.75$, between Electrode, Intensity, Cue and Group, $F(1,13) = 11.1$, $p < 0.006$, $\eta^2_p = 0.46$, and between Electrode, Attention Condition, and Cue, $F(1,13) = 8.7$, $p < 0.02$, $\eta^2_p = 0.40$. To facilitate our understanding of these interactions, we first performed separate analyses per electrode.

Analyses for the Cz electrode revealed a main effect of Stimulus Intensity, $F(1,13) = 12.7$, $p < 0.004$, $\eta^2_p = 0.49$, but this effect differed between Groups, $F(1,13) = 13.8$, $p < 0.004$, $\eta^2_p = 0.51$. A main effect of Cue was observed, $F(1,13) = 12.7$, $p < 0.004$, $\eta^2_p = 0.49$, but we additionally observed an interaction between Stimulus Intensity, Cue, and Group, $F(1,13) = 21.9$, $p < 0.001$, $\eta^2_p = 0.63$. Therefore, separate analyses were carried out per group.

For the low intensity group, we observed an interaction between Stimulus Intensity and Cue, $F(1,6) = 20.9$, $p < 0.005$, $\eta^2_p = 0.78$, which seems due to the reduced positivity for Cued five-pulse stimuli ($1.6 \mu V$ [$0.0 - 3.2$]) relative to the Uncued Two-pulse stimuli ($5.7 \mu V$ [$2.8 - 8.6$]), and the Cued and Uncued Five-pulse stimuli ($5.3 \mu V$ [$3.4 - 7.2$], $7.0 \mu V$ [$4.2 - 9.8$]).

For the high intensity group, we also observed an interaction between Stimulus Intensity and Cue, $F(1,7) = 10.6$, $p < 0.02$, $\eta^2_p = 0.60$. This, however, seems due to the reduced positivity for Cued five-pulse stimuli ($3.1 \mu V$ [$0.0 - 6.2$]) relative to the Uncued Five-pulse stimuli ($6.0 \mu V$ [$4.6 - 7.3$]), and the Cued and Uncued Two-pulse stimuli ($5.0 \mu V$ [$3.5 - 6.5$], $4.2 \mu V$ [$2.9 - 5.5$]).

Analyses for the Pz electrode showed a main effect of Stimulus Intensity, $F(1,13) = 32.2$, $p < 0.001$, $\eta^2_p = 0.71$, which differed between Groups, $F(1,13) = 4.8$, $p < 0.05$, $\eta^2_p = 0.27$. The intensity effect seemed only present for the High Intensity Group (two-pulse: $1.5 \mu V$ [$0.1 - 3.0$], five-pulse: $3.4 \mu V$ [$2.0 - 4.7$]), and not for the Low Intensity Group (two-pulse: $4.0 \mu V$ [$2.4 - 5.6$], five-pulse: $4.8 \mu V$ [$3.4 - 6.2$]). A main effect of Cue was observed, $F(1,13) = 16.2$, $p < 0.002$, $\eta^2_p = 0.55$, which interacted with Attention Condition, $F(1,13) = 5.1$, $p < 0.05$, $\eta^2_p = 0.28$. The difference in P560 amplitude for Cued and Uncued stimuli was larger in the Sustained ($4.9 \mu V$ [$3.7 - 6.0$], $2.3 \mu V$ [$1.4 - 3.2$]) than in the Transient Attention condition ($3.7 \mu V$ [$2.5 - 5.0$], $2.8 \mu V$ [$1.2 - 4.4$]).

4.4 Discussion

The central question to be addressed in this paper is whether sustained and transient spatial attention manipulations differentially affect the processing of nociceptive stimuli. Specifically, one might argue that a sustained manipulation, in which attention is continuously directed to one side during a block of trials, has more impact on early and later processing stages than a transient attentional manipulation, in which attention unpredictably changes from side to side (see Eimer & Forster, 2003). One reason might be

that less errors will be made in directing attention when the relevant side is constant, but the efficiency of the selection process itself may also be improved in the case of sustained attention. This question was addressed by examining lateralized EEG activity in the cue-target interval, which informs us directly about differences in attentional orienting, and by examining ERPs evoked by nociceptive stimuli that were either or not attended, and had a low (two-pulse) or high (five-pulse) stimulus intensity. However, first we will focus on effects on behavioral measures derived from signal detection theory, perceived intensity scores (VAS), and the speed of responses.

Effects on perceptual sensitivity (d') indicated that participants were well able to discriminate the relevant from the irrelevant stimulus intensity. The type of attentional manipulation did not affect this ability. Analyses additionally revealed no differences in response bias between the attentional manipulations, although the group that had to detect five-pulse (high intensity) stimuli tended to be a bit more conservative. This implies that they tended to miss targets, which may be related to the observed reduction in perceived intensity over time (see Blom et al., 2012). The perceived intensity corresponded with the applied stimulus intensity, although the intensity was judged to be higher on the right arm than on the left arm. Finally, no effects were observed on response speed. So, together, the behavioral data do not suggest that sustained spatial attention increases attentional efficiency.

Lateralized activity derived from ERPs (ERLs) revealed an early contralateral negativity that corresponds with the EDAN, and a later contralateral positivity that may be denoted as the LDAP (see Figure 4.1). Both effects were most pronounced above posterior sites, and seem unrelated to advance preparation in somatosensory brain areas. More likely, they reflect changes in visual-related brain areas, so they seem more related to visual orienting. No differences were found between the two attentional manipulations.

Lateralized power in the lower and upper α and β bands (LPS, see Figure 4.2) provided more relevant information. In the sustained spatial attention condition, we observed increased ipsi- vs. contralateral power above occipital sites in the lower α band that may be related with the LDAP. In the $\alpha 2$ band and especially in both β bands we observed increased ipsi- vs. contralateral power above somatosensory sites in later time windows, while an opposite pattern seems present above occipital sites. These phenomena seem related to a change in somatosensory activity due to spatial attention, which may reflect inhibition of the to-be-ignored arm and/or a release of inhibition for the to-be-attended arm. The opposite pattern above occipital sites might reflect more inhibition of the contralateral visual field. A comparable pattern with maxima of increased ipsi vs. contralateral α power above posterior and centro-parietal sites was observed in the transient spatial attention condition. No effect was significant in the $\beta 1$ band, while in the $\beta 2$ band again increased ipsi vs. contralateral power was present above centro-parietal sites. This seems to reflect a change in somatosensory activity due to spatial attention. Interestingly, we also noticed some subtle differences between sustained and transient

spatial attention conditions. In the transient spatial attention condition we observed more ipsi- vs. contralateral power in the α_2 band along lateral centro-parietal sites, while in the β_2 band we observed more ipsilateral centro-parietal power in the sustained spatial attention condition. Thus, it seems that relevant orienting effects involve slightly different frequency bands, with more dominant lateralized α activity in the transient spatial attention condition, and more dominant lateralized β activity in the sustained spatial attention condition.

In line with our expectations (see Figure 4.3, 4.4 and 4.5), ERP components after nociceptive stimulation (N130, N180, P340, P560) peak at a later moment in time than the components in our previous study with intracutaneous stimuli (N100, N150, P260, P500; Van der Lubbe et al., 2012). This seems due to the selective involvement of A δ fibers in the current study, which implies a delay in processing speed.

The N130 had a maximum above contralateral central sites (i.e., T7) and was much smaller above symmetrical ipsilateral sites (T8; see Figure 4.3 and 4.4). Most likely, this component originates from SI and/or SII cortex (see Thees, Blankenburg, Taskin, Curio, & Villringer, 2003; Van der Lubbe et al., 2012). The effect of stimulus intensity concerned the contralateral site, which replicates and extends the findings from our previous study with intracutaneous electrical stimuli to nociceptive stimuli. Likewise, we additionally observed increased negativity for cued relative to uncued stimuli, but this effect did not interact with any other factor. This observation indicates that the influence of spatial attention concerns an early processing level, but it also suggests that it is less specific than the effect of stimulus intensity. This confirms our earlier suggestion that attentional effects are more diffuse and cannot so easily be interpreted as gain modulation (see Van der Lubbe et al., 2012). Unlike the results in the study of Eimer and Foster (2003), the observed attentional effect was independent of attention condition. So, in contrast with our expectations, no evidence was obtained for increased efficiency of attentional selection in the case of sustained spatial attention for this early ERP component.

The N180 also peaked above contralateral (slightly less lateral: C5) central sites but was now also visible above symmetrical ipsilateral sites (C6; see Figure 4.3 and 4.4). This component probably originates from SII and/or the insula (see Van der Lubbe et al., 2012). A main effect of stimulus intensity was found, but it no longer had a clear contralateral focus. Interestingly, observed effects differed depending on the relevant stimulus intensity, which varied between groups. For participants that had to press a foot pedal for low intensity (two-pulse) stimuli, an intensity effect was present only in the transient spatial attention condition but not in the sustained spatial attention condition. As a comparison of effects on the N180 mainly shows an enhancement for five-pulse stimuli in the transient attention condition, this might point to a less interruptive effect of these stimuli when attention is continuously focused on the same arm. Thus, sustained spatial attention seems to dampen the orienting effect towards high intensity (five-pulse) nociceptive stimuli when these stimuli do not require a response. Other support for a

specific effect due to sustained spatial attention was the observation of a selective cuing effect on the N180. This cuing effect was only observed for five-pulse stimuli in the sustained attention condition, but not in the transient attention condition, while no cuing effects were observed for two-pulse stimuli. The cuing effect concerns a reduction of the N180 for uncued five-pulse stimuli in the sustained attention condition, which might point to more efficient inhibition of these stimuli. Thus, for the N180, we observed some support for increased efficiency of attentional selection in the case of sustained spatial attention, although effects were quite different from those observed by Eimer and Foster (2003).

The P340 had a clear maximum above the vertex and given its topography (see Figure 4.3) and slight delay with regard to our previous study it may be considered as a P3a component. Based on previous studies, it seems likely that this component originates from ACC (Thees et al., 2003; Van der Lubbe et al., 2012). Both stimulus intensity and cue had largest effects at this site. However, effects were completely opposed, as five-pulse stimuli produced a larger P340 than two-pulse stimuli, while uncued stimuli produced a larger P340 than cued stimuli. These findings replicate and extend the effects reported in our earlier study (Van der Lubbe et al., 2012). There, we argued that the observed increased P3a component for uncued stimuli reflects “a call for attention”. As no clear interactions were observed with attention condition, our results seem to imply that a sustained focus of attention does not reduce this orienting effect. As a consequence, when nociceptive stimuli belong to the attentional set, orienting effects remain strong, even if attention is continuously directed at another location. Apparently, only in the case of total irrelevance of nociceptive stimuli, when they occur at to be ignored locations and do not belong to the attentional set, then the orienting effect is no longer observed (see Blom et al., 2012; Yamasaki, Kakigi, Watanabe, & Hoshiyama, 2000; Dowman, 2004). Thus, despite some slight differences due to sustained spatial attention for the N180, results for the P340 provided no evidence for the view that sustained attention increases the efficiency of attentional selection.

The P560 was not clearly visible as it was spread over the scalp and over time. Nevertheless, specific effects were observed above central and parietal sites. Above the Cz electrode, we observed a highly selective reduction of positivity for those nociceptive stimuli that required a foot pedal press. Specifically, smallest amplitudes were observed for cued two-pulse stimuli for the low intensity group, and for cued five-pulse stimuli for the high intensity group. This effect replicates our previous findings (Van der Lubbe et al., 2012) and may be understood in terms of increased motor activity, which induces negativity and thereby cancels the earlier positivity. This idea of the involvement of another process that induces negativity for stimuli that require a response could actually provide an alternative account for the earlier reduced positivity (i.e., the P340) for cued stimuli. If this activity is already triggered at an earlier stage for cued stimuli in general, then it may explain the observed reduction in positivity. At a later stage, this effect may vanish

for stimuli that require no response, while it continues for those stimuli that should be followed by a pedal press. Thus, as an alternative, the increased P340 for uncued stimuli might not reflect “a call for attention” but the decreased positivity for cued stimuli might reflect “a call for action”. Nevertheless, this alternative interpretation seems difficult to reconcile with the interpretation of the P3a of Polich (2007).

Above parietal sites, we only observed an effect of stimulus intensity on the P560 (i.e., decreased positivity for two-pulse stimuli) for the high intensity group, and not for the low intensity group. This might reflect less processing of two-pulse stimuli when they are used as non-targets, but apparently, this effect does not occur for five-pulse stimuli for the low intensity group. This might be related to the idea that five-pulse (high intensity) nociceptive stimuli cannot easily be ignored. Finally, we observed that the cuing effect is larger in the sustained than in the transient attention condition, which suggests that attention is more effective when attention is continuously directed at one side. Thus, on the basis of the parietal P560, it may be argued that sustained spatial attention increases the efficiency of attentional selection.

Together, our results revealed some subtle differences in the effects of spatial attention in the sustained and transient attention conditions, but no effect on the earliest component was observed while such an effect was reported in the study of Eimer and Forster (2003). Possibly, some small procedural differences may have played a role. In our setup, we decided to make the difference between the two conditions as small as possible, as we also presented a precue on every trial in the sustained attention condition. In the study of Eimer and Forster (2003) no cue was presented in this condition, as a consequence, there may have been differences in alerting effects as well (e.g., see Van der Lubbe, Keuss, & Stoffels, 1996), which may be responsible for the observed differences. Another reason might be that the level at which spatial attention affects nociception differs. New experiments seem needed to clarify the observed discrepancy.

In conclusion, several aspects of our EEG results show that the type of attentional manipulation employed (sustained or transient) affects the orientation of attention to the upcoming location of a nociceptive stimulus. It appears that the orientation of attention is more efficient when attention is directed to a single location over a longer period of time (sustained attention) compared to when attention is constantly shifted between multiple locations. Nevertheless, sustained attention seems to be insufficient to fully suppress the call for attention towards nociceptive stimuli. This seems to work only if nociceptive stimuli are totally irrelevant. The latter findings may have implications for the development of new therapeutical strategies to deal with chronic pain.

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Chapter 5

Pain attracts and distracts: The effect of nociceptive stimulation on the attentional blink

Abstract

The present study examined the possible disruptive effect of acute pain on the temporal allocation of visual attention by using the attentional blink paradigm. Participants had to detect targets (digits), either one (T1) or two (T1 and T2) that appeared in a stream of non-targets (letters). On one-third of the trials a nociceptive intracutaneous stimulus of three possible intensities was delivered to the forearm at T1 onset. On the other two-third of baseline trials standard findings were replicated: participants correctly reported T1 on most of the trials, a Lag-1 sparing effect was observed when T2 directly followed T1, and an attentional blink was observed when T2 and T1 were separated by two non-targets. Presentation of the nociceptive stimuli resulted in enhanced T1 accuracy scores, which was ascribed to immediate arousal. Interestingly, the influence of nociceptive stimulation showed a biphasic pattern for high intensity stimuli as it enhanced the attentional blink for T2. The fact that only high intensity stimuli displayed this pattern underlines the relevance of the intensity of the nociceptive stimulus for this disruptive effect. In sum, a biphasic effect was observed with an initial benefit and a later cost after the nociceptive stimulus, suggesting that acute pain results in a transient modulation of the available attentional resources.

5.1 Introduction

The subjective perception of pain plays a crucial role in human survival as it stops ongoing behavior and directs attention to its source (Eccleston & Crombez, 1999). Pain enhances immediate arousal, leading to an increase in the available attentional resources (Price & Harkins, 1992; Nissen, 1977). In the current study, we examined the effects of painful stimulation on the availability of attentional resources over time by using the attentional blink (AB) paradigm. In this paradigm a stream of stimuli, generally letters or digits, are presented with a speed of approximately 10 stimuli per second. Remarkably, when only two stimuli in the stream are relevant, a first target (T1) and a second target (T2), participants regularly fail to accurately report T2 when it is presented in a time window up to half a second after T1. Raymond, Shapiro and Arnell (1992) labeled the deficit to accurately identify T2 the ‘attentional blink’. The AB may indicate that there is a limit in the currently available attentional resources. In their review, Dux and Marois (2009) indeed suggested that the AB reflects the competition between targets for attentional resources. As T1 is registered it enters a processing stage that uses up the at that moment available attentional resources. When T2 is presented directly after T1, it may still benefit from the initiated processing of T1. As a result, T2 is correctly reported to the same extent as T1, the so-called Lag-1 sparing (Hommel & Akyürek, 2005). However, T2 cannot benefit from the initiated processing of T1 when T1 and T2 are separated by at least one non-target. It is suggested that the processing of T1 and the subsequently presented non-target renders the attentional resources temporarily unavailable for processing resulting in the impaired T2 report (Dux & Marois, 2009). This trade-off theory incorporates several different theories proposed over the last years to explain the origin of the AB (Bowman & Wyble, 2007; Chun & Potter, 1995; Olivers, Van der Stigchel, & Hulleman, 2007; Raymond et al., 1992; Shih, 2008; Taatgen, Juvina, Schipper, Borst, & Martens, 2009). Based on this trade-off theory, it may be expected that any effect of a concurrent task requiring attentional resources should affect the identification of T1 and/or T2. Therefore, the AB paradigm seems well suited to examine the attentional effects of nociceptive stimuli presentation over time.

In our AB task, T1 was presented on all trials, followed on 75% of the trials with T2 with either zero (lag 1), two (lag 3) or four (lag 5) intervening non-targets. We expected to observe an AB with lag 3 as well as Lag-1 sparing. In order to examine the disruptive effect of pain over time, nociceptive stimuli were presented at T1 onset on 33% of the trials. This low proportion maintains the attentional demanding properties of the nociceptive stimuli (i.e., their novelty), but will result in enough trials for data analysis. On the remaining proportion of trials, no nociceptive stimuli were presented. We expected that simultaneous presentation of nociceptive stimuli with T1 would induce immediate arousal, leading to an increase in the available attentional resources (Price & Harkins, 1992; Nissen, 1977) and thereby increase the amount of attentional resources

allocated to T1. Nociceptive stimuli of low, medium, and high intensity were presented to examine whether increased intensity would induce stronger effects on T1 accuracy and the magnitude of the AB (Nissen, 1977; Vroomen & de Gelder, 2000). We manipulated the intensity of the nociceptive stimuli by varying the number of pulses, which has the advantage that the same amount of pain specific A δ -fibers are stimulated but only to a different extent (see Van der Heide, Buitenweg, Marani, & Rutten, 2009). Based on the trade-off theory of the AB we expected that with an increase in attentional resources allocated to T1 due to the nociceptive stimuli, fewer resources would be left for upcoming targets. This decrease in available resources was therefore expected to result in a larger AB. This effect was additionally thought to be more pronounced when the intensity of the nociceptive stimuli would be larger.

5.2 Methods

Participants

Eighteen healthy participants (4 males and 14 females; age: 19-28 years), without a history of neurological disorder(s), took part in the experiment. Each participant received so called 'participant credits' in return for participation. The experiment lasted for approximately one hour. Handedness was assessed with the Annett Handedness Inventory (Annett, 1970). All participants could be classified as right-handed except for one who scored as ambidextrous. Every participant received a detailed explanation of the procedure and signed a written informed consent before participating. The Medical Ethical Committee of Medisch Spectrum Twente, Enschede, The Netherlands (NL31474.044.11/P11-11) approved the followed procedures.

Stimuli and Procedure

Intracutaneous electrical stimuli were generated by a Digitimer DS5 constant current stimulator (Digitimer, Welwyn Garden City, UK) and were delivered through a bipolar concentric electrode (Inui, Tran, Hoshiyama, & Kakigi, 2002). Bipolar concentric electrodes selectively activate the A δ -fibers using a short needle that slightly penetrates the epidermis (Mouraux, Iannetti, & Plaghki, 2010; Steenbergen, Buitenweg, Trojan, Van der Heide, Van den Heuvel, Flor et al., 2012). The electrode was placed over the median nerve at the left forearm. Stimuli of three intensity levels were used with fixed stimulus currents matching individual participants' thresholds (see below). A difference in stimulus intensity was achieved by using pulse trains with different number of pulses (see Van der Heide et al., 2009). The low intensity stimuli (a single-pulse stimulus) consisted of one rectangular pulse for a duration of 1 ms, the medium intensity stimuli consisted of a volley of three rectangular pulses of 1 ms each (the three-pulse stimulus) and the high intensity stimuli consisted of a volley of five rectangular pulses of 1 ms each (the five-pulse stimulus). An interpulse interval (IPI) between two subsequent pulses in

the pulse train of 5 ms was chosen, which is long enough to control for possible temporal summation of pulses (Van der Heide et al., 2009). The duration of the stimuli were 1 ms for single-pulse stimuli, 13 ms for three-pulse stimuli and 25 ms for five-pulse stimuli. Participants commonly do not perceive any differences in stimulation durations between the different stimuli.

The intensities of the stimulus current matching the participants' individual sensation threshold, pain threshold and pain tolerance threshold were assessed in a pretest. These thresholds were determined by increasing the intensity of a five-pulse stimulus with steps of 0.1 mA starting at a value of zero mA. The sensation threshold was defined as the first intensity that participants were able to detect (mean sensation threshold = 0.5 mA; standard error [SE] 0.02). With increasing current intensities, the perceived intensity of the stimulus changed from a small prickling sensation to a somewhat painful prickling sensation. The latter sensation corresponds with the pain threshold (0.7 mA; SE 0.1). Increasing the current intensity even further causes the sensation to become unpleasant but bearable, corresponding to the pain tolerance level (1.2 mA; SE 0.3). The latter intensity was employed during the experiment.

Task

The experiment consisted of a standard rapid serial visual presentation task (adapted from Slagter, Lutz, Greischar, Francis, Nieuwenhuis, Davis et al., 2007), being divided into four blocks. Each block contained 108 trials. A trial started with a black fixation cross displayed at the center of a grey background for 1780 ms. Subsequently, a 21 elements long stream of non-targets (randomly chosen letters from A-Z), of which one or two were replaced by targets (randomly chosen digits between 2 and 9), was presented at fixation with the following restrictions. The letters B, I, O, Q and S were excluded from the set of non-targets to avoid confusion with targets. Each element was displayed for 60 ms and none of the elements were repeated in a trial. The first part of the stream had a length varying randomly between 8 and 15 non-targets. This initial stream was followed by T1 and T2 if presented on that trial. T2 was presented on 324 trials (75%) and, more specifically, at lag 1, lag 3, and lag 5 in 108 trials (25%) each. Participants were informed that T1 was always present in each stream, but that T2 was absent in some trials. To complete the 21 elements long stream, a varying number between 12 and one of non-targets was displayed depending on the number of non-targets presented in the first part of the stream. At the end of each trial, the participant was asked to report T1 using the computer keyboard. Subsequently, participants were asked to report T2 whenever it was presented. If participants were unsure whether T2 was presented, they were instructed to guess T2. If participants were sure that T2 was absent they had to indicate this by typing in '0'. A new trial started directly after T2 reporting. A short resting break of 35 seconds was provided after each third of a block.

An intracutaneous electrical stimulus was presented at T1 onset on 144 trials (33%

of all trials). This was either a single-pulse, a three-pulse or a five-pulse stimulus, all with equal probabilities (each on 48 trials). The participants were informed beforehand that nociceptive stimuli would be presented with these probabilities but that they should ignore these stimuli.

Finally, before the first block and after each of the four succeeding blocks an intensity-rating session was carried out in which participants were instructed to rate the intensity of the presented nociceptive stimuli using a visual analogue scale (VAS-scale). These ratings were used to control for possible hypervigilance or habituation, which might occur in the experiment due to repeated stimulation. Single-pulse, three-pulse and five-pulse stimuli were each presented twice in random order in each rating session. The scale ranged from “0” to “10”. A value of “0” matched with ‘no feeling at all’, a value of “5” matched with the pain threshold, whereas a value of “10” matched with ‘extremely painful’. Participants received the instructions on the VAS before the first intensity-rating session. Stimulus presentation, response registration and production of external triggers were controlled by E-Prime Software (version 2.0).

Data analysis

Stimulus intensity ratings assessed with the VAS were analyzed with a repeated measures ANOVA with Intensity (single-pulse, three-pulse, and five-pulse) and Session (session 1, session 2, session 3, session 4, and session 5) as within-subjects factors. The differences between single-pulse, three-pulse and five-pulse stimuli were assessed with repeated contrast analyses. The change in intensity ratings over time was assessed with a linear contrast analysis (Blom, Wiering, Van der Lubbe, 2012).

T1 accuracy was analyzed with a repeated measures ANOVA with the within-subject factor Intensity (baseline, single-pulse, three-pulse, and five-pulse). T2 accuracy was analyzed with a repeated measures ANOVA with the factors Lag (lag 1, lag 3, and lag 5) and Intensity (baseline, single-pulse, three-pulse, and five-pulse). T2 was considered correct on trials in which T1 was also correctly reported. However, an effect often observed in AB experiments is that participants report T2 as having appeared before T1 in the lag 1 condition on a substantial proportion of trials (often 25% or more; see e.g. Chun & Potter, 1995; Olivers, Hilkenmeier, & Scharlau, 2011). A similar effect was observed in the current study, namely on 30.8 (2.8)% of the lag 1 trials participants exchanged T1 with T2. The order reversals did not depend on Intensity, $F(3,51) = 0.4$, $p = 0.760$. The trials in which the participant correctly identified both targets but ordered them inappropriately were scored as correct. This procedure was also followed for trials with a lag of 3 and lag 5.

To analyze the effect of nociceptive stimulation on the AB the lag that displayed the largest blink, most likely Lag 3, was selected for further analyses with paired sample one-sided t-tests. The Greenhouse-Geisser ϵ correction was applied to the repeated measures ANOVAs to correct for violations of the sphericity assumption whenever appropriate.

5.3 Results

VAS scores

Figure 5.1 shows the intensity ratings over time as estimated with the VAS. A repeated measures ANOVA with the factors Intensity and Session revealed a main effect of Intensity, $F(2,34) = 98.0$, $\epsilon = 0.57$, $p < 0.001$. Participants rated the intensity of single-pulse stimuli (1.6; SE 0.1) significantly lower than the intensity of three-pulse stimuli (5.0; SE 0.3), $F(1,17) = 100.7$, $p < 0.001$, while three-pulse stimuli received lower intensity ratings than five-pulse stimuli (5.8; SE 0.4), $F(1,17) = 33.7$, $p < 0.001$. Furthermore, a significant main effect of Session was observed, $F(4,68) = 6.0$, $p < 0.001$, which indicates that the ratings to the different stimulus intensities decreased over time (see Figure 5.1). An interaction between Intensity and Time was observed, $F(8,136) = 3.3$, $\epsilon = 0.56$, $p = 0.012$, which is explained by the interaction between single-pulse stimuli and three-pulse stimuli ratings in session one and session two, $F(1,17) = 13.3$, $p = 0.002$. The difference between the single-pulse ratings and three-pulse ratings increases in the session two compared to session one.

Figure 5.1. Mean stimulus intensity ratings for single-pulse, three-pulse and five-pulse stimuli obtained in stimulus rating sessions one to five. Error bars represent standard errors of the mean.

T1 and T2 accuracy

T1 accuracy. A main effect of Intensity was observed for T1 accuracy, $F(3,51) = 7.4$, $\epsilon = 0.64$, $p = 0.003$. Presentation of single-pulse stimuli, $t(17) = -4.5$, $p < 0.001$, three-pulse, $t(17) = -3.2$, $p = 0.003$, and five-pulse stimuli, $t(17) = -4.2$, $p < 0.001$, resulted in improved T1 accuracy as compared to baseline (see Table 5.1). The accuracy scores for the three stimulus intensity conditions did not differ from each other, $t < 1.9$, $p > 0.071$, which was assessed with paired samples t -tests.

T2 accuracy. T2 accuracy (see Figure 5.2) for the different lags shows a standard AB with Lag-1 sparing. As shown in Figure 2, T2 accuracy at lag 1 was as high as T1 accuracy (Lag-1 sparing) and then dropped by more than 30% at lag 3 to a accuracy level of 52.4 (4.4)%, which is indicative of the AB. The repeated measures ANOVA on T2 accuracy revealed a main effect of Lag, $F(2,34) = 42.8$, $p < 0.001$. Accuracy scores on T2 were significantly lower at lag 3 as compared to lag 1, $F(1,17) = 77.9$, $p < 0.001$. After this initial drop in accuracy scores did not significantly change between lag 3 and lag 5 $F(1,17) = 2.4$, $p = 0.139$. Nevertheless, the AB seems most prominent at lag 3, in line with our expectations. Presentation of a nociceptive stimulus at T1 onset did not affect T2 accuracy at lag 1 (see Figure 5.2) irrespective of the intensity of the presented stimulus, $t < 0.6$, $p > 0.290$.

Table 5.1. Overview of the mean accuracy scores ($\pm SE$) of T1 and T2|T1 at lag 1, lag 3 and lag 5 for baseline trials and with either single-pulse, three-pulse, or five-pulse stimuli presented at T1 onset.

	T1 accuracy %	T2 T1 accuracy %		
		Lag 1	Lag 3	Lag 5
Baseline	73.9 (2.3)	88.7 (3.3)	56.2 (5.1)	60.0 (4.3)
Single-pulse	81.3 (3.0)	90.6 (2.7)	50.8 (6.0)	63.1 (5.9)
Three-pulse	78.2 (2.3)	88.3 (4.8)	53.7 (5.5)	53.0 (5.8)
Five-pulse	80.3 (2.0)	86.9 (5.6)	48.7 (5.6)	56.6 (5.5)

Interestingly, detailed analyses on the AB at lag 3 showed that the presentation of nociceptive stimuli at T1 onset affected the magnitude of the AB, although only in the case of five-pulse stimuli. T2 accuracy significantly dropped when five-pulse stimuli were presented at T1 onset, $t(17) = 1.8$, $p = 0.045$, as compared to baseline. In contrast, presentation of single-pulse stimuli, $t(17) = 1.3$, $p = 0.106$, or three-pulse stimuli, $t(17) = 0.5$, $p = 0.322$, at T1 onset had no effect on the AB relative to baseline.

Analyses on lag 5 trials (see Table 5.1) showed that the presentation of single-pulse stimuli, $t(17) = -1.0$, $p = 0.157$, or five-pulse stimuli, $t(17) = 1.1$, $p = 0.138$, had no effect on the T2 accuracy compared to baseline. However, presentation of three-pulse stimuli at T1 onset did have a marginal negative effect on T2 accuracy, $t(17) = 1.8$, $p = 0.046$.

5.4 Discussion

In the current study, we examined the attractive and disruptive effects of nociceptive stimulation on the temporal allocation of visual attention by employing the AB paradigm. Nociceptive stimuli were delivered to the forearm of the participants at T1 onset in one-third of the trials. Intracutaneous pulse train stimulation was used to modulate

Figure 5.2. Mean T2/T1 (T2 accuracy under condition that T1 was correctly identified) accuracy ($\pm$ SE) at lag 1, lag 3, and lag 5 for trials without presentation of nociceptive stimuli at T1 onset (baseline) and the mean percentage of correct responses to T2 for trials with either single-pulse, three-pulse, or five-pulse stimuli presented at T1 onset.

the intensity of the stimuli. It was expected that the nociceptive stimuli would induce immediate arousal, thereby increasing the allocation of attentional resources towards the concurrently presented T1 relative to a baseline condition without nociceptive stimuli. The increased allocation of resources to T1 was additionally expected to decrease the available resources for T2, resulting in an enhanced AB.

Our findings concerning the baseline trials replicated the standard results with the AB paradigm, a relatively high accuracy of T1 report, Lag-1 sparing when T2 occurred directly after T1, and a pronounced AB with two intervening non-targets between T1 and T2 (see Hommel & Akyürek, 2005; Raymond et al., 1992).

Most relevant were the results on trials in which nociceptive stimuli were presented at T1 onset relative to baseline. First, results showed that the intensity manipulation was effective, because with an increasing number of pulses the stimuli were rated as more painful. T1 report was more accurate in the case of the presentation of nociceptive stimuli, although this effect was unaffected by their intensity. With regard to the report of T2 at the AB, we observed that accuracy decreased when high intensity stimuli were presented at T1 onset. The observation that the synchronous presentation of an irrelevant nociceptive stimulus at T1 onset enhanced the identification of T1 suggests that the nociceptive stimulus led to immediate arousal, thereby increasing the available attentional resources (e.g., see Nissen, 1977; Vroomen & de Gelder, 2000). Alternatively, this effect might be due to crossmodal facilitation. The latter explanation would be in line with findings from studies showing the effects of a temporal cue in one modality, which

enhances the processing of a stimulus in another modality (see Coull & Nobre, 1998; Santangelo, Van der Lubbe, Olivetti Belardinelli, & Postma, 2008; Weinbach & Henik, 2012). However, we prefer an explanation in terms of immediate arousal, which freed up more attentional resources for the processing of T1 as it better fits with the results observed at Lag 3 after nociceptive stimulation at T1 onset. Namely, after the initial enhancement in T1 accuracy, T2 accuracy at the AB decreased. The AB at Lag 3 was larger when a five-pulse stimulus was presented at T1 onset compared to when no stimulus was presented. This biphasic effect suggests that the enhancing effect of nociceptive stimuli on attention, as observed at T1, is only temporary and that it comes at a cost, which is an effect that you may predict in the case of immediate arousal changes, and not in case of crossmodal facilitation. The observed effects on T1 and T2 accuracy indeed exhibit remarkable similarities with the trade-off theory of the AB, which argues that the AB reflects a competition for attentional resources (see Dux & Marois, 2009). The effects of the five-pulse stimuli disappeared when four non-targets separated T1 and T2, which also suggests that the disruption due to nociceptive stimulation was temporary.

As indicated above, the biphasic effect at lag 3 was only observed for five-pulse stimuli. The perceived valence of the presented nociceptive stimuli seems quite relevant for this intensity specific effect as the intensity of the five-pulse stimuli was always rated as being painful. Thus, immediate arousal in response to nociceptive stimuli is visible irrespective of the nociceptive stimulus intensity, while it seems that only the stimuli rated above pain threshold display the biphasic effect. This observation seems in line with the suggestion that higher intensity stimuli elicit a faster compulsion to escape compared to lower intensity stimuli, as they signal a higher state of danger (Eccleston & Crombez, 1999).

In conclusion, we provided evidence that the presentation of nociceptive stimuli affects temporal visual attention. Pain, irrespective of intensity, induces immediate arousal, which may be expected by its crucial role for human survival, but this effect comes slightly later with a cost when the pain intensity is high, as awareness of subsequent information is temporally reduced.

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Chapter 6

General discussion

Attention and pain are thought to be strongly interconnected. Namely, pain has the ability to stop ongoing behavior and direct attention to an affected body part in order to deal with a potential life-threatening situation (i.e., exogenous orienting; Eccleston & Crombez, 1999). In contrast, when attention is actively directed away from pain (i.e., distraction, a form of endogenous orienting) this generally results in attenuated pain sensations. The primary aim of this dissertation was to gain further insight in this supposedly close interconnectedness of pain and attention. In this general discussion I will first focus on the underlying mechanisms that explain how attention affects pain. This concerns the level at which attention affects nociception, and the varying roles of attention in the case of different attentional manipulations (Chapter 2 to 4). Secondly, the question was raised under what task conditions pain stimuli induce exogenous orienting effects (Chapter 2 to 5). Thirdly, this orientation of attention towards nociceptive stimuli may differ between various attention manipulations. In addition, it may operate within different spatial reference frames, so the question is what reference frame is actually dominant in the case of nociception (Chapter 3).

Apart from these important aspects, I will also focus on the relation between the pain experience and objective measures of nociceptive processing (Chapter 2 to 5). I will focus on a fundamental problem in the research on pain and attention and its consequences for research in this field. The question will be addressed whether measuring electrophysiological responses might possibly lead to a more objective estimate of a pain experience.

Subsequently, I will focus on the methods used in this dissertation to examine the influence of attention on pain. Here I will focus on the crucial role of the employed stimulation site (Chapter 2), and consider the respective roles of tactile and nociceptive fibers in the various experiments (Chapter 2 to 5) and the possible consequences for the answers to the other research questions.

Finally, I will discuss some practical implications of the current research, and highlight some research topics that should be pursued in future experiments. The general discussion will be closed with a number of concluding remarks

The mechanisms underlying pain and attention

In this first section I will focus on the underlying mechanisms that explain how attention affects pain. This concerns the level at which attention affects nociception and the varying roles of attention in the case of different attentional manipulations. The studies presented in Chapter 2 to 4 employed the EEG technique (see Chapter 1) to measure the electrophysiological responses to electrocutaneous nociceptive stimuli under different attentional manipulations. The study presented in Chapter 2 employed two sustained distraction tasks (word-association or arithmetic task) to direct attention away from the presented nociceptive stimuli. Whereas, the studies presented in Chapter 3 and 4 employed spatial attention tasks (similar to the Posner task) in which endogenous

spatial attention was either directed to the location on the body at which a nociceptive stimulus was presented or to another location.

In general, two distinct components were observed in the ERPs following the presentation of the nociceptive stimuli. The early negative component, the N1, is thought to represent activity within primary and/or secondary somatosensory cortex contralateral to the stimulated body part (Desmedt & Robertson, 1977; García-Larrea, Frot, & Valeriani, 2003; Thees, Blankenburg, Taskin, Curio, & Villringer, 2003; Valentini, Hu, Chakrabarti, Hu, Aglioti, & Iannetti, 2012; Van der Lubbe, Buitenweg, Boschker, Gerdes & Jongasma, 2012). A later positive component, the P2/P3a, is thought to represent activity within the ACC (Van de Lubbe et al., 2012; Lenz, Rios, Zirh, Chau, Krauss, & Lesser, 1998). The results obtained in the different studies reveal that both components are affected by the employed attentional manipulations.

The employed sustained distraction manipulation in Chapter 2 resulted in attenuated amplitudes of the N1 components. The observed attenuation of the N1 component most likely reflects reduced somatosensory processing of the nociceptive stimuli as a result of inhibition of the contralateral somatosensory cortex due to distraction resulting in a diminished response. The studies presented in Chapter 3 and 4 both employed spatial attention tasks to manipulate attention. This employed manipulation did not affect the N1 component in Chapter 3, whereas in Chapter 4 attenuated amplitudes of the N1 component were observed in response to unattended nociceptive stimuli. This difference in results is likely the result of small differences in the employed cueing paradigm. Namely, Chapter 3 involved both valid and invalid cues, while the study in Chapter 4 concerned a 100% valid, and compulsory cue, as ignoring the cue leads to errors. Thus, attention directed away from the location of the pain stimuli or being occupied with a secondary task leads to reduced processing in somatosensory areas, but only if it is 100% sure that the pain stimulus can be ignored. This effect also occurs when the pain stimulus is part of the task set (i.e., when it contains target features).

Until recently it was still a matter of debate whether the late positive deflection should be understood as a P2 or a P3a component. Dowman (2004) suggested that the positive deflection indexes a stimulus evaluation process where the sensory input is compared to an environmental template maintained by working memory and should therefore be denoted as a P2 component reflecting pain-specific activation. The P3a component, however, is thought to reflect an orienting response of attention (Polich, 2007). The common source (i.e., ACC) of these components (P2 and P3a) already indicates that they may very well reflect a single underlying process (see also Lenz et al., 1998). The results presented in Chapter 2 revealed a strong sequential dependency of this P2/P3a component comparable to classical P3a findings (see Polich, 2007). Based on these findings, I conclude that the positive central deflection (maximal at the vertex) around 200 to 400 ms should be understood as a P3a component.

If we accept this interpretation, then I may turn to the question under what

circumstances presentation of a painful stimulus induces an orienting response. A clear orienting response was observed in our studies presented in Chapter 3 and 4 (transient spatial attention manipulation) in response to spatially invalidly cued stimuli relative to validly cued stimuli, while the sustained distraction manipulation employed in the study presented in Chapter 2 resulted in attenuated amplitudes of the P3a component. It was questioned and examined in the study presented in Chapter 4 whether the employed attentional manipulations, sustained versus transient spatial attention, differentially affects the processing of nociceptive stimuli. The employed LPS analyses technique to examine the orienting phase preceding the nociceptive stimuli revealed that the orienting effects involved slightly different frequency bands, with more dominant lateralized alpha activity in the transient spatial attention condition, and more dominant lateralized beta activity in the sustained spatial attention condition. This indicated that the orientation of attention appears to be more efficient when attention is directed to a single location over a longer period of time (sustained attention) compared to when attention is constantly shifted between multiple locations. Nevertheless, the absence of an effect on the P3a component due to the employed attentional manipulation showed that the orienting response is induced irrespective of the employed spatial attention manipulation.

Another difference between the studies presented in Chapter 2 and Chapters 3 and 4 was that all of the presented stimuli were task-relevant in the studies presented in Chapter 3 and 4, as a response is demanded in response to both validly and invalidly cued stimuli, whereas in the study presented in Chapter 2 (Blom et al., 2012) all painful stimuli presented during the distraction tasks had to be ignored. So in general, there seems to be an exogenous orienting effect of nociceptive stimuli, but only if these stimuli are part of the same task set. In other words, the exogenous orienting effect of nociceptive stimuli can be abolished only when they occur at to be ignored locations and do not belong to the task set (e.g., see also Dowman, 2014).

It was further questioned whether the orienting of attention due to the presentation of nociceptive stimuli impairs the maintenance and control of ongoing information processing (Troche, Houlihan, Connolly, Dick, McGrath, Finley et al., 2015) or whether it enhances immediate arousal, resulting in a temporary increase in the available attentional resources (Price & Harkins, 1992; Nissen, 1977; Ring, Kavussanu, & Willoughby, 2013). In Chapter 5, an experiment was described in which participants performed an Attentional Blink task with first (T1) and second targets (T2). On one-third of the trials, a nociceptive intracutaneous stimulus of three possible intensities was delivered to the forearm at T1 onset. Although the presented nociceptive stimuli were not part of the task set, the presentation of the stimuli resulted in enhanced T1 accuracy scores. This suggests that although a painful stimulus can be ignored it does produce an orienting effect, which induces immediate arousal. However, a biphasic pattern was observed for high intensity stimuli as the attentional blink for T2 was enhanced. The fact that only high intensity stimuli displayed this pattern underlines the relevance of the intensity of a nociceptive

stimulus on its interruptive effects on attention (see Chapter 5).

Attention is thought to operate within different spatial reference frames (internal anatomically centered or external body-centered), so it was questioned which reference frame is actually dominant in the case of nociception. Chapter 3 describes two studies in which a conflict between the two reference frames was intentionally induced by instructing participants to cross their hands across the body midline on half of the trials. Participants were still instructed to follow the instruction of the centrally presented directional cue. The outcome of the two different analyses techniques (ERL and LPS) employed to examine endogenous orientation of attention revealed corresponding results. Crossing the hands did not lead to a reversal of neural activity over central sites (neither ADAN, nor mu power). In addition, a late direction attention-related positivity (the LDAP), reflecting the spatial selection process (see Gherri, Van Velzen & Eimer, 2007; Hopf & Mangun, 2000) and increased ipsilateral alpha power over occipito-parietal sites were observed irrespective of the hand position. These findings suggest that endogenous attention towards a location on the body in anticipation of a painful stimulus is primarily based on an external body-centered reference frame and not on an internal somatosensory reference frame (see also Favril, Mouraux, Sambo, & Legrain, 2014).

Is there an objective method to measure the pain experience?

An important question in the introduction of this dissertation concerns the relation between the subjective pain experience and more objective measures of nociceptive processing. As indicated, there seems to be a fundamental problem in research on pain and attention. Namely, to rate the intensity of presented nociceptive stimuli, participants have to be conscious, should be able to communicate, and most importantly, have to attend the pain stimuli. This last requirement implies that it is impossible to examine the effect of distraction on the subjective pain experience. Therefore, the question was raised whether measuring the electrophysiological responses to nociceptive stimuli might shed a light on the pain experience of to-be-ignored stimuli. The results obtained in the various chapters clearly reveal altered stimulus processing due the employed attentional manipulation. However, there is still the question whether observed electrophysiological effects may be related to differences in subjective pain experience. A dependency of the N1 and the P3a components to stimulus intensity was revealed in the various studies, resulting in larger amplitudes in response to high intensity stimuli compared to low intensity stimuli. This implies that there is a correlation between electrophysiological effects and stimulus intensity. So, an increase in the amplitude of the N1 component might reflect an increase in perceived intensity rating. However, the results obtained in the study presented in Chapter 2 revealed no significant difference on the amplitude of the N1 component between medium and high intensity, whereas a significant difference in intensity ratings was observed. This seems to imply that there is no direct correlation between the amplitude of N1 component and the reported subjective pain experience.

The P3a component, reflecting an orienting response of attention towards a presented nociceptive stimulus may be related to the pain experience, but does not seem to represent the amount of subjective pain a person is experiencing. As discussed above, the increased amplitudes of P3a component in response to a higher intensity stimulus is more likely the result of a larger interruptive effect on attention. The observed attenuation of neurophysiological responses over time was thought to reflect habituation to the presented stimuli (see Chapter 2). The fact that this decrease over time was independent from the type of attentional manipulation (attention or distraction) indicates that habituation is independent from attention.

The employed nociceptive stimulation methods

Several different methods can be employed to induce experimental pain for research purposes (see Chapter 1). Here I will consider the crucial role of the employed stimulation site and the respective roles of tactile and nociceptive fibers in the various experiments.

Previous EEG studies in which the effects of sustained distraction on stimulus processing were explored revealed conflicting results on the N1 component. In the study by Yamasaki, Kakigi, Watanabe and Hoshiyama (2000), sustained distraction resulted in a decrease in peak-to-peak (N1 and P3a) amplitude difference, whereas in the study by Dowman (2004) distraction resulted in an enlargement of the N1 component. In Chapter 2 we argued that this observed discrepancy is most likely the result of a difference in the employed stimulation locations. Namely, Dowman (2004) presented stimuli at the ankle, while several other studies stimulated on the fingertip or the forearm (Yamasaki et al., 2000; Van der Lubbe et al., 2012; Blom et al., 2012). Given the somatotopic organization of the somatosensory cortex, stimuli will be processed in different parts of cortex (Penfield & Boldrey, 1937). The representation of the ankle lies medial to the midline of the brain within the longitudinal fissure, whereas the representation of the fingertip or forearm is situated at a more lateral inferior location (Kandel, Schwartz, & Jessell, 2000). The vertical orientation (on the sagittal-plane) of the area representing the ankle in the longitudinal fissure may result in a different topography of the N1 component on the scalp compared to the topography of this component elicited by fingertip or forearm stimulation. In all the experiments presented in this dissertation, the employed stimulation location was always over the median nerve of the left or right forearm. This site of stimulation consistently results in activation above the contralateral somatosensory cortex. It is therefore suggested that the observed differences between other studies is probably the result of differences in the employed stimulation location on the body (see Chapter 2).

Two different methods of nociceptive stimulus presentation were employed in this dissertation, which were based on an electrical stimulation technique; transcutaneous and intracutaneous stimulation. The main difference between these methods is that transcutaneous stimuli are presented on the skin, whereas intracutaneous stimuli are

delivered right under the skin (epidermis). This later method is thought to selectively activate A δ -fibers (Mouraux, Iannetti, & Plaghki, 2010; Steenbergen, Buitenweg, Trojan, Van der Heide, Van den Heuvel, Flor et al., 2012), whereas with the former method tactile fibers (A β -fibers) are activated in addition to the pain specific fibers (A δ -fibers and C-fibers). According to research by Mouraux et al. (2010) the selective activation of the pain-only A δ -fibers can only be achieved with intracutaneous stimulation using low stimulus intensities (around 0.25 mA). The employed stimulus currents in my studies were approximately 5 times higher, which suggest that activation was not restricted to pain specific fibers. An earlier peak latency of the N1 component in response to transcutaneous stimuli was observed relative to when intracutaneous stimuli were employed. This observation suggests that transcutaneous stimulation additionally activated the faster conducting tactile fibers in combination with the slower conducting pain specific fibers, whereas intracutaneous stimulation activated pain specific fibers, at least to a large extent.

Some practical implications

The studies reported in this dissertation were intended to further clarify the interconnectedness between attention and pain on a fundamental level. It was revealed that attention directed away from the location of the pain stimuli or being occupied with a secondary task leads to reduced processing in somatosensory areas (N1 component) even when the pain stimulus is part of the task set. The orienting response of attention to nociceptive stimuli (P3a component) is only attenuated when pain stimuli are completely ignored and are not part of the task set. Altogether, the processing of nociceptive stimuli is affected the most when attention is focused on another modality (intermodal distraction). These observations seem to be quite relevant for the development of clinical therapies employed in relation to (chronic) pain management.

A good example in which intermodal distraction is employed to attenuate pain is the technique employed by some dentists, who hang a poster (e.g., Where's Waldo) or a TV on the ceiling to direct attention away from the dental treatment. In line with the results observed in the studies presented here, this method should attenuate the pain or discomfort associated with the treatment, or at least to a large extent. Indeed, conflicting results have been observed in other studies employing music, video and games to distract patients away from the dental treatment. In general, playing audio or music had no effect on the perceived anxiety, distress, intensity of pain and unpleasantness during the dental treatment (Seyrek, Corah, & Pace, 1984; Aitken, Wilson, Coury, & Moursi, 2002). The presentation of a solely a video has been shown to both non-effective (e.g., see Seyrek et al., 1984; Bentsen, Svensson, & Wenzel, 2001; Hoffman, Garcia-Palacios, Jensen, Furness, & Ammons, 2001; Bentsen, Wenzel, & Svensson, 2001;) and effective (e.g., see Seyrek, et al., 1984; Frere, Crout, Yorty, & McNeil, 2001; Ram, Shapira, Holan, Magora, Cohen, & Davidovich, 2010; Al-Khotani, Bello, & Christidis, 2016). More promising were the results obtained when employing virtual reality to direct attention away from

the dental treatment (Hoffman et al., 2001; Wiederhold, Gao, & Wiederhold, 2014; Asl Aminabadi, Erfanparast, Sohrabi, Ghertasi Oskouei, & Naghili, 2012). Virtual reality (VR) is a technology used to simulate a user's physical presence in a virtual environment using (software-generated) realistic images, sounds and other sensations. SnowWorld is a good example of an immersive VR game used to direct attention away from wound care (changing bandages and gel application). This game represents an ice virtual canyon with a river and waterfalls (Hoffman, Richards, Coda, Richards, Sharar, 2003). Results showed direct modulation of human brain pain responses by VR distraction (Hoffman, Richards, Coda, Bills, Blough, Richards et al., 2004) as it significantly reduced pain-related brain activity in the ACC, SI, SII, insula and thalamus.

It seems that the use of VR to direct attention away from the pain is probably the best practical example of intermodal distraction. A major disadvantage of earlier VR systems was the extremely high costs of these systems to create a fully immersive experience. However, recent technological developments open up new worlds of potential for the application of VR for applied games. Due to the technological progress made in relation to VR, these techniques have become much more affordable and different VR systems are now available for the general public (e.g., Samsung Gear VR, Google Daydream, HTC Vive and the Oculus Rift). This will certainly enable the development of 'Pain VR' applied games, which can be used by patients to manage pain in a home environment.

The observation that attention affects nociceptive processing underlines the effectiveness of cognitive-behavioural therapies based on attentional manipulations in relation to chronic pain management. A specific cognitive-behavioural technique that is completely based on the control of attention is mindfulness. The goal of mindfulness training (e.g., the mindfulness-based stress reduction (MBSR) training; Kabat-Zinn, 1982) is to acquire a state of nonreactive, metacognitive awareness of present-moment that promotes adaptive regulation of attention and emotion (Lutz, Slagter, Dunne, & Davidson, 2008). A meta-analysis investigating the effects of MBSR for adults with chronic medical conditions (including chronic pain) concludes it is able to reduce distress and disability (Bohlmeijer, Prenger, Taal, & Cuijpers, 2010). Chapter 4 is based on data collected as part of a larger study examining the effects of mindfulness (MBSR training) on the processing of nociceptive stimuli. Preliminary results from this study showed that mindfulness reduces the call for attention (decreased amplitudes of the P3a component) by nociceptive stimuli (Van der Lubbe, De Kleine, Blom, Schreurs, & Bohlmeijer, 2013). These results underline the high potential of mindfulness, as a part of a behavioural therapy, in treating and coping with chronic pain.

Future research

As described in Chapter 1, the presentation of nociceptive stimuli activates a large neural network (see Chapter 1). The data presented in this dissertation only display the effects of attention on the neural processing of nociceptive stimuli thought to be generated in

individual brain areas. Future research should further examine the influence of attention on this (inter)connectivity between the different areas in response to nociceptive information. This makes it possible to obtain an even better understanding on the effects of attention on the neural processing of nociceptive stimuli.

Furthermore, the method used to induce experimental pain in our studies resulted in a painful stimulus that is generally perceived as a small pinprick. Although it is excellent for experimental research, as it only selectively activates A δ - and C-fibers, it cannot be compared to pain induced by actual real events. The affected area in such an event is usually much larger, therewith activating a much larger area of the somatosensory cortex and other areas in the brain. Future research should address this issue, but it is questionable whether this is possible. Namely, the selection of a homogeneous group with participants experiencing similar amounts pain to study will be very difficult. Additionally, it is probably difficult to calculate ERPs from EEG measurements, as multiple trials are needed to obtain good data and pain induced by normal conditions is usually continuous. At the same time it will be difficult to obtain a baseline session of the participants without pain and a session with pain or vice versa. Medication could be used to attenuate the pain for the recording of a pain free session, but this will likely affect the attentional capabilities of the participants. In addition, earlier research has shown that the allocation of attentional resources is deficient in patients suffering from chronic pain (Veldhuijzen, Kenemans, Van Wijck, Olivier, Kalkman, & Volkerts, 2006) further impeding the comparison of differences in nociceptive processing or the effects of attention on this processing between pain free and pain patients. So before participants with ‘real’ pain can be included in future studies these problems need to be addressed and avoided.

In conclusion, it was debated in this discussion that it seems to be impossible to examine the effects of distraction on the subjective experience of pain, as attention is required to define the intensity of a presented stimulus. It was proposed that measuring electrophysiological responses in response to nociceptive stimuli might possibly lead to a more objective estimate of a pain experience. The observed results in the studies presented in this dissertation provide electrophysiological evidence that attention has distinct effects on pain processing. However, to what extent attention affects pain is highly dependent on the type of attentional manipulation used to direct attention to or away from the pain. Distraction of attention to another modality (attentional set) is the most effective way to affect the processing of painful stimuli.

Finally, I would like to present a simple medical hint based on the observations made in this dissertation (disclaimer: use at your own risk and of course always consult a doctor). This hint can be used in unfortunate event that you experience pain. If it is severe pain that you are experiencing then you should seek relieve in pain medication. However, if it is light or moderate pain then I propose that you should try to resist the temptation of running to your medicine cabinet. If you are lucky enough to own a VR-headset then put

on the device, select one of the full immersive games and start playing. If you're not that fortunate, don't panic. A puzzle book with crosswords or Sudoku's is a good alternative, even an old mathematics book from the primary school will do. Sit down, open the book, focus on the content and complete the puzzle or task and let attention be your natural painkiller.

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Summary

The ability to sense pain may be considered as a prerequisite for human survival. The experience of pain helps humans to avoid the execution of actions that can seriously endanger their lives; pain is therefore evolutionarily predisposed to interrupt and capture attention. As clarified in the overview on pain in Chapter 1, a clear omission of early theories (up to 1948) on the underlying mechanisms of pain is the absence of any cognitive factor in constructing a pain experience. Although more recent theories take cognitive factors into account when trying to explain the mechanisms of pain processing and the experience of pain, the supposed interconnectedness between pain and attention is still sparsely examined. The primary aim of this dissertation was to gain further insight in this relation between pain and attention, and more specifically the underlying mechanisms that explain how attention affects pain. In most of the chapters in this thesis, the electroencephalographic (EEG) technique was employed to examine and demonstrate the effects of both attention and distraction (achieved by different attentional manipulations) on the electrophysiological responses to experimentally induced nociceptive stimuli (delivered transcutaneous or intracutaneous) in healthy pain free participants.

Chapter 2 describes a study in which the effects of attention versus distraction on the processing of transcutaneous stimuli were examined, in an attempt to resolve a number of debates on the effects of the sustained attention-distraction paradigms on the electrophysiological responses to nociceptive stimuli. The obtained results revealed that distraction away from painful stimuli, achieved with the presentation of a cognitive task (word-association and arithmetic), reduces both early (N1 component) and late (P3a component) electrocutaneous stimulus evoked potentials. The observed attenuation of the N1 component most likely reflects reduced somatosensory processing of the nociceptive stimuli as a result of inhibition of the contralateral somatosensory cortex due to distraction, resulting in a diminished response. In addition, it was concluded that the late positive deflection generally observed in the ERPs recorded in response to the presentation of a nociceptive stimulus is a P3a component and reflects an orienting response towards the nociceptive stimulus.

In Chapter 3, the results of two experiments are reported in which the allocation and the role of covert spatial attention towards upcoming nociceptive stimuli (transcutaneous and intracutaneous) was further examined. More specifically, the study was intended to determine the primary reference frame, internal (somatotopic) or external (body-centered), employed to direct attention. Two different methods were employed to examine the orientation of (spatial) attention during a cue-stimulus interval, namely the known event-related lateralization (ERL) technique, and a recently introduced alternative, the lateralized power spectra method (LPS). The later method enables the assessment of lateralized activity that is not strictly time-locked to a specific event. This study shows that endogenous spatial attention to nociceptive stimuli primarily occurs within an external reference frame. A clear orienting response towards initially unattended stimuli was observed, displayed by increased amplitudes of the P3a component in response to

uncued stimuli relative to cued stimuli.

Chapter 4 describes a study that further examined whether sustained (attention is consistently directed to one side) vs. transient (attention is continuously and unpredictably shifted from side to side) spatial attention differently affect the processing of intracutaneous electrical stimuli. In this study the LPS data provided more information than the standard ERL method, and revealed that the orientation of attention appears to be more efficient when attention is directed to a single location over a longer period of time (sustained attention) compared to when attention is constantly shifted between multiple locations. The absence of an effect of the applied attentional manipulation on the P3a component suggest that the attenuation of the P3a component in Chapter 2 was not due to the applied sustained attentional manipulation. A more likely explanation is a difference in employed task instructions. Namely, only in the case of total irrelevance of nociceptive stimuli, when they occur at to be ignored locations and do not belong to the task set, then the orienting effect is no longer observed. A reduction in processing in somatosensory areas is observed when attention is directed away from the location of the pain stimuli or being occupied with a secondary task, but only if it is 100% sure that the pain stimulus can be ignored. This effect also occurs when the pain stimulus is part of the task set (i.e., when it contains target features).

In the last empirical chapter (Chapter 5), a study is described in which the disrupting effects of nociceptive stimuli on temporal visual attention were examined. The effect of attentional orienting due to the presentation of a nociceptive stimulus was analysed by examining its effect on the attentional blink. The presentation of nociceptive stimuli at T1 onset resulted in enhanced T1 accuracy scores, which was suggested to be due to immediate arousal. An interesting result is that the presentation of high intensity stimuli resulted in a biphasic effect displayed by an enhanced attentional blink at T2. This biphasic effect, an initial benefit and a subsequent cost, suggests that acute pain results in a transient modulation of the available attentional resources.

It was concluded in Chapter 6 (the General Discussion) that the studies reported in this dissertation clearly highlight the interconnectedness between pain and attention. The studies revealed that the neural processing of pain is consistently affected by attention. However, to what extent attention affects pain is highly dependent on the type of manipulation used. Distraction of attention to another modality (not within the same task set) has been shown to be most effective. These results underline the high potential of attention as part of behavioural or clinical therapies in treating and coping with pain (e.g., employing mindfulness, cognitive therapy or with the application of other techniques like virtual reality).

Nederlandstalige samenvatting

Het kunnen voelen van pijn is een belangrijke voorwaarde voor de mens om te overleven. De ervaring van pijn is daarmee evolutionair voorbestemd om onze aandacht te kunnen trekken en zorgt ervoor dat we specifieke gevaren vermijden. Pijn en cognitie (of aandacht) en de verschillende onderliggende mechanismen worden uitgebreid besproken in Hoofdstuk 1. Deze review laat zien dat er in de vroege theorieën over pijn (zelfs tot het jaar 1948) geen ruimte was voor cognitieve factoren bij het construeren van pijnervaring. Meer recente theorieën met betrekking tot pijn en pijnverwerking nemen deze cognitieve factoren inmiddels wel in aanmerking, maar de veronderstelde onderlinge verbondenheid tussen pijn en aandacht is nog steeds weinig onderzocht. Het primaire doel van dit proefschrift is daarom om meer inzicht te krijgen in deze relatie tussen pijn en aandacht, en in het bijzonder de onderliggende mechanismen die de invloed van aandacht op pijn zouden kunnen verklaren. Dit proefschrift beschrijft een aantal studies waarbij de effecten van aandacht en/of afleiding op de verwerking van pijn bij gezonde pijnvrije proefpersonen is onderzocht. Specifiek bij de studies beschreven in Hoofdstukken 2 t/m 4 van dit proefschrift is de elektro-encefalogram (EEG) techniek gebruikt om deze effecten op de elektrofysiologische reacties op experimenteel geïnduceerde nociceptieve stimuli (transcutaan of intracutaan) te meten.

Hoofdstuk 2 beschrijft een studie waarin de effecten van (aangehouden) aandacht versus distractie op de verwerking van transcutaan gepresenteerde pijnlijke stimuli is onderzocht. Deze studie geeft antwoord op een lopende discussie aangaande de effecten van aandacht-distractie paradigma's op de door de pijnstimuli geïnduceerde elektrofysiologische responses. De resultaten laten zien dat distractie middels het presenteren van een secundaire cognitieve taak (woordassociatie- of rekentaak) leidt tot verminderde vroege (N1) en late (P3a) componenten in de 'event related potentials'. De verlaging van de N1 component reflecteert waarschijnlijk verminderde somatosensorische verwerking van de stimuli door inhibitie van de contralaterale somatosensorische cortex als gevolg van de distractie. Daarnaast kan er geconcludeerd worden dat de latere positieve component in de ERP een P3a component is en een oriëntatiereactie naar de nociceptieve stimulus weerspiegelt.

In Hoofdstuk 3 wordt een uit twee experimenten bestaande studie beschreven waarbij de toewijzing en de rol van de ruimtelijke aandacht in afwachting van op het lichaam gepresenteerde nociceptieve stimulus (transcutaan in experiment 1 en intracutaan in experiment 2) verder is onderzocht. Specifiek doel is het kunnen bepalen van de primaire referentiekader, intern (somatotopic) of extern (ruimtelijk), welke wordt ingezet voor het richten van aandacht in afwachting van een pijnlijke stimulus. Hiervoor worden twee verschillende analysemethodieken toegepast welke het mogelijk maakt om de oriëntatie van de (ruimtelijke) aandacht in de cue-stimulus interval te bepalen. De eerste methode is de event gerelateerde lateralization (ERL) techniek en de tweede methode is de onlangs geïntroduceerde methode waarbij wordt gekeken naar de gelateraliseerde power spectra (LPS). Deze tweede methode maakt het mogelijk om naar activiteit te kijken

die niet tijdgebonden is aan een specifiek event. Op basis van de resultaten kan worden geconcludeerd dat aandacht richting een specifieke locatie op het lichaam, in afwachting van een nociceptieve stimuli voornamelijk plaatsvindt binnen het externe referentiekader. Daarnaast is er een duidelijke oriëntatiereactie richting aanvankelijk niet-geattendeerde stimuli waar te nemen. Dit wordt weergegeven door verhoogde amplitudes van de P3a component in reactie op niet-geattendeerde stimuli ten opzichte van geattendeerde stimuli.

Hoofdstuk 4 beschrijft vervolgens een studie waarin onderzocht is of de wijze waarop ruimtelijke aandacht wordt gericht van invloed is op de verwerking van (in dit geval transcutane) pijnstimuli. Specifiek werd er gekeken of de manier waarop aandacht wordt gericht, bijvoorbeeld constant naar een kant gericht versus continue verschuiving van aandacht tussen twee locaties leidt tot specifieke verschillen in het richten van aandacht (cue-stimulus interval) en de pijnverwerking. De LPS-methode verschaft in deze studie meer informatie dan de standaard ERL-methode en laat zien dat de oriëntatie van aandacht efficiënter lijkt te zijn wanneer deze constant wordt gericht op dezelfde locatie over een langere periode dan wanneer gewisseld dient te worden tussen verschillende locaties. De afwezigheid van een effect op de P3a component als gevolg van de aandachtmanipulaties suggereert dat de geobserveerde reductie van de P3a component in Hoofdstuk 2 waarschijnlijk niet een gevolg is van toegepaste 'sustained' aandachtmanipulatie. Een betere verklaring is een verschil in de toegepaste taakinstructie. Het oriëntatie-effect wordt niet meer waargenomen wanneer de stimuli totaal irrelevant zijn, gepresenteerd worden op te negeren locaties en niet behoren tot de zogenaamde 'task set' (d.w.z. wanneer het kenmerken bevat waarop gelet dient te worden). Een verminderde somatosensorische verwerking wordt enkel waargenomen wanneer aandacht op een andere locatie is gericht of bezet wordt met een secundaire taak. Dit effect is alleen waarneembaar als het 100% zeker is dat de pijnprikkel kan worden genegeerd, maar treedt ook op wanneer de pijnprikkel onderdeel is van 'task set'.

In het laatste empirische hoofdstuk (Hoofdstuk 5), wordt een studie beschreven waarin de effecten van gepresenteerde nociceptieve stimuli op temporele visuele aandacht zijn onderzocht. Dit effect werd onderzocht middels de toepassing van de Attentional blink fenomeen waarbij de limieten van de temporele visuele aandacht zichtbaar worden. De presentatie van nociceptieve stimuli op T1 resulteerde in verbeterde nauwkeurigheid van T1 scores, waarschijnlijk als gevolg van onmiddellijke arousal (paraatheid) veroorzaakt door de pijnstimulus. Een interessante observatie is dat de presentatie van stimuli met een hoge intensiteit een bifasisch effect liet zien. Namelijk een hogere attentional blink op T2 (lagere correcte responses) als gevolg van de gepresenteerde hoge intensiteit stimuli. Dit bifasische effect, een eerste baten en latere kosten suggereert dat acute pijn resulteert in een tijdelijke modulatie van de beschikbare capaciteit van aandacht.

In Hoofdstuk 6 (de algemene discussie) wordt geconcludeerd dat de gerapporteerde studies in dit proefschrift de onderlinge verbondenheid tussen pijn en aandacht duidelijk

laat zien. De verschillende studies tonen aan dat de neurale verwerking van pijn constant wordt beïnvloed door aandacht. Maar in hoeverre aandacht deze pijnverwerking beïnvloedt is sterk afhankelijk van het type manipulatie dat wordt toegepast. De studies laten zien dat afleiding van aandacht naar een andere modaliteit (niet binnen dezelfde ‘task set’) het meest effectief blijkt te zijn. Deze resultaten onderstrepen het grote potentieel van de aandacht in het kader van gedrags- of klinische therapieën bij de behandeling van en het omgaan met pijn (bijvoorbeeld mindfulness, cognitieve therapie of met de toepassing van nieuwe technieken, zoals virtual reality).

Dankwoord

“Have lots of fun... Pain is temporary, the experience will last a lifetime”

Unknown author

Deze quote stond geschreven op een whiteboard met extra informatie over de Minnesing Mountain Bike Trail. Deze mountainbikeroute brengt je door een werkelijk prachtig deel van het Algonquin Provincial Park (Ontario, Canada). Op een mooie zomerochtend in 2005 stond ik samen met Bart en Maurice tijdens een vakantie door het oosten van Amerika en Canada voor dit bord.

De Minnesing Mountain Bike Trail wordt aangeduid als een “steep, rugged mountain bike trail consisting of hilly, sometimes muddy, terrain filled with rock, roots and obstacles unsuitable for small children and unfit adults”. Een aantal waarschuwingen op het bord hadden ons nog kunnen weerhouden om te starten: “BRING WATER”, “BRING BUG SPRAY”, “NOT FOR BEGINNERS”

Jong en overmoedig hebben we deze adviezen naast ons neergelegd en zijn we vol overgave gestart. Ja, de route was niet voor beginners. Het was warm, zwaar, losse stenen, technisch zeer lastig. Het was afzien, maar ook fantastisch mooi!!! Wat een prachtige natuur, wildlife en vergezichten. Het ongemak was snel weer vergeten, de ervaring daarentegen nog steeds niet.

Terug naar het heden en naar de ervaring van het promoveren. Nee, wees maar niet bang. Geen klaagzang over de afgelopen periode. Ok, er waren de afgelopen jaren momenten die wel pijnlijk waren. Het testen van je door jezelf geprogrammeerde onderzoekstaken met echte pijnstimuli doet niemand voor zijn lol. Daarentegen waren de afgelopen jaren een leuke en vooral leerzame ervaring!

Na het afronden van mijn master Psychologie aan de Universiteit Twente kwam ik terecht in het bedrijfsleven. Ik had daar een leuke tijd, maar in die tijd bleef het idee van promoveren in mijn hoofd ronddwalen. In die tijd was ik voor mijn werkzaamheden veel in contact met onderzoekers waardoor het idee bleef bestaan. De mogelijkheid om te kunnen promoveren heb ik daarom met beide handen aangegrepen. Mijn promotor Willem Verweij wil ik bedanken voor het bieden van deze mogelijkheid. Caro Wiering wil ik specifiek bedanken omdat jij de eerste aanzet hebt gemaakt voor het onderzoek, apparatuur hebt uitgezocht en alles zo goed mogelijk aan mij hebt overgedragen. Nog meer wil ik mijn dagelijks begeleider Rob van der Lubbe bedanken. Dank je wel dat ik na het aflopen van mijn contract bij de universiteit nog alle begeleiding van je kreeg. Hierdoor is het mogelijk geworden om dit proefschrift af te ronden.

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Curriculum Vitae

Jorian Blom, de auteur van dit proefschrift, werd geboren op 28 maart 1984 te Ede. De middelbare school volgde hij aan Het Streek te Ede waar hij in 2001 het eindexamen havo behaalde. Aansluitend startte hij met de bachelor Technische Bedrijfskunde aan de Hogeschool van Utrecht die hij in 2006 met goed gevolg afrondde. Hierna begon hij aan de Master Psychologie met specialisatie-richting Cognitie, Media en Ergonomie aan de Universiteit Twente. In 2008 ronde hij zijn master af met zijn masterthesis (Using fERN as a predictor for learning efficiency) bij de vakgroep Cognitieve Psychologie & Ergonomie (CPE) van de faculteit Gedragswetenschappen aan de Universiteit Twente. Na een korte periode werkzaam te zijn geweest in het bedrijfsleven, keerde hij in 2009 terug bij de vakgroep CPE om daar zijn promotieonderzoek uit te voeren. Op dit moment begeleidt hij als adviseur (inter)nationaal mkb-ondernemers, grote ondernemingen, kennisinstellingen en (semi-)overheidsinstanties bij het verwerven van subsidies en andere financieringsvormen voor het uitvoeren van onderzoek en ontwikkeling.

Acronyms

AB	Attentional blink
ACC	Anterior cingulate cortex
ADAN	Anterior directing attention negativity
BG	Basal ganglia
COX	Cyclooxygenase
EDAN	Early directing attention negativity
EEG	Electroencephalography
ERP	Event related potential
ERL	Event related lateralization
fMRI	Functional magnetic resonance imaging
HT	Hypothalamus
IASP	International Association for the Study of Pain
IC	Insular cortex
LDAP	Late directing attention positivity
LPS	Lateralized power spectra
MEG	Magnetoencephalography
MI	Primary motor cortex
NRS	Numerical Rating Scale
NSAID	Non-steroidal anti-inflammatory drug
PAG	Periaqueductal gray
PB	Parabrachial nuclei
PCC	Posterior cingulate cortex
PF	Prefrontal cortex.
PPC	Posterior parietal cortex
SG	Substantia gelatinosa
SI	Primary somatosensory cortex
SII	Secondary somatosensory cortex
SMA	Supplementary motor cortex

T-cells	Transmission cells
VAS	Visual Analogue Scale
VRS	Verbal Rating Scale
WHO	World Health Organization