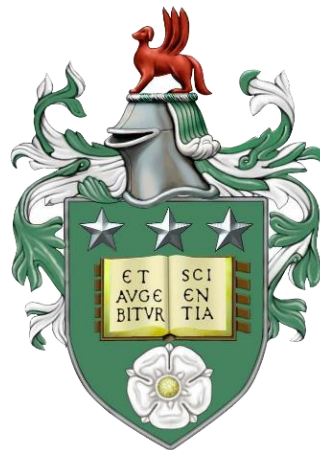


**A multi-method approach to understanding pain  
experience using non-pharmacological interventions  
that target alpha brain activity**

Laura Janine Arendsen

Submitted in accordance with the requirements for the degree of  
Doctor of Philosophy



University of Leeds

School of Psychology

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The candidate confirms that the work submitted is her own and that appropriate credit has been given where reference has been made to the work of others. The contribution of the candidate and others to this work is indicated explicitly below.

*The work in Chapter 5 of this thesis:*

I was responsible for the implementation and management of the study. Two Master students (C. Harney and B. Davison) collected the data under my supervision. They collected data for three experimental conditions: a binaural beat condition, a music listening condition, and a control condition. The Master students and I used separate data for statistical analysis. C. Harney and B. Davison used the data from the music listening condition for their dissertations. I used the data from the binaural beat condition in Study 2 of this thesis. I was responsible for running the statistical analysis and writing the chapter.

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## Thesis abstract

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This thesis aimed to examine the relationship between pre-stimulus somatosensory alpha activity and pain experience. Four studies were included to assess: 1) if, and how pre-stimulus somatosensory alpha activity might affect pain experience; and 2) if the relationship between pre-stimulus somatosensory alpha activity and pain experience is influenced by uncertainty about pain intensity, fear of pain and pain catastrophising. Study 1 was designed to replicate the negative correlation between pre-stimulus somatosensory alpha activity and pain. Studies 2-4 each investigated the potential of a different intervention to reduce pain by increasing alpha: binaural beats, transcranial alternating current stimulation (tACS), and mindfulness meditation. Study 1 confirmed the correlation between pre-stimulus somatosensory alpha activity and pain experience, but it was the findings of Studies 3 and 4 that were crucial in advancing the understanding of the relationship between somatosensory alpha activity and pain. They provided novel findings suggesting that modulation of somatosensory alpha (to increase alpha) results in reduced pain experience, thus demonstrating that pre-stimulus somatosensory alpha activity and pain experience might be causally related. This thesis also provided evidence for an influence of uncertainty about pain intensity on the relationship between alpha activity and pain experience. Study 1 showed an influence of uncertainty on pre-stimulus somatosensory alpha activity. Moreover, the application of tACS (to increase alpha) only resulted in a significant reduction of pain experience when pain intensity was uncertain. Finally, Study 3 demonstrated a relationship between pain catastrophising and the reduction of pain by tACS, higher pain catastrophising was associated with a larger reduction of pain experience. Together, the studies of this thesis not only provided a first indication of a causal relationship between pre-stimulus somatosensory alpha activity and pain, but also initial evidence for the effectiveness of interventions targeting alpha activity in the management of pain.

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**List of abbreviations**

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ACC	Anterior cingulate cortex
CBT	Cognitive-behavioural therapy
CHIME	Comprehensive inventory of mindfulness experiences
EEG	Electroencephalography
EOG	Electrooculogram
ERP	Event-related potential
ERS/ERD	Event-related synchronisation/event-related desynchronisation
FFMQ	Five-factor mindfulness questionnaire
fMRI	Functional magnetic resonance imaging
FPQ-SF	Fear of pain questionnaire-short form
FPS-R	Faces pain scale-revised
HADS	Hospital anxiety and depression scale
IASP	International Association for the Study of Pain
ICA	Independent component analysis
IMMPACT	Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials
IQR	Interquartile range
MAAS	Mindful attention awareness scale
MBCT	Mindfulness-based cognitive therapy

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MBSR	Mindfulness-based stress reduction
MEG	Magnetoencephalography
NRS	Numerical rating scale
PCA	Principle component analysis
PCS	Pain catastrophising scale
PET	Positron emission tomography
PFC	Prefrontal cortex
PLV	Phase-locking value
RNS	Random noise stimulation
S1	Primary somatosensory cortex
S2	Secondary somatosensory cortex
STAI	State-trait anxiety inventory
STDP	Spike-time dependent plasticity
tACS	Transcranial alternating current stimulation
tDCS	Transcranial direct current stimulation
tES	Transcranial electrical stimulation
TFR	Time-frequency representation
TMS	Toronto mindfulness scale
TMS	Transcranial magnetic stimulation
VAS	Visual Analogue Scale
VRS	Verbal rating scale

## Chapter 1 Thesis introduction and overview

---

Chronic pain is a debilitating condition that affects many people. An estimated 20% of adults in Europe are thought to suffer from chronic pain, in particular women, the elderly, and those with a lower socio-economic status (Van Hecke, Torrance, & Smith, 2013). The Classification of Chronic Pain (Task force on taxonomy of the International Association for the Study of Pain, 1994) qualifies chronic pain as distinct from acute pain. Chronic pain is defined as prolonged pain with a duration of at least three months (Gatchel & Okifuji, 2006), or pain that persists beyond the normal time of healing. However, this is not a conclusive definition. A considerable number of chronic pain conditions exist that vary in location of pain, underlying pathology, and characteristics of the pain experienced. Chronic pain, as a disease in its own right, takes many different shapes and the definition of chronic pain should be considered as flexible, strongly depending on the specific chronic pain condition in question (Task force on taxonomy of the International Association for the Study of Pain, 1994).

Chronic pain has a wide-reaching impact on a person's well-being. In a large-scale survey undertaken in 15 European countries and Israel, 21% of respondents with chronic pain reported to have been diagnosed with depression because of their pain, and a majority reported a negative impact of pain on sleep, exercise, and taking part in social activities (Breivik, Collett, Ventafridda, & Cohen, 2006). Chronic pain poses a major economic impact. It is a major reason for absence at work, reduced productivity, and leaving the labour market (Phillips et al., 2008). It also puts a heavy load on healthcare services: chronic pain is associated with increased hospitalisation and GP

consultations. In Europe, the financial cost of chronic pain is estimated to be more than €200 billion a year (Van Hecke et al., 2013). Despite its wide-reaching and severe impact, conventional treatment options in the management of chronic pain only demonstrate a modest improvement of pain and minimal improvement of physical and emotional functioning (Turk, Wilson, & Cahana, 2011). A common and increasingly prescribed treatment for chronic pain are opioids; however, there is a little evidence for the effectiveness of long-term opioid treatment in the relief of chronic pain (Turk et al., 2011). There are limited placebo-controlled randomised studies available that assess the long-term effectiveness of opioid treatment in chronic pain. Importantly, the long-term use of opioids is associated with serious adverse effects: e.g., overdose, opioid abuse, cardiovascular events, and fractures (Chou et al., 2015). For many patients treatment outcome is not satisfactory, and in a majority of patients prescription pain medication at times does not successfully control the pain (Breivik et al., 2006).

As defined by the International Association for the Study of Pain (IASP), pain is “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” (IASP Taxonomy, 2011). Pain is a subjective and individual experience. For an identical painful stimulus the amount of pain experienced varies considerably from one individual to the next. This variation in subjective experience of pain is related to activity in a number of brain regions, including the anterior cingulate cortex (ACC), prefrontal cortex (PFC), and primary somatosensory cortex (S1) (Coghill, McHaffie, & Yen, 2003). Thus, the experience of pain relies on processing in the brain; processing within a widespread neural network (Melzack, 2001). Pain experience is not only dependent on neural processing in response to a painful event (processing after pain onset), but is also influenced by processing before a painful event has even taken place (pre-stimulus neural activity) (Ploner, Lee, Wiech, Bingel, & Tracey, 2010; Wiech et al., 2010).

Supporting the communication within the pain-related neural network, are neural oscillations (Basar, Basar-Eroglu, Karakas, & Schurmann, 1999;



Fries, 2005). In particular alpha activity, oscillatory neural activity within a frequency range of 8-12Hz, has received considerable attention in the processing of pain and has been implicated in pain processing not only during pain but also before the onset of pain (Babiloni et al., 2003; Del Percio et al., 2006; May et al., 2012). Crucially, fluctuations in pre-stimulus somatosensory alpha activity have been related to the subsequent experience of pain, a significant negative correlation between pre-stimulus somatosensory alpha activity and pain experience has been found (Babiloni et al., 2006; Tu et al., 2016).

With neural oscillations fulfilling an important role in the communication within the pain-related neural network (Ploner, Sorg, & Gross, 2016), they offer a potential target for the treatment of pain. Jensen, Hakimian, Sherlin, and Fregni (2008) emphasised the potential of neuromodulatory interventions targeting oscillatory neural activity to reduce pain. They proposed that these interventions could offer patients with a chronic pain condition a promising alternative in the management of their pain, as currently adequate treatment for chronic pain is limited. The aim of this thesis is to investigate whether neuromodulation to reduce pain might be particularly promising when applied to alpha activity, and specifically, whether increasing pre-stimulus somatosensory alpha reduces pain experience.

There is some initial evidence to suggest a change in alpha activity during rest in patients with chronic pain. The dominant peak in the electroencephalogram (EEG) spectrum (the frequency at which EEG power is maximum) can usually be found somewhere within the alpha frequency range (8-12Hz). A number of studies that compared the peak frequency for patients with chronic pain to healthy pain-free controls found a significantly lower peak frequency in the patients (Boord et al., 2008; De Vries et al., 2013; Lim, Kim, Kim, & Chung, 2016; Sarnthein, Stern, Aufenberg, Rousson, & Jeanmonod, 2006). For example, Sarnthein et al. (2006) demonstrated a significantly lower peak frequency for patients with chronic neurogenic pain, which is pain initiated by a lesion or dysfunction of the peripheral or central nervous system. Healthy controls had a median peak frequency of 9.4Hz, whilst in the patients the

median peak frequency was 8.6Hz. Similarly, a significantly lower peak frequency within the alpha range was found in patients with pain following spinal cord injury (Boord et al., 2008), patients with fibromyalgia (Lim et al., 2016), and patients with abdominal pain as a result of chronic pancreatitis (De Vries et al., 2013). Importantly, Camfferman, Moseley, Gertz, Pettet, and Jensen (2017) also demonstrated a significant negative relationship between alpha power during rest and chronic pain intensity, for a group of 103 patients with a variety of chronic pain conditions. Moderate negative associations between alpha power and chronic pain intensity were found in frontal and somatosensory regions (electrode locations F3, F4, CP3, and CP4; based on the 10-20 system). Thus, modulation of alpha activity could be a particularly promising means of reducing chronic pain.

This PhD thesis comprises four studies that were designed to collectively examine the relationship between pre-stimulus somatosensory alpha activity and pain experience (Figure 1.1). The first two chapters of the thesis will provide a justification of the objectives of the PhD and the methodology applied to address these objectives:

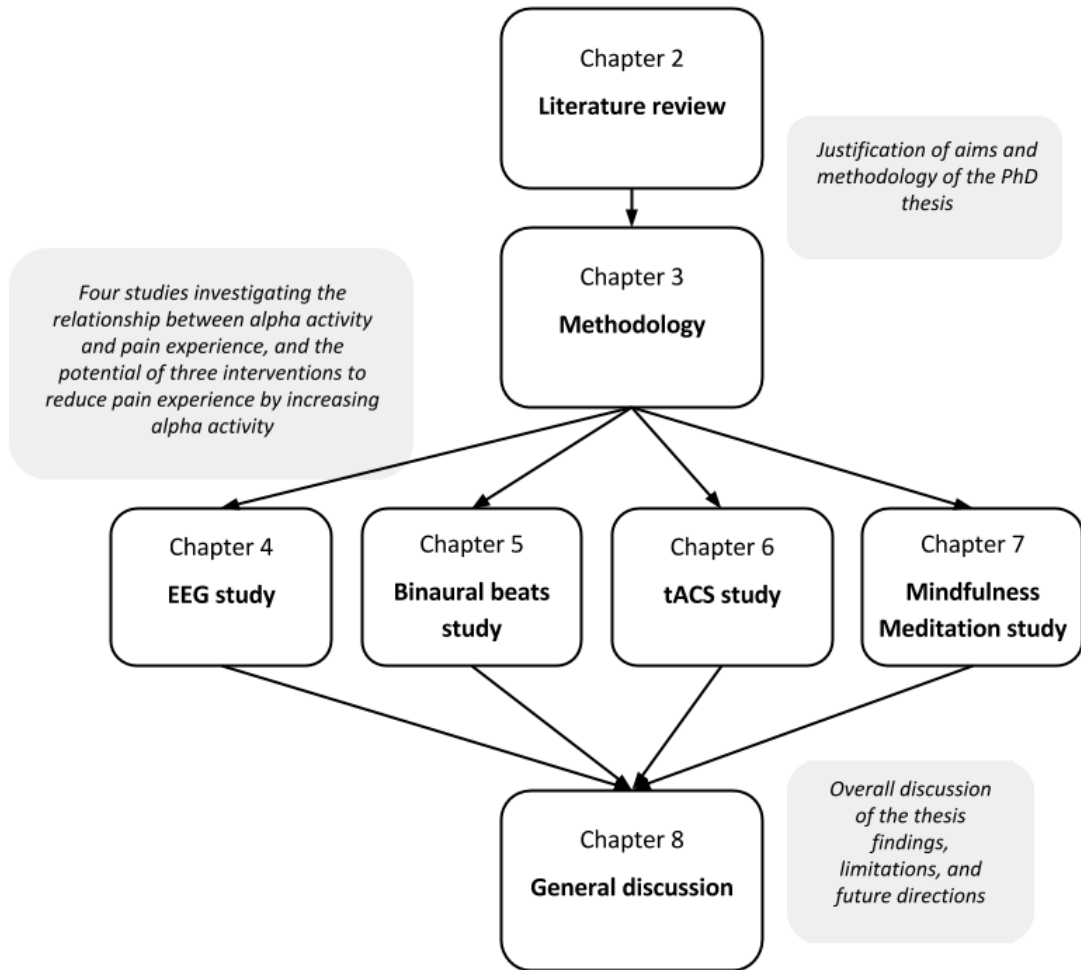
- Chapter 2 provides a critical review of the existing literature on the role of alpha activity in pain perception, and the relationship between pre-stimulus somatosensory alpha activity and pain experience specifically. Essential gaps in the literature will be identified, ultimately leading to the aims of the PhD thesis.
- Chapter 3 will explain the rationale for the key stimuli, manipulations, measures, and analyses that were applied across the studies of this thesis.

The following four chapters will describe the four studies of the PhD thesis. The first study was designed to assess the relationship between pre-stimulus alpha activity and pain experience without any specific intervention. The following three studies each investigate the potential of a different

intervention to reduce pain experience by increasing alpha activity, to assess if, and how the manipulation of somatosensory alpha activity might affect pain experience.

- Chapter 4: an EEG study that was designed to replicate the negative relationship between pre-stimulus somatosensory alpha activity and pain experience, and to assess the influence of uncertainty about pain intensity on this relationship.
- Chapter 5: a behavioural study that assessed the potential of auditory stimulation - binaural beats at alpha frequency - to reduce pain experience.
- Chapter 6: a behavioural study that addressed the reduction of pain experience by application of transcranial alternating current stimulation at alpha frequency (alpha tACS) over the somatosensory cortex.
- Chapter 7: an EEG study investigating the potential of a standardised 8-week mindfulness-based stress reduction (MBSR) course in modifying both pain experience and somatosensory alpha activity.

Finally, Chapter 8 comprises the general discussion of the thesis. This final chapter will provide a summary of the key findings of the four studies of the thesis and how these findings together address the aims of the thesis. This will be followed by a discussion of limitations and future directions.



**Figure 1.1** Thesis overview.

## **Chapter 2** The role of alpha brain activity in pain processing and its relationship with pain experience

---

Over the past 25 years a number of studies have been dedicated to the investigation of alpha activity in pain perception (e.g., Backonja et al., 1991; Chang, Arendt-Nielsen, & Chen, 2002; Chang, Arendt-Nielsen, Graven-Nielsen, Svensson, & Chen, 2001a, 2001b; Ferracuti, Seri, Mattia, & Cruccu, 1994; Peng, Babiloni, Mao, & Hu, 2015). These investigated changes in alpha activity not only during pain but also before a painful event has even occurred, i.e., during the anticipation of pain (Babiloni et al., 2003; Del Percio et al., 2006; May et al., 2012) and suggested a relationship between pre-stimulus alpha activity and the experience of pain (Babiloni et al., 2006; Tu et al., 2016). However, a clear interpretation of the role of alpha activity in pain, i.e., the mechanism through which alpha activity is involved in the experience of pain, is largely lacking. This thesis focuses on the relationship between alpha activity directly before a painful event, i.e., pre-stimulus alpha activity, and the experience of pain, and assesses the potential of active manipulation of alpha activity (specifically increasing alpha activity) to reduce pain experience. This chapter will provide a critical assessment of the existing literature on alpha activity in pain perception to identify essential gaps in our understanding of the relationship between alpha activity and pain experience. This will ultimately lead to the aims of the thesis.

## 2.1 Neural oscillations and pain processing

The experience of pain is multidimensional (Melzack, 2001) and depends not only on the intensity of a painful stimulus but is the result of an integration of sensory input and various other factors such as attention (Miron, Duncan, & Bushnell, 1989), emotions (Villemure, Slotnick, & Bushnell, 2003), context (Malenbaum, Keefe, Williams, Ulrich, & Somers, 2008), and individual characteristics such as pain catastrophising (Hirsh, George, Bialosky, & Robinson, 2008). As Melzack's (2001) neuromatrix theory of pain proposes, the multidimensional experience of pain results from activity across a widespread neural network. This neural network is commonly referred to as the 'pain matrix' (Iannetti & Mouraux, 2010; Legrain, Iannetti, Plaghki, & Mouraux, 2011). Two meta-analyses that investigated the neural regions most consistently activated in response to a painful stimulus (Apkarian, Bushnell, Treede, & Zubieta, 2005; Peyron, Laurent, & García-Larrea, 2000) both pointed to the primary somatosensory cortex (S1), secondary somatosensory cortex (S2), anterior cingulate cortex (ACC), insula cortex, and the thalamus as key regions of this pain matrix. In addition, Apkarian et al. (2005) identified the prefrontal cortex as another key region, and Peyron et al. (2000) reported less consistent but still frequent activity in a set of motor-related brain regions (striatum, cerebellum, supplementary motor area) and regions involved in pain control, such as the periaqueductal grey.

Although the studies above provide us with a clear understanding of where in the brain the processing of pain takes place, there are limitations with respect to what we can understand about neural processing of pain based on these types of findings. The brain regions identified above relied on the neuroimaging methods functional magnetic resonance imaging (fMRI) and positron emission tomography (PET). These two techniques are optimally suited to find the exact neural location of activity for a certain type of behaviour as they have a high spatial resolution. Pain experience, as a complex neurocognitive process, involves quick dynamic changes in neural activity over time. Whereas PET and fMRI are good for the localisation of neural activity, they are not particularly suitable to detect changes in neural activity over time on a scale of tens/hundreds of milliseconds (Luck, 2005). Electro-

encephalography (EEG), on the other hand, has a high temporal resolution, which makes it particularly suitable to answer questions about quick dynamic changes in neural activity (Cohen, 2014). Furthermore, EEG allows for the assessment of oscillatory neural activity.

Hans Berger, was the first to record and describe neural oscillations using EEG (Berger, 1929). Over time, a number of rhythms have been identified in the EEG, with each rhythm reflecting a specific frequency range, for example theta (4-8Hz), alpha (8-12Hz), beta (15-30Hz), and gamma (30-80Hz), and each associated with specific (albeit a wide range of) cognitive and behavioural processes (Sauseng & Klimesch, 2008; Wang, 2010). Oscillatory activity refers to activity that is rhythmic or periodic in nature, that alternates around a set point over time. With respect to neural activity, these oscillations can be thought of as rhythmic fluctuations in the excitability of neurons or neuronal networks over time (Cohen, 2014). Neural oscillations can be described using three main parameters: frequency, amplitude, and phase. These three parameters all carry information useful for investigating neural oscillations and analysing EEG data (Sauseng & Klimesch, 2008). A related term, power, reflects the amount of energy in a frequency band and is an indication of the strength of neural oscillations at a certain frequency or frequency band. Further detail on EEG analysis involving these parameters will be given in the methodology chapter (Chapter 3). Whereas oscillatory activity within the neural system can be found at the level of single neurons and at the level of networks of neurons (Wang, 2010), neural oscillatory activity as measured with EEG reflects oscillatory neural activity of a population of neurons and is the synchronised neural activity of groups of neurons in superficial cortical layers (10.000-50.000 neurons) (Cohen, 2014).

Neural oscillations, supporting the communication across functional networks (Basar, Basar-Eroglu, Karakas, & Schurmann, 1999; Fries, 2005), are relevant for the processing of pain in the widespread pain-related neural network. Fries (2005) proposed that oscillations support effective and flexible communication between groups of neurons, through coherence of oscillations across neural networks. Coherence in oscillations between two neural regions means that oscillations in the first region relate to oscillations in the second region in a fixed manner. If two neural regions demonstrate phase coherence,

they demonstrate a similar lag in phase angle, i.e., there is phase consistency (Sauseng & Klimesch, 2008). Coherence in oscillations between neural regions leads to enhanced communication, whereas lack of coherence can prevent effective communication (Fries, 2005). In this thesis EEG was used to investigate the role of alpha activity - a certain type of neural oscillatory activity - during the anticipation of pain and its relationship with pain experience.

## **2.2 Alpha oscillations during pain and their general function in information processing**

Alpha activity is oscillatory neural activity within a frequency range of 8-12Hz and can be recorded over widespread scalp regions, but usually has a maximum amplitude over posterior scalp regions (Nunez, Wingeier, & Silberstein, 2001). Multiple studies have found a change in alpha power during the delivery of a tonic pain stimulus. However, the findings are variable in relation to the direction of change (alpha increase/decrease) and location of alpha response. For example, Le Pera et al. (2000), who investigated tonic pain as a result of a painful injection in the muscle, found a significant increase of alpha power during painful stimulation compared to baseline, at electrode locations P3 and P4 (based on the 10-20 system). This increase was based on the change in alpha power over a 1-minute EEG recording that was started about 5 minutes after the onset of pain (on average 5.8 minutes after pain onset). However, other studies that investigated changes in alpha activity during tonic pain found a significant decrease of alpha power during pain compared to baseline when EEG was recorded immediately after pain onset. Chang et al. (2001b) found a significant decrease of alpha power during tonic muscle pain over a widespread scalp region ranging from central to posterior-parietal electrode locations. This same group also found a significant decrease of alpha power at centro-posterior scalp regions (electrode locations Cz, P3, Pz, P4, CP1, CP2, POz, O1, and O2) compared to baseline during tonic pain as a result of a painful injection in the skin (Chang et al., 2001a). Chang et al., (2002) found a significant decrease of alpha power in posterior-parietal and occipital regions compared to baseline during immersion of the hand in



painfully cold water, predominantly during the first 60 seconds of immersion. Finally, Backonja et al. (1991) also found a significant change in alpha power; however, the direction of change depended on the time period during the painful stimulation. Significantly increased alpha power during immersion of the hand in painfully cold water was found from 60-240 seconds, compared to immersion in non-painfully cool water and baseline. This increase was present at frontal and posterior scalp locations only (and not central locations). In contrast, during the first minute of immersion in painfully cold water a decrease in alpha power at central scalp locations only was found (averaged over electrodes T3, C3, Cz, C4, and T4).

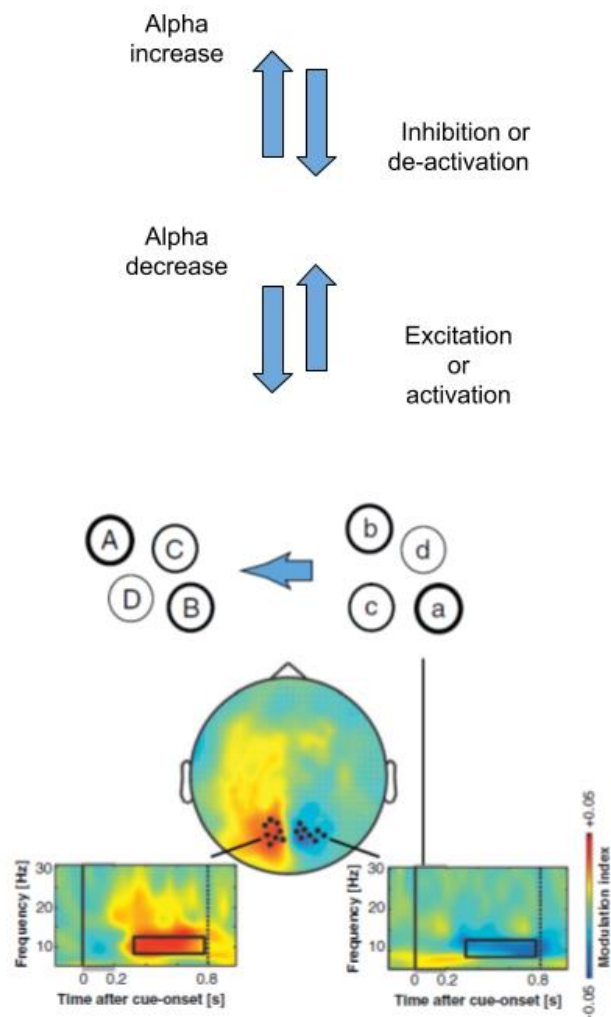
Together these initial studies demonstrated that during tonic pain stimulation changes in alpha activity were present. This change was found for a variety of experimental tonic pain stimuli, and tended to be present over widespread scalp regions covering central and more posterior scalp regions. However, with respect to the direction of change of alpha power during pain (an increase or decrease), findings were inconsistent. Although a majority found a decrease of alpha power (Chang et al., 2003; Chang et al., 2002, 2001a, 2001b), not all did (Backonja et al., 1991; Le Pera et al., 2000). Together with other variations in study design such as type and duration of pain stimulus and EEG analysis approach, these inconsistencies might be related to the time window used for the alpha power calculation. A decrease of alpha power was found for a time window starting more or less immediately after tonic pain onset. An increase of alpha power was not found directly after pain onset, but when at least a minute had past. This suggests that the role of alpha power in pain perception might depend on time, where alpha activity is decreased during the earlier phase of pain, but during a later phase alpha activity is increased. Despite the inconsistencies, these studies provide an initial indication of the involvement of alpha activity in pain. However, an interpretation of how alpha activity is involved in pain perception, or what mechanism might explain the changes in alpha activity during pain perception, remains very limited based on these early studies. The experience of pain was accompanied by a simultaneous change in alpha power, but this does not tell us much about the nature of the relationship between pain experience and alpha activity.

Although an understanding of the mechanism through which alpha activity is involved in neural processing for pain perception is limited, insight can be gained from findings on alpha activity in other sensory domains. The influence of alpha activity is not tied to one specific type of sensory or cognitive domain, but is instead likely to reflect a more general domain-independent mechanism. Alpha activity has been implicated in a variety of tasks across sensory domains, such as visual discrimination and detection (Mathewson, Gratton, Fabiani, Beck, & Ro, 2009; van Dijk, Schoffelen, Oostenveld, & Jensen, 2008), visual-spatial attention (Bauer, Stenner, Friston, & Dolan, 2014; Rihs, Michel, & Thut, 2007), cross-modal visual-auditory attention (van Diepen, Cohen, Denys, & Mazaheri, 2015) and perception of tactile stimuli (Haegens, Luther, & Jensen, 2012; Schubert, Haufe, Blankenburg, Villringer, & Curio, 2008).

A number of hypotheses on the role of alpha activity in neural processing have been proposed. With slight differences, each hypothesis in some way emphasises the importance of alpha activity in actively guiding information processing across a variety of sensory and cognitive domains through a mechanism of functional inhibition. Jensen and Mazaheri (2010) proposed in their 'gating by inhibition' hypothesis that alpha oscillations are involved in the routing of information processing through inhibition; i.e., an increase of alpha activity in task-irrelevant neural regions inhibits the processing of information in these regions. This results in the gating of information processing towards task-relevant neural pathways (Figure 2.1). Klimesch et al. (2007) similarly argued that alpha oscillations direct information processing through the inhibition of processing of irrelevant information by an increase of alpha activity, and describe it as a mechanism of top-down control. Alpha's inhibition function has also been linked to attention. For example, Foxe and Snyder (2011) proposed that alpha oscillations reflect a mechanism of guiding neural processing mediated by attention. They suggest that the increase of alpha power over neural regions processing irrelevant information (resulting in inhibition of these regions) reflects a mechanism of attentional suppression. These authors also suggest that the directing of neural processing by alpha activity can take place before the start of a task, and that the modulation of alpha activity before task onset (pre-stimulus alpha activity) is

related to performance on the task (Foxye & Snyder, 2011; Klimesch, 2012). For example, Thut, Nietzel, Brandt, and Pascual-Leone (2006) investigated changes in alpha activity during the anticipation of a visual target, using visual cues to direct attention to either the right or left visual field. In the period before the onset of the visual target, whilst directing attention towards the left visual field, alpha activity was lower over the right (contralateral) posterior-occipital region compared to the left (ipsilateral) posterior-occipital region. The authors argued that this reflected facilitation of processing in task-relevant visual regions and inhibition in task-irrelevant visual regions. In addition, the extent of the difference in contralateral and ipsilateral alpha activity (lateralisation) was related to performance on the visual detection task with a larger difference related to better performance.

To conclude, pre-stimulus alpha activity is involved in the preparation for an anticipated stimulus and likely reflects an attentional mechanism, which is found across different sensory domains (domain-independent), and is thought to apply to the perception of pain as well.



**Figure 2.1 Top:** Where an increase in alpha activity leads to the inhibition of neural regions, a decrease of alpha activity leads to facilitation of processing in neural regions. **Bottom:** direction of attention to a certain hemifield leads to a pattern of lateralised changes in alpha activity. When attention is directed to visual objects in the left hemifield posterior alpha activity in the contralateral, right hemisphere processing the attended visual objects is decreased, whilst alpha activity in the ipsilateral, left hemisphere (processing distracting visual objects) is increased (adapted from Jensen, Bonnefond, & VanRullen, 2012).

### 2.3 Alpha oscillations and somatosensory perception

The organisation of processing towards a painful event by alpha activity mediated by attentional mechanisms, fits with the function of pain perception. A key function of acute pain is to motivate behaviour to protect oneself from the

threat of injury imposed by pain. Acute pain serves as a warning signal that captures attention and promotes an efficient response to the threat (Legrain, Iannetti, Plaghki, & Mouraux, 2011). This is illustrated by the results of studies using a primary task paradigm, where experimental pain stimuli delivered whilst participants carried out a primary task (e.g., an auditory discrimination task) resulted in a reduction in task performance (Crombez, Baeyens, & Eelen, 1994; Crombez, Eccleston, Baeyens, & Eelen, 1998).

Studies on non-painful somatosensory stimuli offer a useful starting point to better understand the mechanism through which alpha activity is involved in pain experience. In the non-painful somatosensory domain, a number of studies provide support that pre-stimulus alpha activity in somatosensory brain regions is involved in the preparation for an anticipated tactile stimulus and modulated by attention. For example, Van Ede, De Lange, Jensen, and Maris (2011) used visual cues to direct attention to either the left or right hand, before the onset of a tactile stimulus on the hand. Pre-stimulus somatosensory alpha activity contralateral to the attended hand was significantly lower than ipsilateral alpha before tactile stimulus onset. Thus, pre-stimulus somatosensory alpha activity facilitated processing in task-relevant regions responsible for processing information from the attended location (contralateral lower alpha) and inhibited processing in task-irrelevant regions (ipsilateral higher alpha). Similarly, Jones et al. (2010) found that in the primary somatosensory region (representing the stimulated hand), pre-stimulus alpha activity was decreased when participants were cued to attend to the hand, and increased when they were cued to attend to the foot. This attentional modulation of pre-stimulus somatosensory alpha was confirmed by a number of other studies (Anderson & Ding, 2011; Haegens et al., 2011).

Not only is pre-stimulus somatosensory alpha activity modulated by attention, demonstrating a pattern of lateralised alpha activity, but the modulation of pre-stimulus somatosensory alpha activity is also related to subsequent somatosensory perception. Lower pre-stimulus somatosensory alpha activity (contralateral to the hand that was stimulated) was associated with higher probability of correct perception of tactile stimulation (Baumgarten, Schnitzler, & Lange, 2016; Jones et al., 2010). Likewise, Haegens et al. (2011), using visual cues to direct attention to either the left or the right hand, found

that more pronounced lateralisation of pre-stimulus somatosensory alpha (the extent of difference between alpha activity contralateral and ipsilateral to the attended location, with lower alpha contralateral and higher alpha ipsilateral) was related to improved accuracy and speed of response on a tactile discrimination task.

The attentional modulation of pre-stimulus somatosensory alpha activity also applies to painful somatosensory stimuli. Two studies focused on somatosensory alpha activity, pain, and the influence of distraction. Peng, Hu, Zhang, and Hu (2014) investigated the influence of distraction, or direction of attention away from pain, during the experience of a tonic painful heat stimulus. They found that during tonic pain, alpha power in the upper alpha-band (10-15Hz) was significantly lower when attention was directed towards pain than when participants were distracted from pain by a cognitive task, predominantly in the somatosensory region contralateral to the location of the pain stimulus (electrode locations C2, C4, CP2, CP4). Del Percio et al. (2006) investigated changes in pre-stimulus alpha activity during the anticipation of a pain stimulus. They found evidence for lateralisation of pre-stimulus alpha activity over somatosensory regions, for what the authors defined as lower-range alpha or 'alpha-1' activity (alpha activity around 6-8Hz). The event-related decrease in pre-stimulus alpha power was more prominent in the contralateral central region than the ipsilateral central region, with respect to the location of pain stimulation. Furthermore, the event-related decrease of pre-stimulus alpha power in the central region (electrode location Cz) was significantly larger for the pain only condition, compared to two pain and distraction conditions (a cognitive task and a motor task). Thus, both studies found an effect of attention on somatosensory alpha activity for pain perception, with lower levels of alpha power when attention was directed to pain compared to attention directed away from pain, both during tonic pain (Peng et al., 2014), and pre-stimulus during the anticipation of pain (Del Percio et al., 2006).

Two other studies also demonstrated an attentional modulation of pre-stimulus somatosensory alpha activity for pain. In Hauck, Domnick, Lorenz, Gerloff, and Engel's (2015) study, participants were instructed either to direct

their attention to the finger where the pain stimulus was applied or to a finger where no stimulation took place. Laser pain stimuli were applied at a high and low intensity. Both pain intensity and direction of attention demonstrated an effect on somatosensory alpha activity (at a central region of interest including 31 electrodes around Cz), with a stronger reduction of alpha power as a result of high compared to low intensity stimuli, and a stronger reduction in alpha power for attended compared to unattended stimuli. May et al. (2012) similarly investigated the effect of attention on alpha activity in the primary somatosensory region but during the period before pain onset. They found that pre-stimulus somatosensory alpha activity was lateralised, with lower alpha power at the contralateral S1 region and higher alpha power at the ipsilateral S1 region with respect to the stimulated hand. Pre-stimulus somatosensory alpha power over the contralateral region was lower during attended compared to unattended conditions whilst pre-stimulus somatosensory alpha activity over the ipsilateral S1 region was higher in attended than unattended conditions. Thus, these two studies supply further evidence for a modulation of somatosensory alpha activity by attention, this time for attention directed towards or away from the location of stimulation, again both during pain (Hauck et al., 2015) and before pain onset (May et al., 2012).

Together, these findings (Del Percio et al., 2006; Hauck et al., 2015; May et al., 2012; Peng et al., 2014) show that the inhibitory function of alpha activity to guide information processing (Jensen & Mazaheri, 2010) possibly reflecting top-down attentional control (Foxe & Snyder, 2011; Klimesch et al., 2007), also applies to the painful somatosensory domain. Of particular interest is that changes in somatosensory alpha power were found during the anticipation of pain (Del Percio et al., 2006; May et al., 2012) suggesting that pre-stimulus somatosensory alpha activity is involved in the preparation for anticipated pain. However, these studies on somatosensory alpha activity and pain perception all depend on an active (top-down) manipulation of attention to pain, which limits the generalisability of these findings to pain perception in general, without an explicit manipulation of attention. The studies did not address the role of alpha activity in the bottom-up capture of attention by pain or anticipated pain, to facilitate the processing of the upcoming painful event.

A limited number of studies have investigated changes in pre-stimulus alpha activity (during the anticipation of pain), without an explicit top-down manipulation of attention. Babiloni et al. (2003) assessed pre-stimulus alpha activity during the anticipation of a predictable moderately painful stimulus and compared this to the anticipation of a non-painful stimulus. Painful and non-painful stimuli were delivered in separate blocks. To guide the expectation about an upcoming stimulus visual cues were presented during the anticipation period. The total anticipation period was 12s with a visual cue presented every 4s. An event-related synchronisation/event-related desynchronisation (ERS/ERD) calculation was applied to assess the change in alpha during a period of interest (E) compared to a baseline period, with two periods of interest: early pain anticipation (-2 to -1s before pain onset) and late pain anticipation (-1 to 0s). They found a significant reduction in pre-stimulus alpha power in the bilateral somatosensory region (electrode location C3 and C4, based on the 10-20 system) for predictable moderately painful stimuli compared to non-painful stimuli, in the -1 to 0s period. This reduction was most prominent over the contralateral somatosensory region with respect to the stimulated hand, the region relevant for the processing of the anticipated pain stimulus. This suggests that pre-stimulus somatosensory alpha activity is also involved in the preparation for a painful stimulus without an explicit top-down attentional modulation, but instead possibly reflecting involuntary bottom-up capture of attention by pain. However, this study did not assess the experience of pain that the participants had in response to the painful stimuli. In the non-painful somatosensory domain a significant relationship between pre-stimulus somatosensory alpha activity and the following perception of the non-painful somatosensory stimulus has been found (Baumgarten et al., 2016; Haegens et al., 2011; Jones et al., 2010). A link between pre-stimulus somatosensory alpha activity and the subsequent experience of pain could prove a promising target for the development of novel pain treatment approaches. It is therefore critical that the relationship between pre-stimulus somatosensory alpha activity and somatosensory perception is also investigated for painful somatosensory stimuli.



## 2.4 Pre-stimulus somatosensory alpha activity and the experience of pain

A small number of studies has shown a relationship between pre-stimulus somatosensory alpha activity and the experience of pain. Babiloni et al. (2006) assessed both pre-stimulus somatosensory alpha activity and perceived pain intensity. Participants were asked to rate the intensity of each pain stimulus on a numeric rating scale (NRS) ranging from 0 (no pain) to 10 (most intense pain imaginable). The study design was similar to that of Babiloni et al. (2003), with the application of predictable moderately painful stimuli preceded by a pain anticipation period of 12s and a visual cue presented every 4s. They used the ERS/ERD calculation but with two different periods of interest, from -1 to -0.5s for early pain anticipation and from -0.5 to 0s for late pain anticipation. In agreement with the findings of Babiloni et al. (2003), a reduction of somatosensory alpha power before the onset of a predictable moderately painful laser stimulus was found, which was most prominent at the contralateral somatosensory region with respect to the stimulated hand (electrode location CP3). Furthermore, a significant negative correlation between pre-stimulus somatosensory alpha activity at electrode location CP3 and pain intensity ratings was found during the early anticipation period. This significant negative correlation was present in what the authors referred to as the mid-alpha frequency range (7.6-9.6Hz;  $r = -.87$ ,  $p < .001$ ) and the higher-alpha range (9.6-11.6Hz;  $r = -.86$ ,  $p < .001$ ).

However, as all stimuli were of the same moderately painful intensity, habituation over the course of the experiment took place and pain intensity ratings during the first half of the experiment were significantly higher ( $5.23 \pm 0.32$ ) than the second half ( $4.90 \pm 0.39$ ). To address this, the correlations were calculated again, but with the decline of the pain intensity ratings in the second half compared to the first half of the experiment entered as a covariate. When controlling for the effects of habituation, only the correlation between pain intensity ratings and pre-stimulus somatosensory alpha activity in the higher-alpha band remained significant (partial correlation:  $r = -.67$ ,  $p = .048$ ). For the mid-alpha range, the partial correlation was no longer significant ( $r = -.41$ ,  $p = .274$ ). Thus, the correlations between pre-stimulus somatosensory alpha

activity and perceived pain intensity were affected by habituation, and after controlling for habituation the evidence remaining for a relationship between pre-stimulus alpha and perceived pain intensity was considerably reduced.

More recently, Tu et al. (2016) also found evidence for a negative relationship between pre-stimulus somatosensory alpha activity and experienced pain intensity. Laser pain stimuli were applied at 4 increasing intensities. Forty stimuli, 10 at each intensity, were delivered in a pseudorandomised order and with a random interstimulus interval between 10 and 15s. Therefore, both stimulus intensity and stimulus onset were unpredictable. Participants rated the intensity of each stimulus on a visual analogue scale (VAS) ranging from 0 (no pain) to 10 (most intense pain). To assess the relationship between EEG activity and perceived pain intensity at a range of frequencies, including alpha frequency, first the normalised EEG data and pain intensity ratings (at each stimulus intensity) were entered in a multivariate linear regression model for each participant and each electrode. The model coefficients reflected the importance of the EEG power data at each time-frequency point in the prediction of perceived pain intensity. Next, a non-parametric permutation test was applied. EEG and magnetoencephalography (MEG) studies usually include a large number of time-frequency pairs for a large number of electrodes, which results in a large number of statistical comparisons. Cluster-based non-parametric statistical testing offers a solution to the multiple comparisons problem for EEG/MEG data and is used to identify clusters of significant difference between conditions in EEG activity over frequency and time (Maris & Oostenveld, 2007). The model coefficients were entered into a non-parametric permutation test to identify time-frequency clusters for each electrode that had a significant relationship with perceived pain intensity. One pre-stimulus cluster in the alpha frequency range significantly related to reported pain intensity was identified. A cluster over the bilateral somatosensory region with a maximum contralateral to the stimulated hand (electrode location C4) was found for a frequency range of 8-15Hz and a time period of -0.221 to -0.031s before pain onset. Pre-stimulus somatosensory alpha power had a negative relationship with pain intensity ratings. They did not find evidence to suggest that this relationship was influenced by laser pain stimulus intensity.

Together, Babiloni et al. (2006) and Tu et al. (2016) provide some initial but limited evidence for a negative relationship between pre-stimulus somatosensory alpha activity and reported pain intensity. However, there were slight differences in their findings. The pre-stimulus time period in which the significant relationship was found was different. Whereas in one study the relationship was significant in a brief period directly before pain onset (-0.221 to -0.031s) (Tu et al., 2016), in the other study a negative correlation was not found for the period directly before pain onset (-0.5 to 0s) but only in an earlier anticipation period (-1.0 to -0.5s). In addition, Tu et al. (2016) identified a significant relationship between perceived pain intensity and alpha over bilateral somatosensory regions (albeit with a maximum in the contralateral region), in contrast with Babiloni et al. (2006) who only found a significant relationship for the contralateral somatosensory region. There are also differences in study design between the studies of Babiloni et al. (2006) and Tu et al. (2016) however, that might (in part) account for the differences in results. These differences in study design will be discussed in more detail in the next paragraph.

## **2.5 The influence of uncertainty about pain intensity**

One crucial difference between the studies of Babiloni et al. (2006) and Tu et al. (2016) that is important to address is that they induced a different expectation about pain intensity during the pre-stimulus period. The studies discussed above on pre-stimulus somatosensory alpha activity and non-painful and painful somatosensory perception together suggest the involvement of alpha activity during the anticipation of a (painful) somatosensory stimulus, linked to attentional mechanisms. For pain perception specifically, not only voluntary (top-down) direction of attention, but also the bottom-up capture of attention by pain could play a role. A critical factor to take into account when looking at the involuntary capture of attention during the anticipation of pain, is that this is influenced by expectations about pain intensity. The capture of attention by (anticipated) pain is moderated by several variables other than the physical intensity of the pain stimulus, such as novelty and predictability of the

anticipated pain stimulus, variables that together influence the perceived threat value of an anticipated painful stimulus (Eccleston & Crombez, 1999; Morley, 2008). It is not just pain that interrupts and captures attention, but particularly pain that is uncertain or unpredictable, or more threatening (Morley, 2008). For example, the interruption of an ongoing task by pain, as demonstrated using the primary task paradigm, was found to be enhanced when participants were uncertain about pain onset, or when they were uncertain about intensity of an upcoming pain stimulus (Crombez, Baeyens, & Eelen, 1994; Crombez, Eccleston, Baeyens, & Eelen, 1998). Therefore, when we investigate pre-stimulus somatosensory alpha activity and its relationship with pain experience, it is important to consider the possible influence of expectations about pain intensity, specifically uncertainty about pain intensity.

There is some initial evidence to suggest that expectations about pain intensity indeed have an effect on alpha activity before the onset of pain. Huneke et al. (2013) found that placebo conditioning, resulting in an expectation of pain relief, had a significant effect on alpha activity during rest. Pain ratings were compared for two blocks of moderately painful stimuli delivered before and after the placebo procedure. To induce an expectation of pain relief a placebo cream was applied with the suggestion that it would have an analgesic effect. Following this, the placebo participants received a block of pain stimuli at a reduced intensity. As they were not informed about this reduction in stimulus intensity they attributed the reduction in pain to an effect of the cream. A group of control participants underwent the exact same procedure, only they were informed that the cream was inactive and that the intensity of the stimulus following the application of the cream would be reduced. Therefore, they did not think that the cream had an analgesic effect. Resting-state alpha activity, i.e., when participants were not engaged in a particular task or receiving pain stimuli, was measured at four time points during the experiment: 1) at the start of the experiment before any pain stimulation; 2) after the first block of moderately painful stimuli; 3) after the placebo procedure (after the application of the cream and the pain stimuli at a reduced intensity); and 4) after the final block of moderately painful stimuli. Only the placebo group demonstrated a significant reduction in pain ratings for

the moderately painful stimuli after the placebo procedure. This was accompanied by a significant increase in resting-state alpha power. Resting-state alpha power was significantly increased in the placebo group only, when comparing alpha at time point 3 and 4. As there was no difference in the actual intensity of pain stimuli for the placebo and control groups, the reduction in pain ratings and increase of alpha activity can only be attributed to a difference in expectations. Although this study indicates that expectations about pain intensity can modulate alpha activity and pain experience, there are some limitations with respect to how much we can apply this finding directly to an effect of expectations on pre-stimulus somatosensory alpha activity and its relationship with pain experience. Huneke et al. (2013) did not find an effect of expectation about pain intensity on somatosensory alpha activity specifically. Source localisation estimated that the increase of alpha originated from other components of the pain network, including the left insula and bilateral medial prefrontal cortex. Moreover, the findings did not apply specifically to pre-stimulus alpha activity; instead an effect of expectations on alpha activity during rest was demonstrated, reflecting non-event-related background activity more distal in time from the pain stimulation.

Another study did find an effect of expectations about pain intensity on pre-stimulus alpha activity specifically. Franciotti et al. (2009) investigated the effect of uncertainty about pain intensity on pre-stimulus alpha activity. Two conditions were compared, one condition where all stimuli were non-painful (certainty about stimulus intensity), and one condition where both non-painful (40%) and painful (60%) stimuli were delivered in a randomised order (uncertainty about stimulus intensity). Alpha power was calculated over three alpha-frequency sub-bands and two pre-stimulus time windows, -0.90 to -0.40s and -0.55 to -0.05s. Relative alpha power was calculated and used for statistical analysis, reflecting the change in average alpha power at the region of interest and time window of interest compared to the average alpha power over the whole brain. An effect of uncertainty on pre-stimulus alpha activity was found in the anterior insula: a larger reduction of pre-stimulus alpha power was found when participants were uncertain about the intensity of an upcoming stimulus during the period of -0.55 to -0.05s before stimulus onset. As the modulation of pre-stimulus alpha activity by uncertainty was investigated in

insula cortex specifically, these findings cannot be generalised to somatosensory alpha activity directly. However, both regions have been implicated in the anticipation of pain and associated with the subsequent experience of pain. During the anticipation of pain, a stronger reduction of pre-stimulus somatosensory alpha activity has been found when participants expected a painful stimulus compared to a non-painful stimulus (Babiloni et al., 2003). Moreover, the modulation of pre-stimulus somatosensory alpha activity has been associated with pain experience (Babiloni et al., 2006; Tu et al., 2016). Based on fMRI findings, activity in the insula cortex has also been found during the anticipation of pain, which was related to whether a stimulus was perceived as painful or non-painful. For a stimulus at pain threshold intensity that sometimes resulted in a painful and sometimes a non-painful experience, pre-stimulus activity in the anterior insula was enhanced when the pain threshold stimulus was perceived as painful (Ploner, Lee, Wiech, Bingel, & Tracey, 2010; Wiech et al., 2010). Furthermore, both pre-stimulus activity in the insula and the somatosensory cortex has been found modulated by attention. Pre-stimulus activity in the insula cortex was increased when experienced threat was high during the anticipation of pain (Wiech et al., 2010), with higher threat value related to stronger capture of attention (Crombez et al., 1998). Pre-stimulus somatosensory alpha activity is modulated by the voluntary direction of attention towards or away from the anticipated pain (Del Percio et al., 2006; May et al., 2012). Finally, both the reduction in pre-stimulus somatosensory alpha activity (Babiloni et al., 2003, 2006; Del Percio et al., 2006; May et al., 2012; Tu et al., 2016) and the modulation of pre-stimulus alpha activity in the insula as a result of uncertainty (Franciotti et al., 2009) were found during a similar time window. Although slight differences were present, all of these studies found a change in pre-stimulus alpha activity during the final second directly before pain onset. Thus, together these findings provide some indication that both the somatosensory and insula cortex are involved in a similar underlying mechanism related to the anticipation of pain and the bottom-up capture of attention by pain.

Not only does uncertainty about pain intensity have an influence on pre-stimulus alpha activity, it also has an effect on pain experience. Being uncertain (compared to certain) about the intensity of an upcoming painful event (high or

low pain) is associated with higher perceived pain intensity (Lin, Hsieh, Yeh, & Niddam, 2014; Ploghaus et al., 2001). Similarly, an increase in perceived unpleasantness has been found when participants were uncertain about stimulus intensity (painful or non-painful) (Sawamoto et al., 2000). Moreover, in a clinical setting, uncertainty about the effectiveness of pain treatment, i.e., a context of certainty (“it does work”) versus uncertainty (“it may work”), impacts treatment outcome (Benedetti, 2002). For instance, uncertainty about the effectiveness of a painkiller led to a significant increase in painkillers requested over a 3-day period post-surgery: a higher amount of painkillers was needed to achieve a similar reduction of pain (Pollo et al., 2001).

As uncertainty about pain intensity affects pain experience and possibly also pre-stimulus alpha activity, uncertainty about pain intensity could be a confound in the relationship between pre-stimulus somatosensory alpha activity and pain experience. However to date, no study has identified an effect of uncertainty about pain intensity on pre-stimulus somatosensory alpha activity specifically. Unfortunately, none of the studies investigating pre-stimulus somatosensory alpha activity during the anticipation of pain (Babiloni et al., 2003) and its relationship with pain experience (Babiloni et al., 2006; Tu et al., 2016) directly addressed the influence of uncertainty about pain intensity by comparing a certain and uncertain condition. Babiloni et al. (2003) compared the perception of moderately painful stimuli to non-painful stimuli but only used predictable pain stimuli, resulting in certainty about pain intensity. Furthermore, the application of visual cues during the anticipation of pain resulted in a predictable pain stimulus onset. Babiloni et al. (2006) applied moderately painful stimuli only, again combined with visual cues. This also resulted in a highly predictable stimulus intensity and stimulus onset. In contrast, Tu et al. (2016) used an unpredictable setting where the intensity of an upcoming pain stimulus was unknown to the participant. Furthermore, the variable inter-stimulus interval resulted in unpredictable stimulus onset. Thus, whilst the two that demonstrated a relationship between pre-stimulus somatosensory alpha activity and pain experience included different levels of certainty about pain intensity (and found slightly different results) (Babiloni et al., 2006; Tu et al., 2016), a direct comparison of certainty and uncertainty is lacking.

Previous studies on pre-stimulus alpha activity and pain perception predominantly point to a modulation of alpha activity in the somatosensory cortex (Babiloni et al., 2003; Del Percio et al., 2006; May et al., 2012). Importantly, a relationship between alpha activity before the onset of pain and subsequent pain experience was identified in the somatosensory regions specifically (Babiloni et al., 2006; Tu et al., 2016). Therefore, the studies of this thesis focus on the role of somatosensory alpha activity specifically with the aim to better understand the relationship between pre-stimulus somatosensory alpha activity and pain experience. Despite some initial evidence for a relationship between pre-stimulus somatosensory alpha activity and perceived pain intensity (Babiloni et al., 2006; Tu et al., 2016), with higher pre-stimulus alpha related to lower perceived pain intensity, the limited number of studies to date does not allow for any firm conclusions. Furthermore, there were some differences in the findings of Babiloni et al. (2006) and Tu et al. (2016) with respect to pre-stimulus time window and location of somatosensory alpha activity related to pain experience. Differences that could be related to the difference in expectations about pain intensity (certain versus uncertain expectation about pain intensity) and the accompanying difference in capture of attention that was present for these two studies. Unfortunately, to date, no studies directly investigated the influence of uncertainty about pain intensity (by comparing certainty and uncertainty) on pre-stimulus somatosensory alpha activity and its relationship with pain experience. Therefore, in this thesis the relationship between pre-stimulus somatosensory alpha activity and pain experience was assessed both when participants were certain about pain intensity (intensity of an upcoming stimulus was known) and when participants were uncertain about pain intensity (intensity of an upcoming stimulus was unknown). To address the influence of uncertainty in this thesis, a visual cue – pain stimulus paradigm was developed. Similar to Babiloni et al. (2003, 2006) visual cues were presented during the anticipation of pain to guide expectations about the upcoming pain stimulus. However, here visual cues were applied specifically to manipulate certainty about the intensity of an upcoming pain stimulus to create a setting of certainty and uncertainty about pain stimulus intensity. Further details about this paradigm can be found in the Methodology chapter (Chapter 3).



Finally, the relationship between pre-stimulus somatosensory alpha activity and pain experience and the influence of uncertainty was assessed for perceived pain intensity and unpleasantness. Whereas the two existing studies on the relationship between pre-stimulus somatosensory alpha activity and pain experience only assessed perceived pain intensity (Babiloni et al., 2006; Tu et al., 2016), the studies of this thesis included a measurement of both perceived pain intensity and unpleasantness to allow for a further exploration of the relationship between pre-stimulus somatosensory alpha activity and pain experience. Pain intensity and pain unpleasantness, albeit highly correlated (Turk, Rudy, & Salovey, 1985), represent distinct dimensions of pain experience (sensory-discriminative and affective-motivational dimensions, respectively). Furthermore, manipulations/interventions to change pain experience not always affect experienced pain intensity and unpleasantness in the same way (e.g. Perlman, Salomons, Davidson, & Lutz, 2010; Price, Harkins, & Baker, 1987; Villemure et al., 2003). Thus, even though reported pain intensity and unpleasantness are related aspects of pain experience, they can show different responses to experimental manipulations. More detail on the assessment of perceived pain intensity and unpleasantness will be provided in the Methodology chapter (Chapter 3).

## **2.6 The modulation of alpha activity to reduce pain experience**

Based on the negative correlation between pre-stimulus somatosensory alpha activity and pain experience (Babiloni et al., 2006; Tu et al., 2016), increasing somatosensory alpha power before pain onset could be a promising approach to reducing pain experience. However, current evidence for a role of pre-stimulus alpha activity in pain experience relies largely on correlation-based findings. This limits an interpretation on the nature of the relationship between pre-stimulus somatosensory alpha activity and pain experience and prohibits any claim of causality. Some other findings do suggest that altering levels of alpha activity prior to pain could change the experience of pain. As described in detail earlier in the chapter (p. 23-24), Huneke et al. (2013) showed that the application of placebo cream to induce an expectation of pain relief not only led

to a significant reduction of pain ratings but was accompanied by an increase in resting-state alpha activity. Thus, this study demonstrates that a change in pain experience is accompanied by a change in resting-state alpha activity.

However, the significant increase in resting-state alpha activity was measured after the application of the painful stimuli, therefore we cannot conclude, based on this study, that an increase in alpha caused the reduction in pain experience. Finally, these findings did not apply to somatosensory alpha activity specifically. Source localisation estimated that the increase of alpha as found by Huneke et al. (2013) took place in the insula and medial prefrontal cortex, two neural regions considered part of the pain network that have previously been found activated during the anticipation of pain (Ploghaus et al., 1999). Furthermore, activity in these regions has been associated with expected pain intensity as reported by participants (Koyama, McHaffie, Laurienti, & Coghill, 2005) and perceived threat during the anticipation of pain (Wiech et al., 2010).

Another study did show that manipulations with the potential to modulate alpha activity can have an effect on pre-stimulus somatosensory alpha activity specifically. Mindfulness meditation has been related to an increase of alpha power (Bing-Canar, Pizzuto, & Compton, 2016; Wong, Camfield, Woods, Sarris, & Pipingas, 2015). Kerr et al. (2011) demonstrated that mindfulness meditation affects pre-stimulus somatosensory alpha activity, during the anticipation of a non-painful somatosensory stimulus. During the anticipation of a tactile stimulus, a visual cue was presented to instruct participants to detect a tactile stimulus either on the hand or the foot. There was a difference in alpha power in the S1 hand area when participants received instruction to detect tactile stimuli on the foot (S1 hand area processing irrelevant information) or on the hand (S1 hand area processing relevant information). Importantly, after an 8-week mindfulness meditation course, the modulation of pre-stimulus somatosensory alpha activity was significantly enhanced. Participants in the mindfulness meditation group demonstrated a significantly larger modulation of pre-stimulus alpha activity in the S1 hand area than control participants after the mindfulness meditation course, i.e., the difference in alpha power for detecting a tactile stimulus on the foot versus the hand was larger as a result of the mindfulness meditation course. This suggests that an intervention that has

the potential to modulate alpha activity, such as mindfulness meditation, might also have an effect on pre-stimulus somatosensory activity during the anticipation of a painful stimulus.

Interventions that increase somatosensory alpha activity could have potential in reducing pain experience. Moreover, investigation of interventions that increase somatosensory alpha activity and their effect on pain experience allows for examination of causality between pre-stimulus somatosensory alpha activity and pain experience. A number of interventions have the potential to increase alpha power, not only mindfulness meditation, but also transcranial alternating current stimulation at alpha frequency (alpha tACS) (Helfrich et al., 2014; Kasten, Dowsett, & Herrmann, 2016; Neuling, Rach, & Herrmann, 2013; Vossen, Gross, & Thut, 2015; Zaehle, Rach, & Herrmann, 2010) and binaural beats at alpha frequency (auditory stimulus with a perceived beat at alpha frequency) (Ecsy, 2014; Ioannou et al., 2015; Solcà et al., 2016). Very little work has been conducted on the effects of these manipulations on pain experience. A brief account of each of these three manipulations is given below. More detail on each of these manipulations will be covered in the relevant experimental chapters (Chapters 5, 6, and 7).

### **2.6.1 Binaural beats at alpha frequency**

Binaural beats are produced by presenting two tones at a slightly different frequency to each ear, resulting in a perceived beat at a frequency representing the difference in frequency between the two tones (Oster, 1973). Binaural beats are thought to be able to increase oscillatory neural activity through a mechanism of neural entrainment (Cohen, 2014; Thut, Schyns, & Gross, 2011), where binaural beats at a certain frequency increase oscillatory neural activity at the binaural beat frequency specifically. There are a few studies that suggest that listening to binaural beats at alpha frequency might result in a change in alpha activity (Ecsy, 2014; Ioannou et al., 2015; Solcà et al., 2016). However, so far, the number of studies are low and findings inconsistent (Beauchene, Abaid, Moran, Diana, & Leonessa, 2016; Gao et al., 2014; Vernon, Peryer, Louch, & Shaw, 2014). Some initial positive evidence for an effect of alpha binaural beats on pain experience is available (Ecsy et al.,

2016; Ecsy, 2014). However, only two studies have assessed changes in reported pain intensity after alpha binaural beat offset (offline changes) and only for moderately painful stimuli. Therefore, critical assessment of the potential of listening to alpha binaural beats during pain to reduce pain experience (intensity and unpleasantness) is warranted. This study will be addressed in detail in Chapter 5.

### **2.6.2 Transcranial alternating current stimulation (tACS) at alpha frequency**

Another type of manipulation that could be used to increase alpha activity is tACS. TACS is a type of non-invasive transcranial electrical stimulation (tES) (Cohen Kadosh, 2015) that is thought to directly modulate oscillatory neural activity in a frequency-specific manner, where oscillatory neural activity is modulated predominantly at the tACS frequency (Herrmann, Strüber, Helfrich, & Engel, 2016). Thus, the application of tACS at a frequency within the alpha range (e.g., 10Hz) allows for the enhancement of oscillatory neural activity in the alpha-band specifically. Although there is evidence to suggest that alpha tACS has the potential to increase alpha power, the evidence for an effect of alpha tACS on pain perception, and somatosensory perception in general is limited. To our knowledge only two studies (Feurra, Paulus, Walsh, & Kanai, 2011; Gundlach, Müller, Nierhaus, Villringer, & Sehm, 2016) provide some initial evidence to suggest that alpha tACS applied over the somatosensory scalp region could affect somatosensory perception, but for non-painful tactile stimuli only. Thus, in this thesis a first investigation of the effects of alpha tACS on pain experience was carried out. This study will be addressed in detail in Chapter 6.

### **2.6.3 Mindfulness meditation**

Mindfulness meditation has been investigated in terms of its effect on pain management for a variety of clinical/chronic pain conditions, with significant improvement not only in pain intensity, but also factors such as pain acceptance and pain interference as found in patients with headache pain (Day

et al., 2014), and quality of life and coping with pain as found for patients with fibromyalgia (Grossman, Tiefenthaler-Gilmer, Raysz, & Kesper, 2007). For experimental pain a positive effect of mindfulness meditation on perceived pain has been demonstrated as well, when interventions had a duration of at least 3-4 days (Zeidan et al., 2011; Zeidan, Gordon, Merchant, & Goolkasian, 2010) up to several weeks (Kingston, Chadwick, Meron, & Skinner, 2007).

Although there is some initial evidence to suggest that mindfulness meditation might have a positive effect on pain experience in an experimental pain setting, little is known about the possible neural mechanisms behind the changes in pain experience. It has been hypothesised that the effect of mindfulness meditation programmes might be related to a modulation of somatosensory alpha activity (Kerr, Sacchet, Lazar, Moore, & Jones, 2013). This hypothesis is supported by a number of studies that found a modulation of alpha activity related to mindfulness meditation: 1) a modulation of pre-stimulus alpha activity following an 8-week mindfulness meditation course (Kerr et al., 2011); 2) a significant increase of alpha power during a mindfulness breathing exercise (Bing-Canar et al., 2016); and 3) significantly higher alpha activity during rest for experienced mindfulness meditators compared to meditation-naïve control participants (Wong et al., 2015). To conclude, the literature indicates that mindfulness meditation can have a positive effect on pain experience. A few studies have also suggested that mindfulness meditation can lead to an increase in alpha power. However, to our knowledge no study has investigated the effects of mindfulness meditation on somatosensory alpha activity for pain perception. In this thesis, the effects of a standardised 8-week mindfulness-based stress reduction (MBSR) course on somatosensory alpha activity and pain experience were investigated. This study will be addressed in Chapter 7.

## **2.7 The rationale for the key outcome variables of this thesis**

This thesis investigates the relationship between somatosensory alpha activity and pain perception and the potential of three interventions to reduce pain, focusing on a number of key outcomes: 1) pre-stimulus somatosensory

alpha activity, somatosensory alpha activity before the onset of pain; 2) the experience of pain, the relationship between pre-stimulus somatosensory alpha activity and pain experience; and 3) the influence of fear of pain and pain catastrophising on the relationship between pre-stimulus somatosensory alpha activity and pain experience.

To investigate the role of somatosensory alpha activity in pain perception, this thesis focuses on pre-stimulus somatosensory alpha activity specifically. An important advantage of measuring changes in pre-stimulus somatosensory alpha activity, i.e., before the onset of the pain stimulus, is that any change in pre-stimulus alpha activity purely reflects the effect of contextual processing, i.e., processing related to the anticipation of pain and the affective and cognitive influences during this period such as expectations about pain. It is not 'contaminated' by any pain-stimulus-related processing, processing in response to painful input (Ploner, Sorg, & Gross, 2016). Thus, investigating pre-stimulus somatosensory alpha activity in this thesis allowed for the selective assessment of the role of somatosensory alpha activity in the preparation for pain, and how this is influenced by for example uncertainty about pain intensity or interventions that modulate the strength of alpha.

Investigating pre-stimulus somatosensory alpha activity is also relevant from a clinical point of view. The potential of increasing somatosensory alpha activity before pain onset to reduce pain may offer opportunity not just in reducing pain experience when pain is present but also in the prevention of pain, for instance, in the prevention of postoperative persistent pain. There are preoperative factors that can predict the intensity of postoperative acute pain. In patients undergoing breast reconstruction it has been found that severity of pain, anxiety, and depression before the operation were associated with the severity of postoperative acute pain (Kulkarni et al., 2017). Importantly, intensity of postoperative acute pain is associated with the risk of developing persistent postoperative pain (Kehlet, Jensen, & Woolf, 2006; Yarnitsky et al., 2008). Therefore, applying interventions in the preoperative period to reduce postoperative pain, might be a promising approach to prevent the development of persistent pain. If increasing pre-stimulus somatosensory alpha activity -

alpha before the onset of pain - proves effective in reducing pain in an experimental pain setting, this might offer a novel approach to the management of postoperative (persistent) pain. Moreover, the outcome of pain treatment is influenced by the state we are in before the onset of the treatment. For example, our expectations about treatment success affect the effect of pain treatment (Benedetti, 2002; Pollo et al., 2001). It has also been suggested that neural oscillatory activity during rest before the application of a neuromodulatory intervention (e.g., mindfulness) might be related to the success of these interventions in reducing pain. Higher theta activity before a hypnosis intervention was associated with a larger reduction of pain ( $r = 0.46$ ,  $P = 0.009$ ), further exploratory analysis also identified a significant negative association between alpha activity before the meditation intervention and pain reduction as a result of the intervention ( $r = -0.45$ ,  $P = 0.011$ ) (Jensen et al., 2014). Thus, manipulations that successfully increase alpha activity could also be useful in improving the effectiveness of treatment to reduce pain.

Although this thesis assessed the neurophysiological response (changes in pre-stimulus somatosensory alpha activity) during the anticipation of pain, and the effect of uncertainty about pain intensity on pre-stimulus somatosensory alpha activity and pain perception, ultimately the aim was to find out if an increase of pre-stimulus somatosensory alpha activity would result in a reduction of pain experience. In most (but not all) cases, the starting point leading to an experience of pain is a painful stimulus, a painful stimulus that triggers a neurophysiological response, ultimately leading to an experience of pain. The study of the neurophysiological processing of a given painful stimulus can improve our understanding of how an experience of pain comes about in the brain. However from a practical point of view, with respect to a clinical application of findings in particular, we cannot limit our study of pain to the neurophysiological response to pain. Ultimately, we would want to know if the changes in neurophysiological response also lead to a reduction in the pain experience. Therefore, in this thesis I focussed on pain experience and its relationship with pre-stimulus somatosensory alpha activity, to assess if the modulation of pre-stimulus somatosensory alpha activity would lead to a reduction in the amount of experienced pain.

Finally, the influence of two pain-related individual characteristics on the relationship between pre-stimulus somatosensory alpha activity and pain experience, and on the effectiveness of the interventions (tACS, binaural beats, and mindfulness meditation) to reduce pain experience was investigated: fear of pain and pain catastrophising. Both fear of pain and pain catastrophising have been implicated as important factors in the development and maintenance of chronic pain, as part of the fear-avoidance model of chronic pain (Leeuw et al., 2007; Vlaeyen, Kole-Snijders, Boeren, & van Eek, 1995). Originally developed to explain why some patients with acute low back pain progress to develop chronic low back pain, this cognitive-behavioural model describes how cognitive and emotional responses to pain can lead to the development of chronic pain. As part of this model, pain catastrophising, where pain is interpreted as highly threatening, leads to fear of pain. This in turn results in escape/avoidance behaviour with respect to pain. It is this chain of an interpretation of pain as highly threatening, excessive fear towards pain, and avoidance behaviour that can lead to further/continued pain and pain-related disability. Both fear of pain and pain catastrophising affect the amount of pain experienced, for experimental pain and chronic pain. For example, in an experimental pain setting, stronger fear of pain has been related to higher perceived pain intensity for immersion of the hand in painfully cold water, in normally pain-free healthy participants (Hirsh et al., 2008). Both stronger fear of pain and stronger pain catastrophising were related to higher perceived pain intensity for experimentally-induced muscle pain, also in normally pain-free healthy participants (Parr et al., 2012). In relation to chronic pain, higher levels of catastrophising have been found to be related to higher levels of pain, pain-related disability, and psychological distress, across patients with lower back pain, other types of musculoskeletal pain, headache pain, and abdominal pain (Severeijns, Vlaeyen, Van Den Hout, & Weber, 2001). A meta-analysis has also shown a moderate to large positive relationship between fear of pain and pain-related disability, this relationship did not vary much based on the participant characteristics (gender, age) and pain characteristics (pain intensity, location, duration), suggesting that higher fear of pain was related to more pain-related disability across a variety of patients and pain conditions (Zale, Lange, Fields, & Ditre, 2013). Moreover, pain catastrophising might have an influence



on the outcome or effectiveness of treatment, in chronic pain. For example, a systematic review on treatment outcome in patients with low back pain found that catastrophising not only predicted treatment outcome (levels of pain and disability at follow-up) but also mediated treatment outcome. A greater decrease of catastrophising over treatment time was related to a greater improvement as a result of treatment (Wertli et al., 2014). For patients undergoing knee surgery, pre-operative pain catastrophising was found to be related to pain outcomes over a follow-up period of 6 months (Riddle, Wade, Jiranek, & Kong, 2010). It has therefore been suggested that assessing the role of fear of pain and pain catastrophising could assist in the tailoring of existing pain treatment programmes to individual needs to optimise individual outcome (McCracken & Turk, 2002). It should be stressed however, that these findings are all based on effectiveness of treatment to reduce chronic pain. Based on these findings it cannot be concluded with certainty that an influence of pain catastrophising and fear of pain on the effectiveness of interventions to reduce pain experience is also present for experimental pain stimuli and in normally pain-free healthy participants. In the studies of this thesis the role of fear of pain and pain catastrophising on pain experience was assessed in a setting of acute experimentally-induced pain.

## **2.8 Thesis aims**

This thesis comprises four studies that collectively aimed to generate a better understanding of the relationship between pre-stimulus somatosensory alpha activity and pain experience.

The first study presented in Chapter 4, was designed to replicate the negative relationship between pre-stimulus somatosensory alpha activity and perceived pain intensity, which has been demonstrated previously by a limited number of studies (Babiloni et al., 2006; Tu et al., 2016). In addition, this relationship was for the first time also assessed for perceived unpleasantness. Uniquely, in this study the relationship between pre-stimulus alpha activity and pain experience was assessed in a setting of certainty and uncertainty about the intensity of an upcoming pain stimulus, as uncertainty about pain intensity

could have an influence on the relationship between pre-stimulus somatosensory alpha activity and pain experience. This could lead to a better understanding of how somatosensory alpha activity is involved in pain perception and related to pain experience.

Chapters 5, 6, and 7 present three further studies that assessed the potential of three manipulations to reduce pain experience, by increasing somatosensory alpha power - alpha binaural beats, alpha tACS, and mindfulness meditation respectively. The effects of these three manipulations on pain experience were assessed in a state of certainty and uncertainty about pain intensity.

The study presented in Chapter 5 is a behavioural study investigating the effects of binaural beats at alpha frequency on pain experience. A small number of studies have demonstrated an increase of alpha power during alpha binaural beats as a result of entrainment (Ecsy, 2014; Ioannou et al., 2015), and a reduction of pain experience (Ecsy et al., 2016; Ecsy, 2014). However, to date, a reduction of pain experience as a result of listening to alpha binaural beats has only been found offline, after listening to the binaural beats. This study uniquely investigated whether listening to alpha binaural beats could reduce the amount of pain experienced online, with participants rating pressure pain stimuli whilst listening to the alpha binaural beats, and thus assessing whether alpha entrainment directly influenced pain experience.

Chapter 6 describes a second behavioural study assessing the potential of tACS at alpha frequency to reduce pain experience. Although there is evidence to suggest that alpha tACS has the potential to increase alpha power, to our knowledge, no investigation of the effects of alpha tACS (via an increase of somatosensory alpha activity) on pain experience has taken place. This study was the first to investigate the effects of alpha tACS on pain experience for pressure pain stimuli at three different intensities (non-painful, pain threshold, and moderately painful), with the application of alpha tACS over bilateral somatosensory scalp regions.

The study presented in Chapter 7 is an EEG study that investigated the effect of a mindfulness meditation on both pain experience and somatosensory

alpha activity. Although there is evidence for a positive effect of mindfulness meditation on pain experience in an experimental pain setting, little is known about the possible neural mechanisms behind these changes in pain experience. By measuring both somatosensory alpha activity and pain experience before and after an 8-week mindfulness meditation course, this study investigated the hypothesis that the effects of mindfulness meditation on pain experience might be mediated by a change in somatosensory alpha activity (Kerr et al., 2011). To our knowledge, this study is the first to directly investigate the effects of mindfulness meditation on somatosensory alpha activity for the perception of pain.

Together, these three studies investigating the manipulation of somatosensory alpha activity to reduce pain experience provide a first indication of the potential of interventions that target alpha activity to reduce clinical pain. Furthermore, as the relationship between somatosensory alpha activity and pain experience to date largely depends on correlations, these studies provide an important initial step in assessing causality between somatosensory pre-stimulus alpha activity and pain experience.

## Chapter 3 Methodology

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This thesis comprises four studies that were designed to collectively examine the relationship between pre-stimulus somatosensory alpha activity and pain experience. These four studies will be reported in the upcoming Chapters 4-7. This Chapter details the methodological issues pertinent to those studies. Chapter 4 describes an EEG study assessing pre-stimulus somatosensory alpha activity during the application of an experimental pressure pain stimulus. To investigate the influence of uncertainty on the relationship between somatosensory alpha activity and pain experience a paradigm was developed to manipulate uncertainty about pain intensity where each pressure pain stimulus was preceded by a visual cue. This visual cue paradigm was employed in three further studies investigating the effect of three interventions on pain experience in a setting in which pain intensity was uncertain and a setting in which pain intensity was known; binaural beats at alpha frequency (Chapter 5), tACS at alpha frequency (Chapter 6), and mindfulness meditation (Chapter 7). This chapter explains the key stimuli, manipulations, measures, and analyses that were applied across the four studies. In the first two sections, the key stimuli and manipulations will be addressed (pressure pain stimuli and the application of visual cues). In the subsequent three sections, the rationale for the key outcome measures will be explained (pain rating scales, EEG outcome measures, and questionnaires).

### 3.1 Experimental pain stimulation: pressure pain

In all four studies, an experimental pain stimulus was used to investigate pain experience. Although investigating clinical pain has several advantages in being able to translate this work directly to a pain population, clinical pain is difficult to control and highly individual to each person's pain. An experimental pain stimulus, in contrast, can be applied in a controlled fashion with respect to stimulus intensity, location, and duration (Rollman, 1983). Moreover, an experimental pain stimulus allows for a precise assessment of pain experience with a clear relationship between pain stimulus intensity and pain experience; changes in pain stimulus intensity result in measurable and reliable changes in pain experience (Beecher, 1957). The studies in this thesis are investigating the impact of interventions that target alpha at an early stage of development and therefore it is important to use such a controlled stimulus.

A large variety of methods to deliver experimental pain are available, the majority of which are applied on the skin and within the physical categories of mechanical (e.g. pressure), thermal (e.g. heat, cold), electrical, and chemical stimulation (e.g. injection of painful substance in skin or muscle) (Rollman, 1983). Where some experimental pain methods activate both the nociceptive receptors (A delta and C fibre receptors) and innocuous, touch receptors in the skin (A beta fibre receptors), other experimental pain methods selectively activate nociceptive receptors. Laser pain stimulation is a prime example of a selective pain method, it selectively activates nociceptive receptors in the skin and not touch A beta fibre receptors, as laser stimulation does not require any contact with the skin. Laser pain stimuli are particularly useful when investigating the nociceptive system and nociceptive processing (Plaghki & Mouraux, 2003). In the studies of this thesis pressure pain was used, which is a mechanical pain method. In contrast to laser pain stimuli, pressure pain stimuli are not selective, activating both nociceptive receptors and touch receptors (Plaghki & Mouraux, 2003). This lack of selectivity means that pressure pain stimuli might be less suitable for investigation of the nociceptive system or nociceptive processing specifically. However, in this thesis, the aim was to investigate pain experience, the 'outcome' of nociceptive processing after the application of an experimental pain stimulus, not nociceptive processing itself.

Furthermore, in the two EEG studies where neurophysiological processing related to pain was examined, the focus was on pre-stimulus neural activity. As pre-stimulus neural activity reflects activity before the pain stimulus is applied, selectivity of the pain stimulus is not an influencing factor.

Although the study of pain experience using an experimental pain stimulus has clear advantages, it has been questioned to what extent findings based on experimental pain are relevant for the experience of clinical and chronic pain (Edwards, Sarlani, Wesselmann, & Fillingim, 2005). Experimental pain is different from naturally occurring pain in fundamental ways; they differ with respect to pain duration, range of pain intensities, and controllability (Edwards et al., 2005). Furthermore, experimental pain is often much more predictable and less threatening (participants are informed that no tissue damage will be done and that they can stop at any moment). Also, the consequences of acute/chronic clinical pain, pain as a result of a medical condition or trauma or an invasive medical procedure such as surgery, are different and go further than 'just' an experience of pain but also affect daily life and emotional wellbeing (Edens & Gil, 1995). However, this does not mean that the application of experimental pain to investigate pain experience is not relevant for clinical pain settings. Pressure pain has been applied in the study of healthy and clinical populations and is the most commonly applied stimulus to assess the pain response in clinical pain populations (Plaghki & Mouraux, 2003). For example, in patients with chronic low back pain a significant positive correlation was found between pain sensitivity for pressure pain stimuli (pressure pain threshold and tolerance) and clinical pain and physical functioning (Clauw et al., 1999). Moreover, assessment of preoperative pressure pain sensitivity has potential as a method in the prediction of risk of developing post-operative clinical pain. In patients undergoing abdominal surgery, preoperative pressure pain tolerance was significantly negatively correlated with experienced postoperative pain and morphine consumption: lower preoperative pressure pain tolerance was associated with higher levels of postoperative pain and morphine consumption 24h post-surgery (Hsu et al., 2005). As a diagnostic tool, pressure pain has been used to assess pressure pain thresholds in a variety of pain syndromes, such as fibromyalgia, temporomandibular disorder, and tension-type headache, usually by means of

a hand-held pressure algometry device (Treede, Rolke, Andrews, & Magerl, 2002).

Although in a clinical setting, pressure pain is often applied with a hand-held pressure algometry device, this is not as suitable a technique for experimental pain research. Hand-held devices are not optimal for standardised and controlled pain stimulation, and not ideal for the repeated delivery of pain stimuli at one specific intensity (Plaghki & Mouraux, 2003). To reliably assess pain experience in an experimental setting, a controlled means of delivering pressure pain is essential (Beecher, 1957). To this end, electromechanical pressure devices have been developed that can be controlled with a computer (Treede et al., 2002). To deliver pressure pain in a controlled and standardised manner the studies of this thesis used a computer-controlled, custom-built MRI-compatible pneumatic pressure pain stimulator (manufactured by DancerDesign, St. Helens, UK) (Figure 3.1). This pressure pain device comprises a pneumatic force controller that uses compressed air to lower a probe at a variable force. The delivery of each pressure stimulus is controlled by passing a certain voltage value into the stimulator. This voltage value translates into a certain amount of pressure at the probe, at a range from 0.00 kg/cm<sup>2</sup> (0.00 v input) to 7.28 kg/cm<sup>2</sup> (generated from 1.00V input). The specific voltage values for each participant were delivered to the pneumatic force controller using a bespoke program running under E-Prime 2.0 software (Psychology Software Tools, Pittsburgh, PA). Pressure stimuli were delivered to the middle finger of the non-dominant hand using a circular probe. A circular 1 cm<sup>2</sup> rubber pad was lowered onto the fingernail bed centrally placed to cover an equal area of nail and skin. Pressure stimuli with a duration of several seconds were applied to the fingertip at three intensities: non-painful, pain threshold, and moderately painful. In a study using the same pressure pain stimulator, participants described the sensation during painful pressure stimulation as throbbing, tingling, pressing or shooting in nature, and as "quite sharp" and "heavy pushing down" (Rowbotham, Holler, Lloyd, & Wearden, 2014).

The pain response to pressure pain stimuli is relevant in experimental and clinical pain settings. Therefore, the pressure pain method is particularly favourable in the translation of the findings of this thesis to a clinical pain

population. Nonetheless, as acute experimental pain and clinical/chronic pain are distinct phenomena, some care should be taken when generalising findings from an experimental setting to a clinical setting. The primary focus of the studies of the thesis is on pain experience in healthy, pain-free participants. The studies investigated the effects of a number of manipulations on pain experience for experimentally-induced pressure pain. The potential of these manipulations in a clinical setting to manage pain will be considered as a point of discussion, but taking into account the limitations of a direct comparison between experimentally-induced acute pain and chronic pain.



**Figure 3.1** The pneumatic pressure pain stimulator used in the studies of this thesis (manufactured by DancerDesign, St. Helens, UK). A series of pressure pain stimuli were applied to the finger tip of the middle finger at three intensities: non-painful, pain threshold, and moderately painful (as set for each participant individually using a ramping procedure).

### **3.2 Uncertainty about pain intensity: visual cues**

In this thesis a visual cue - pain stimulus paradigm was developed to examine the influence of uncertainty about pain intensity on the relationship between pre-stimulus somatosensory alpha activity and pain experience. Visual cues were used to create two conditions: one in which participants knew what pressure intensity to expect and one in which participants did not know what pressure intensity to expect. The use of visual cues to manipulate expectations



about upcoming pain is well-established method, visual cues have reliably induced an expectation about pain intensity and a modulation of pain experience across a variety of settings (e.g., Brown, Seymour, Boyle, El-Deredy, & Jones, 2008; Keltner et al., 2006; Lin et al., 2014; Ploghaus et al., 1999).

Visual cues have been applied successfully to manipulate uncertainty about the intensity of an upcoming stimulus. Participants are aware of a relationship between visual cue and pain stimulus; participants all correctly report which visual cue is predictive and which one is not predictive of pain intensity post-experiment (Lin et al., 2014). Moreover, the application of visual cues to induce uncertainty has been found to modulate pain experience. Ploghaus et al. (2001) used two different visual cues to create a predictable condition where the visual cue (a triangle) was always followed by a low intensity pain stimulus (pain intensity was known) and an unpredictable condition where another visual cue (a square) was followed by either a low intensity or occasionally a high intensity pain stimulus (pain intensity was uncertain). The visual cues successfully modulated pain experience: when uncertain, the moderately painful stimulus was rated as significantly more intense than when pain intensity was known. Furthermore, participants rated their anxiety about the impending pain stimulus as significantly higher when they were uncertain (as rated before the onset of the pain stimulus). Lin et al. (2014) found similar results, using the same visual cue – pain stimulus paradigm as Ploghaus et al. (2001).

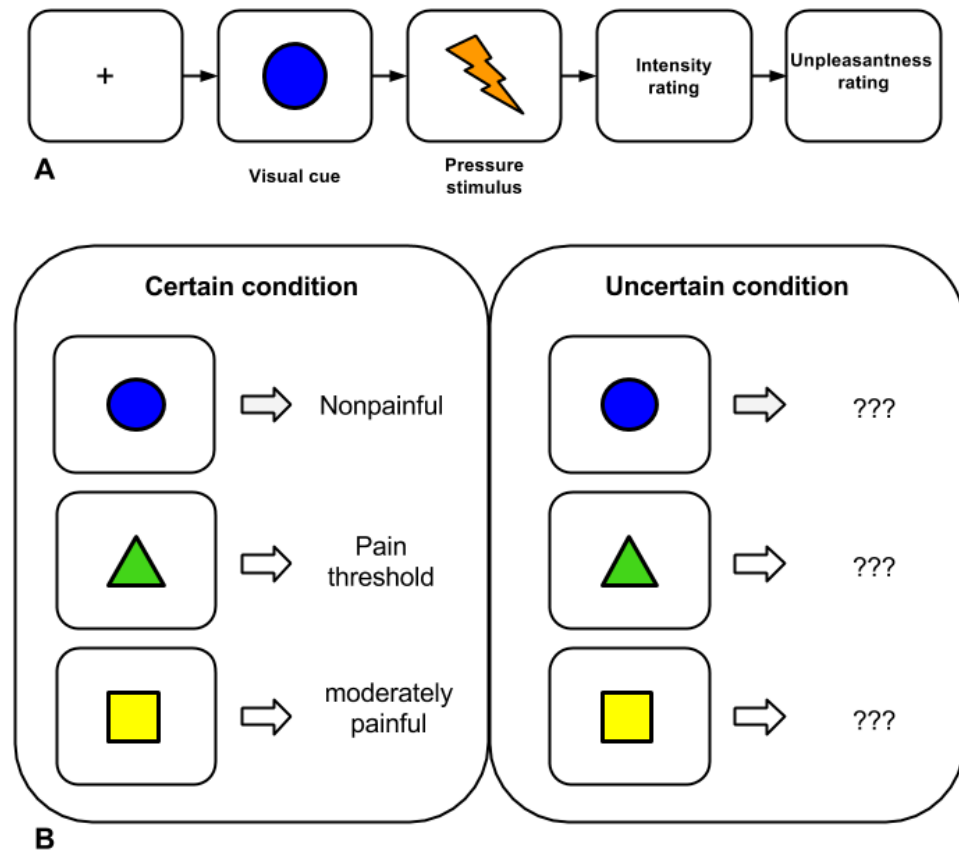
Although these two studies (Lin et al., 2014; Ploghaus et al., 2001) found an effect of uncertainty about pain intensity on pain experience using visual cues, the visual cue – pain stimulus protocol they applied had a limitation. Where perceived pain intensity for an uncertain versus a predictable or certain setting could be compared for the low intensity pain stimulus, there was no certain condition for the high intensity pain stimulus. Therefore, a potential difference in perceived pain intensity as a result of uncertainty could not be explored for high intensity pain stimuli. Brown et al. (2008) did compare uncertain pain intensity to certain pain intensity for both low intensity and high intensity pain stimuli. They used three stimulus intensities (non-painful, low intensity mild pain, and high intensity moderate pain), combined with four

different visual cues. The visual cues were four visually presented words, three words each creating a setting in which the intensity of an upcoming stimulus was certain ('low', 'medium', and 'high') and the word 'unknown' resulting in a setting of uncertainty about stimulus intensity. Thus, perceived pain intensity in an uncertain setting (either non-painful, mildly painful, or moderately painful) could be directly compared to three conditions where stimulus intensity was certain: certain – non-painful, certain - mildly painful, and certain – moderately painful. Uncertainty about stimulus intensity led to significantly higher ratings for the non-painful stimulus compared to when participants knew that stimulus intensity would be non-painful. In contrast, uncertainty led to significantly lower pain ratings for the moderately painful stimulus compared to when participants knew that the stimulus intensity would be moderately painful. For mildly painful stimuli no significant effect of uncertainty was found. Thus, their results suggested that the change in perceived pain intensity as a result of uncertainty depended on pain stimulus intensity. As the effect of uncertainty might be different depending on stimulus intensity, in the studies of this thesis, we utilised a visual cue – pain stimulus paradigm that included a predictable condition for each of the pressure stimulus intensities (non-painful, pain threshold, and moderately painful) to equally allow for an assessment of the effects of uncertainty at each of the pressure stimulus intensities.

Our visual cue – pain stimulus paradigm to manipulate uncertainty with respect to stimulus intensity was similar to the paradigm of Brown et al. (2008) in two ways: 1) it also involved the application of pain stimuli at three intensities (non-painful, pain threshold, and moderately painful); 2) visual cues were applied to allow for assessment of the effect of uncertainty about pain intensity at each of the three pain stimulus intensities. However, the present paradigm also had some unique features that differentiated it from the three studies described above (Brown et al., 2008; Lin et al., 2014; Ploghaus et al., 2001). Those studies intermixed the trials where pain intensity was predictable and where pain intensity was uncertain. Thus, participants alternated between a state of certainty and uncertainty from trial to trial, resulting in a brief within-trial state of uncertainty. In contrast, in the four studies of this thesis, the predictable and uncertain trials were delivered in separate blocks. This resulted in an investigation of uncertainty not as a brief trial-to-trial state, but uncertainty as a

more prolonged state over an entire block (with a duration of around 15-20 minutes). It is for a more prolonged state of uncertainty that an effect on pre-stimulus alpha activity has previously been demonstrated. Franciotti et al. (2009) did not use visual cues to induce uncertainty, but an uncertain and predictable condition were delivered in separate blocks. In the predictable condition participants only received non-painful stimuli, in the uncertain condition participants received painful and non-painful stimuli in a random order (40% painful and 60% non-painful). A significant effect of a prolonged state of uncertainty about pain intensity on pre-stimulus alpha activity was found in the anterior insula. Thus, in this thesis we similarly applied a certain and uncertain condition in two separate blocks to investigate the effect of uncertainty on somatosensory alpha activity. Finally, Franciotti et al. (2009) only compared uncertainty about stimulus intensity (painful or non-painful) to certainty that a stimulus would be non-painful. In this thesis we compared uncertainty about stimulus intensity (non-painful, pain threshold, moderately painful) to certainty about stimulus intensity for non-painful, pain threshold, and moderately painful stimuli.

In the visual cue – pain stimulus paradigm of the present thesis, as in the paradigm developed by Ploghaus et al. (2001), simple shapes were used as visual cues. However, where Brown et al. (2008), Lin et al. (2014), and Ploghaus et al. (2001) used different visual cues for the certain and uncertain condition, in this thesis the same visual cues were used to create the certain and uncertain condition (Figure 3.2). Three different visual cues were used (a green triangle, a blue circle, and a yellow square) to manipulate uncertainty about the intensity of an upcoming pressure stimulus. In the certain condition, each of these three visual cues was paired with one particular pressure stimulus intensity and predicted one particular pressure intensity. In the uncertain condition, the same three visual cues were used, but here the visual cues were randomly combined with one of the three pressure stimulus intensities, resulting in visual cues that were not predictive of the pressure intensity of an upcoming pressure stimulus (see Fig 3.2).



**Figure 3.2** Manipulation of certainty about pressure stimulus intensity. Visual cues were used to induce a state of certainty and uncertainty about pressure stimulus intensity (non-painful, pain threshold, moderately painful). Three visual cues were predictive of the three different pressure intensities in the certain condition. The same three visual cues were randomly combined with one of the three pressure stimulus intensities in the uncertain condition, resulting in visual cues that were not predictive of pressure stimulus intensity.

### 3.3 Pain rating scales

A variety of methods are available to measure the pain response, e.g., assessment of pain threshold and tolerance, pain evoked neural responses (such as Pain Evoked Potentials as measured with EEG), and pain measures based on self-report such as questionnaire-based assessment of pain experience (Rollman, 1983), e.g. the McGill Pain questionnaire (Melzack, 1975). In this thesis, pain rating scales were used to assess pain experience. Three of the most commonly used pain rating scales, for both clinical and research purposes, are The Visual Analogue Scale (VAS), the Numerical

Rating Scale (NRS), and the Verbal Rating Scale (VRS) (Ferreira-Valente, Pais-Ribeiro, & Jensen, 2011; Williamson & Hoggart, 2005). The VAS entails a 10-cm horizontal line with descriptors labelling the two end points, usually “no pain” and “worst imaginable pain”. Participants are asked to draw a mark on the line representing the amount of pain they experienced. The VAS score reflects the distance from the zero end point to the participant’s mark in millimetres (resulting in a 101-point scale). The NRS is usually an 11-point numerical scale from 0 to 10, with 0 representing “no pain” and 10 representing “worst imaginable pain” or other similar descriptors. Here participants are asked to select the number that best represents their pain experience. Finally, the VRS is usually a 5-point scale consisting of 5 phrases that describe increasing levels of pain intensity (e.g. no pain, mild pain, moderate pain, intense pain, maximum pain). Participants select the phrase that best represents their experience.

A number of studies have compared and evaluated these rating scales (e.g. Ferreira-Valente et al., 2011; Price, Bush, Long, & Harkins, 1994; Williamson & Hoggart, 2005). and all conclude that the VAS, NRS, and VRS are reliable and suitable to assess pain experience, and that the psychometric difference in performance between the scales is small. Price et al. (1994) concluded that both the VAS and the NRS are reliable and consistent measures to assess experienced pain intensity and pain unpleasantness, both in an experimental and a clinical pain setting. More recently, Ferreira-Valente et al. (2011) investigated how responsive the VAS, NRS, VRS, and Faces Pain Scale-Revised (FPS-R) were in detecting differences in pain stimulus intensity for an experimental pain stimulus. Each scale was able to successfully detect differences in pain stimulus intensity, as reflected by significantly different ratings for stimuli at different intensities. Best performance was found for the NRS, indicated by a larger effect size and F statistic value. The NRS was closely followed by the VAS, with the VRS and FPS-R slightly less responsive.

The studies in this thesis used NRSs to assess pain experience. Two 11-point NRSs were used ranging from 0 to 10. These were presented after each pressure stimulus. With pain being a multidimensional experience, this thesis applied two scales to assess perceived pain intensity and unpleasantness separately, the intensity scale reflective of sensory-discriminative aspects and the unpleasantness scale of affective aspects of

pain experience. It has been proposed that measuring the sensory and affective dimensions separately might not result in any unique information, as the sensory and affective component of pain experience (as assessed by the Pain Rating Index of the McGill Pain Questionnaire; Melzack, 1975) were found to be highly intercorrelated in patients with chronic pain (Turk et al., 1985). However, there are also findings to support a separate assessment of pain intensity and unpleasantness. Experimental pain methods can be distinguished by different relationships between intensity and unpleasantness ratings. For example, Rainville, Feine, Bushnell, and Duncan (1992) found significant differences in how unpleasantness ratings related to intensity ratings for four types of experimental pain stimuli. Two types of phasic pain methods, electrical stimuli and contact heat stimuli, resulted in significantly lower unpleasantness ratings compare to intensity ratings. In contrast, two types of tonic pain methods, painfully cold water and ischemic muscle pain, resulted in equally high unpleasantness ratings and intensity ratings. Crucially, manipulations/interventions to change pain experience do not always affect perceived pain intensity and unpleasantness in the same way. For example, Price et al. (1987) found that when women were instructed to focus on the birth of the child instead of on the pain during labour, this led to a significant reduction in experienced pain unpleasantness but not experienced pain intensity. Villemure et al. (2003) investigated the effects of manipulating mood (using odours) on pain experience. They found that a change in mood was related to a change in pain unpleasantness, but not pain intensity. Perlman et al. (2010) assessed the effects of two types of meditation practices (focused attention and open monitoring) on pain experience in novice and long-term meditators. They found that only for open monitoring a significant reduction in self-reported pain unpleasantness was present in long-term meditators compared to novices, no significant reduction in self-reported pain intensity was found. Thus, even though perceived pain intensity and unpleasantness are related aspects of pain experience, they can show different responses to experimental manipulations. This thesis therefore assessed both changes in perceived pain intensity and unpleasantness for the interventions targeting alpha activity to reduce pain. Furthermore, to date, no studies investigating the relationship between somatosensory pre-stimulus alpha activity and pain

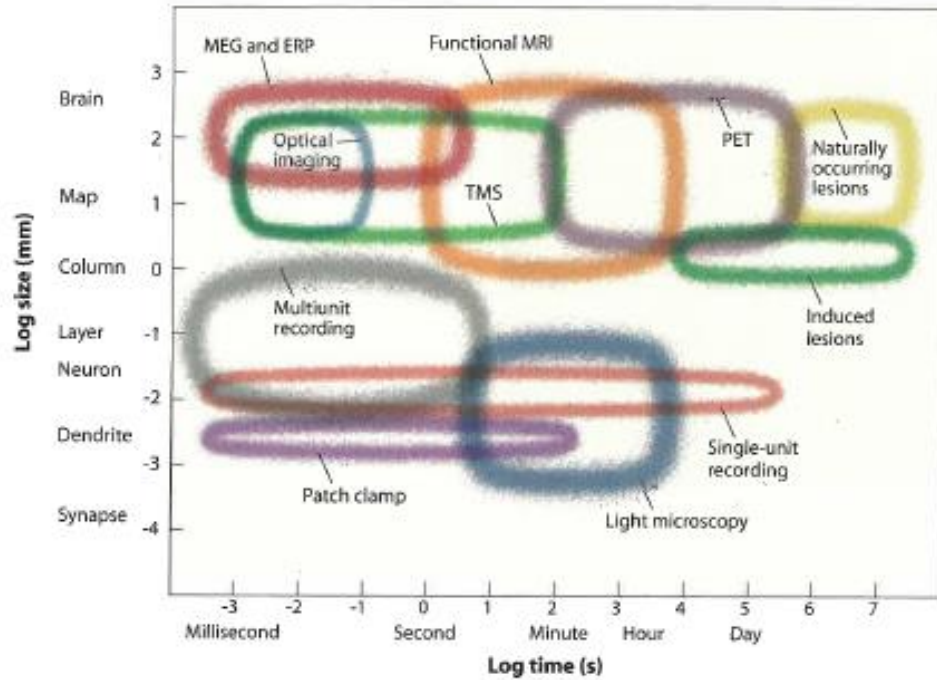
experience (Babiloni et al., 2006; Tu et al., 2016) have assessed perceived pain unpleasantness, only perceived pain intensity. Thus, this thesis uniquely assessed the relationship between pre-stimulus somatosensory alpha activity and pain experience including both perceived pain intensity and pain unpleasantness as measures of pain experience.

### **3.4 EEG recording and analysis**

The first and fourth study of this thesis (Chapters 4 and 7 respectively) not only assessed perceived pain intensity and unpleasantness, but also the neurophysiological response during the anticipation of pain. EEG was recorded to assess somatosensory alpha activity. Below, a summary on EEG as a technique to measure neurophysiological activity and common EEG analysis approaches is provided. Details on specific analysis settings will be provided in Chapters 4 and 7.

#### **3.4.1 The EEG method**

Many methods are available to investigate neural activity, and each technique comes with its own advantages and disadvantages. These (dis)advantages relate to two important attributes; temporal and spatial resolution. Where some methods measure neural changes on a temporal scale of milliseconds, others measure on a scale of seconds or minutes. Similarly, where some methods measure neural activity at the level of a single neuron, others measure changes at the level of brain regions (large populations of neurons) (Figure 3.3).



**Figure 3.3** Graph illustrating the spatial and temporal resolution of a number of methods to assess neural function. Temporal sensitivity on the x axis refers to the timescale over which a measurement takes place for each method. Spatial sensitivity on the y axis refers to localisation capability of each method (adapted from Gazzaniga, Ivry, & Mangun, 2009). With respect to EEG recordings (MEG and ERP) this graph shows that temporal resolution is high, but spatial resolution is relatively low. In contrast, functional MRI has a lower temporal resolution but a higher spatial resolution.

Here, EEG recordings were carried out to investigate neurophysiological changes during the anticipation of a painful stimulus. EEG is a method that measures the summated electrical activity of large groups of neurons on the scalp (Luck, 2005). It is a non-invasive and relatively inexpensive method to directly measure neural activity. Its biggest advantage lies in its high temporal resolution as it can measure voltage changes at a level of milliseconds (Cohen, 2014; Davidson et al., 2000; Luck, 2005). A major limitation of EEG is its spatial resolution. EEG measures neural activity with a set of electrodes placed on the scalp. It is difficult to reconstruct the exact neuroanatomical origin of the activity as measured on the scalp, which related to the inverse problem. Although it is possible to estimate neuroanatomical locations of the electrical neural activity that was measured on the scalp, there is not a single solution to the problem; a particular distribution of electrical neural activity on the scalp can be produced



by many different combinations of neural sources (Davidson et al., 2000; Luck, 2005) although modern techniques for source localisation can estimate neuroanatomical sources, EEG is not the most suitable technique to answer a neuroanatomical question (Luck, 2005).

As EEG has a high temporal resolution, it is particularly suitable to answer questions about quick, dynamic changes in neural activity. EEG is suggested as a key technique to assess neurocognitive processes, as these are usually processes that take place on a scale of tens/hundreds of milliseconds (Cohen, 2014). Moreover, EEG can be used to assess neural oscillatory activity. Neural oscillations are thought to support the communication across functional neural networks (Basar et al., 1999; Fries, 2005). Thus, neural oscillatory activity is likely to support the communication within the widespread pain-related neural network. Moreover, alpha activity, oscillatory neural activity within a frequency range of 8-12Hz, appears particularly important in the experience of pain (e.g. Chang et al., 2003; Chien, Liu, Kim, Markman, & Lenz, 2014; Peng, Hu, Zhang, & Hu, 2014).

In the two EEG studies of this thesis, EEG was applied to investigate changes in pre-stimulus somatosensory alpha activity during the anticipation of pain and how this related to pain experience. EEG was selected as it is particularly suitable to examine neural oscillatory activity and to address the question of how the processing in preparation for pain is organised during the short time period before pain onset. However, it is important to keep in mind the limitations with respect to localisation that come with using EEG. As electrical activity spreads throughout the tissues when it travels from its neural generator through the brain, membranes, skull, and scalp, the activity that is measured on the surface of the scalp is blurred. Activity measured by an electrode on the scalp reflects activity not only from regions directly below the electrode but from more distal regions as well. This limits how specific we can be in our conclusions about the EEG activity as measured over somatosensory scalp regions originating from somatosensory neural regions solely.

To assess changes in alpha activity in the somatosensory cortex in this thesis we calculated average alpha power (8-12Hz) for two regions of interest, an ipsilateral and contralateral somatosensory region with respect to the

stimulated hand. Alpha power was averaged over four electrodes for each somatosensory region, the ipsilateral somatosensory region was represented by electrode locations C3, C5, CP3, and CP5, and the contralateral region by electrode locations C4, C6, CP4, CP6. These selected electrode locations corresponded with electrode locations where a significant negative correlation between pre-stimulus alpha activity and pain experience was identified by Babiloni et al. (2006) and Tu et al. (2016). Babiloni et al. (2006) found a significant relationship at electrode location CP3 specifically. Tu et al. (2016) found a significant relationship for electrodes over the bilateral somatosensory scalp region with a maximum at electrode location C4. Although the application of EEG unavoidably comes with a limitation of low spatial resolution, there is support available that the alpha activity as measured over the somatosensory scalp regions reflects somatosensory alpha activity. Tu et al. (2016) who found a significant relationship between pre-stimulus alpha and pain over bilateral somatosensory scalp regions, also carried out a fMRI study in an independent sample of participants to identify the specific brain areas whose functional state showed a similar relationship with perceived pain. The authors reported a pattern of spatial congruence between the results of the EEG and fMRI experiment; the scalp distribution of the alpha oscillations related to pain experience was congruent with the spatial distribution of a subset of regions identified in the fMRI experiment, i.e., the bilateral primary somatosensory cortex. Another approach that has been applied to increase certainty about effectively measuring changes in somatosensory alpha activity with sensors over the scalp, is to select electrodes for analysis based on their EEG response to a tactile or painful somatosensory stimulus (the post-stimulus alpha response). Thus, sensors demonstrating the largest response after the application of a somatosensory stimulus were selected to examine pre-stimulus somatosensory alpha activity. For instance, Anderson and Ding (2011) identified EEG electrode locations CP3 and CP4 using this approach (as demonstrating the largest evoked response for a tactile stimulus). This further supports the selected electrode locations to measure somatosensory alpha activity in this thesis. Finally, some studies that identified a significant pre-stimulus somatosensory alpha response applied further analysis to identify the neural source of this response. For instance, Baumgarten, Schnitzler, and

Lange (2016) who used MEG to measure alpha activity, also included a structural MRI scan for every participant that was used for source reconstruction analysis. They found that the significant pre-stimulus alpha response for a tactile discrimination task that they detected at sensor level over the somatosensory scalp region, mainly originated from a source located in the contralateral postcentral gyrus, i.e., the primary somatosensory cortex. Thus, although it is important to keep in mind the limitations in localisation that come with EEG, there is diverse evidence to support that the changes in pre-stimulus alpha activity as measured in this thesis originate from the somatosensory cortex.

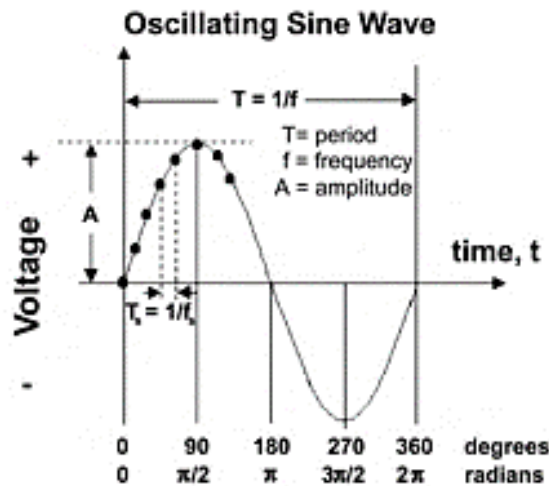
### **3.4.2 EEG analysis**

The EEG signal is a multi-dimensional signal that can be described using dimensions such as time, space, frequency, power, and phase. A variety of EEG analyses can be applied, that each access different dimensions or parts of the information available in the EEG signal (Cohen, 2014). Two main types of EEG analysis are ERP-based and frequency-based analysis. In this section a more general account of the types of EEG analysis as applied in this thesis will be provided. The details on the specific analysis settings applied in each of the two EEG studies of this thesis will be provided in the two experimental chapters (Chapter 4 and 7).

A commonly applied EEG analysis is ERP analysis. ERPs are considered to reflect brain activity in preparation for or in response to a distinct event (Fabiani, Gratton, & Coles, 2000). The EEG signal contains both the ERP waveform and random background noise. The ERP is small in comparison to the noise. To create an ERP, first a segment of the EEG signal is extracted for each trial that is time-locked to the onset of certain event. Next, all of these segments are aligned with respect to that time-locked event and an average is calculated over all the segments. The purpose of averaging over trials is to discriminate the 'signal' (the ERP) from the noise. As the background noise is considered to be random, averaging over a sufficient number of trials will result in a reduction of the noise (Fabiani et al., 2000; Luck, 2005). ERPs have the

advantage that they have a high temporal precision and are relatively easy and fast to compute (they require relatively little processing and filtering). However, there are some disadvantages. ERPs only represent relatively little of the information available in the EEG signal. Within task-related EEG data two types of activity can be described: phase-locked and non-phase-locked (further explanation on this will follow in the next paragraph). Only phase-locked activity is visible when averaged over time, non-phase-locked activity is not. Therefore, ERPs only reflect part of the information of the EEG signal, a considerable amount of information may be lost (Cohen, 2014; Cohen, 2011). Another disadvantage is the lack of clear understanding of the neural origin of ERPs; the neurophysiological mechanisms that are reflected by the ERP are not very well understood (Cohen, 2014).

Another category of EEG analysis is frequency-based analysis. Where for ERP's there is a lack of understanding of what neurophysiological mechanism they reflect, the results of frequency-based analysis are better understood in the context of the neurophysiological processes they reflect. They are usually interpreted as reflecting oscillatory neural activity (Cohen, 2014). Neural oscillations can be described using three main dimensions: frequency, power, and phase. These three dimensions (each carrying information) can be accessed using frequency-based analysis (Sauseng & Klimesch, 2008). In the context of neural oscillatory activity, an oscillation can be described as a repetitive variation in magnitude (voltage) around a central point over time, where a cycle is one full repetition of the oscillation. Frequency refers to the speed of an oscillation, and is measured as the number of cycles (or repetitions) per second (in Hz). Power is a measure of the amount of energy at a specific frequency (or frequency band) and is measured as the squared amplitude of an oscillation (in units of  $\mu V^2$ ). The phase of an oscillation refers to the position along the cycle of a waveform at a certain point in time, and is measured in radians or degrees. For instance, if the position at a certain time point reflects a full cycle this means a phase of 360 degrees (or  $2\pi$ ), a position reflecting a quarter of a cycle means a phase of 90 degrees ( $\pi/2$ ), etc. (Figure 3.4).



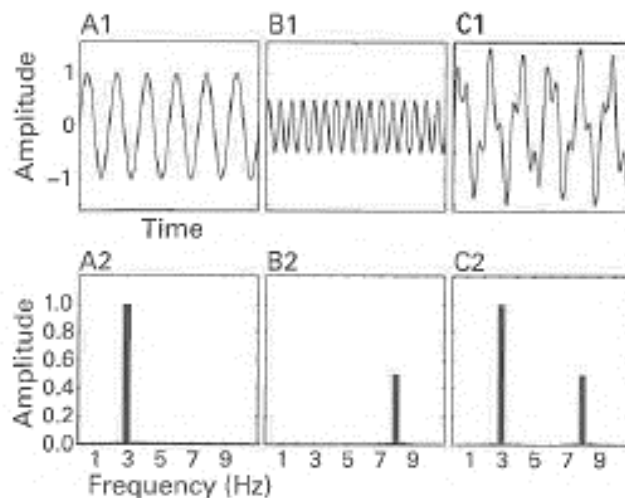
**Figure 3.4** An example of an oscillation is a sine wave. Above one cycle of a sine wave is depicted. The term phase refers to the position along a cycle of a waveform (such as a sine wave) at a given time point and is measured in radians or degrees. A full cycle of the sine reflects a phase of 360 degrees or  $2\pi$ . In the same way, a phase of 180 degrees or  $1\pi$  refers to half a cycle of a sine wave.

With respect to task-related EEG data containing phase-locked and non-phase-locked activity, phase-locked activity is activity that has a very similar phase for each trial at a specific time point (for example the onset of a stimulus); i.e., the activity is phase-aligned with respect to this time point. Non-phase-locked activity is activity with a different phase for each trial; the activity does not have the same phase for a specific time point (Cohen, 2014). Non-phase-locked activity is not visible when averaged in the time domain (e.g., ERPs), but it can be observed with frequency-based analysis.

To summarise, two clear benefits of frequency-based analysis compared to ERP analysis are that 1) frequency-based analysis accesses more of the information available in the EEG signal; and 2) the neurophysiological mechanism behind the findings of frequency-based findings is much better understood.

The EEG signal contains oscillatory neural activity at a variety of frequencies. The basic principle underlying frequency-based analysis is that any signal in the time domain (like EEG data) can be represented by adding up a number of sine waves with different frequencies, amplitudes, and phases

(Cohen, 2014; Luck, 2005). This is what the Fourier Transform does. The Fourier Transform is a mathematical procedure that takes a time-domain signal (e.g. EEG data) as input and works out which sine waves with which specific frequencies, amplitudes and phases can be added together to reconstruct the original time-domain signal (Cohen, 2014; Luck, 2005). The result of the Fourier transform is a three-dimensional representation (of frequency, power, and phase) of the original time-domain signal. It provides the power and phase of the signal at each frequency, which can be used for further (statistical) analysis. Where a time-domain EEG signal is usually represented as a plot of amplitude (voltage) over time, a frequency-domain representation of the data is usually a plot of amplitude (or power) at each frequency (Figure 3.5). Importantly, these two representations contain exactly the same information, just from different perspectives, the time-domain signal can be perfectly reconstructed from the Fourier outcome, and vice versa (Cohen, 2014).

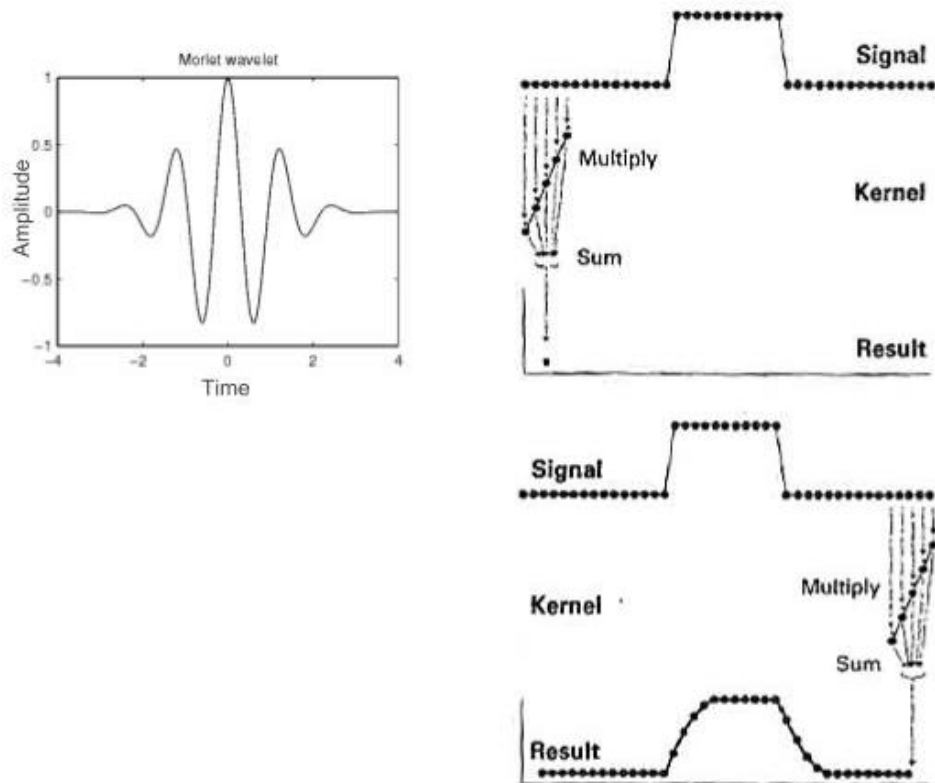


**Figure 3.5** Example of time domain representations (top row) and frequency domain representations (bottom row) of the sine wave or combination of sine waves, containing equivalent information. Where the time domain representations display the amplitude of the signal over time, the frequency domain representations display the amplitude of the signal at each frequency (adapted from Cohen, 2014).

Where the Fourier Transform as discussed above will provide information about the power (and phase) of a signal at each frequency, it does not provide information on how power might change over time. A different

variety of frequency analysis, time-frequency analysis, does allow for the assessment of changes in power over time (at a specific frequency or frequency range). In the current studies a time-frequency analysis was used to investigate somatosensory alpha power (frequency range of 8-12Hz) during the pre-stimulus time period (-1 s to 0 s before pain onset).

There are different approaches available for time-frequency analysis, such as Fourier-based time-resolved analysis (or short-time Fourier analysis using a sliding time window), Hilbert analysis (or the filter-Hilbert method), and wavelet convolution. Although each of these approaches uses different computations to retrieve power and phase information for each frequency over time, these methods are equivalent and give very similar power and phase results (when analysis parameters are matched) (Bruns, 2004; Cohen, 2014). In this thesis the wavelet convolution approach was used. The main components of wavelet convolution analysis are the signal (the EEG data) and a kernel (a wavelet). At the base of convolution lies the dot product. To compute the dot product each element of one vector (the signal) is multiplied with the corresponding element in another vector (the kernel). For convolution, this dot product is computed repeatedly over time, with the kernel sliding along the signal (Figure 3.6). The result of convolution can be considered as a mapping over time between signal and kernel (i.e. EEG data and wavelet), indicating what features signal and kernel have in common.



**Figure 3.6 Top left:** a Morlet wavelet, which is created by windowing a sine wave with a certain frequency by a Gaussian. **Top and bottom right:** overview of the process of convolution. The top right panel shows one step of convolution, the calculation of the dot product between kernel and signal. Each point in the kernel is multiplied by each corresponding point in the signal, and these multiplications are summed together. This value (the dot product) is placed in a position corresponding to the centre of the kernel. The bottom right panel shows the result of convolution, where the dot product is calculated repeatedly over time. The dot product is calculated at a certain time point, the kernel is moved one time point to the right, and the dot product is computed again. This is repeated until the end of the signal is reached (adapted from Cohen, 2014).

When wavelet convolution is applied for EEG data, a number of wavelets with different frequencies are used. The result of convolution between the EEG signal and a wavelet with a certain frequency indicates how much the EEG signal has in common with that wavelet at that frequency. Carrying out convolution with a number of wavelets with a variety of frequencies, allows us to compute the power and phase information of the EEG signal over time at the frequencies of interest. A wavelet that is commonly used as a kernel for wavelet convolution is the Morlet wavelet (Figure 3.6). It is used for its favourable properties for localisation of frequency information in time (Cohen, 2014).

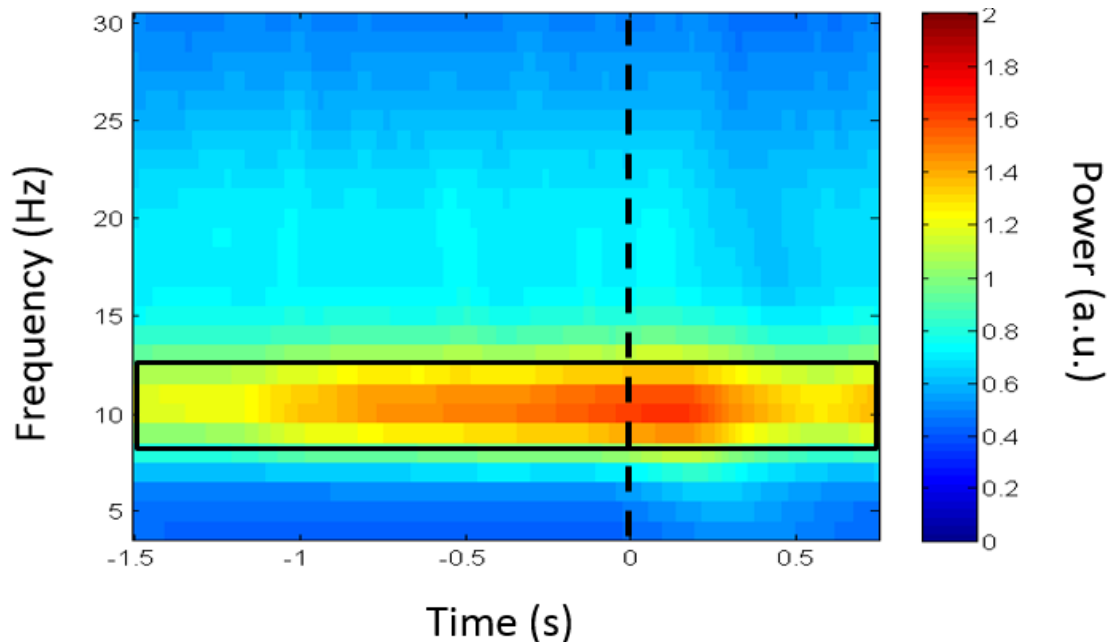


One point that has to be taken into account with time-frequency analysis is its effect on temporal and frequency precision. By applying a wavelet and computing the convolution between wavelet and EEG signal the result at one particular time point is not only the value at that single time point, but a weighted average of the value at that specific time point and adjacent time points. In the same fashion, the result for one frequency value is the weighted average of the value at that specific frequency and adjacent frequencies. For this weighted average a maximum weight is given to the time/frequency point of interest and a decreasing weight to time/frequency points as they are further away from the time/frequency point of interest (Cohen, 2014). For instance, if power information is extracted for activity at 10Hz, the power value acquired reflects power with a maximum contribution of activity at 10Hz but also contribution of adjacent frequencies such as 9.9Hz, 10.1Hz, and 10.2Hz, with a smaller contribution as the frequency is further away from 10Hz.

The outcomes from time-frequency analysis used for further (statistical) analysis are usually the power or phase values of the EEG signal at a specific frequency or frequency range, over a specific time period. The power values can be visualised using a time-frequency representation (TFR) showing the power at each frequency over time (Figure 3.7).

Time-frequency analysis provides a large amount of outcomes (a range of frequencies x a range of time points x 64 electrodes), and power and phase outcomes. This translates into a large amount of analysis options. In this thesis the selection of analysis approach and outcomes of interest was driven by the literature. The rationale for this thesis was driven by two key findings: 1) that there are fluctuations in pre-stimulus somatosensory alpha power during the anticipation of pain, possibly reflecting an attentional mechanism (Babiloni et al., 2003; Del Percio et al., 2006; May et al., 2012); and 2) that these fluctuations in pre-stimulus somatosensory alpha power might be related to the experience of pain, with higher pre-stimulus somatosensory alpha power related to lower perceived pain intensity (Babiloni et al., 2006; Tu et al., 2016). These findings led to the aim of this thesis: to examine the relationship between pre-stimulus somatosensory alpha power and pain experience. Therefore, in this thesis the analysis was focused on power outcomes. Time-frequency

analysis was carried out to assess changes in power in the alpha-frequency range (8-12Hz) and in the pre-stimulus time period directly before pain onset.



**Figure 3.7** TFR demonstrating the power of alpha activity over time, with time = 0 representing stimulus onset. The x-axis represents time, the y-axis frequency, and power at each frequency over time is represented by a colour scale.

Although this thesis focuses on the analysis of pre-stimulus somatosensory alpha activity and its relationship with pain experience, it should be stressed that alpha activity is not the only type of neural oscillatory activity investigated in relation to pain. A number of recent studies demonstrate a change in oscillatory activity during the application of a tonic pain stimulus (not pre-stimulus) across a range of frequency bands and particularly the gamma range (30-100 Hz). For instance, Schulz et al. (2015) showed a significant positive correlation between perceived pain intensity and gamma activity at prefrontal electrodes during the application of a tonic pain stimulus. Furthermore, a significant negative correlation between pain stimulus intensity and beta activity (15-30 Hz) was found. Peng, Hu, Zhang, and Hu (2014) found a reduction of alpha activity and an increase of gamma activity during tonic heat pain. Both alpha and gamma activity were significantly correlated with perceived pain intensity. In addition, both alpha and gamma activity were

affected by attention to pain. Nickel et al. (2017) demonstrated a negative association between pain stimulus intensity and alpha and beta activity in the sensorimotor region during the application of a tonic heat stimulus. In contrast, a positive association was found for perceived pain intensity and gamma activity in the prefrontal cortex. Finally, Tu et al. (2016) who studied pre-stimulus activity specifically, found a significant relationship between pain experience and pre-stimulus oscillatory activity not only in the alpha frequency range but also the gamma range. A negative relationship between pre-stimulus gamma activity in parietal regions and perceived pain intensity was found.

Whereas the role of neural oscillatory activity in other frequency ranges and particularly the gamma range deserves further investigation, when the studies of the PhD thesis were developed the most substantial evidence for a role of oscillatory activity in pain perception was present in for pre-stimulus somatosensory alpha activity (Babiloni et al., 2003, 2006; Del Percio et al., 2006; May et al., 2012), and further supporting evidence demonstrating a relationship between pre-stimulus somatosensory alpha and the perception of non-painful somatosensory stimuli (Baumgarten, Schnitzler, & Lange, 2016; Haegens et al., 2011; Jones et al., 2010). Moreover, the assessment of gamma activity using EEG is not entirely without problems. The main issue revolves around muscle artifacts arising from cranial muscles and ocular muscles. Gamma activity as measured at sensor level is strongly compromised by these artifacts and can even become undetectable when conventional pre-processing steps are applied. It has even been proposed that gamma activity at sensor level, as measured with EEG, almost exclusively reflects artifactual activity resulting from small eye movements (microsaccades) instead of neural activity (Yuval-Greenberg, Tomer, Keren, Nelken, & Deouell, 2008). Others were less negative and stated that gamma activity can be recorded with EEG, but that EEG spectral analysis to extract gamma activity remains challenging and should be approached with caution (Fries, Scheeringa, & Oostenveld, 2008).

Gamma activity and muscle artifacts have a similar frequency range of 30-100Hz. Therefore, the common application of a low-pass filter (e.g., 30Hz cut-off) to correct for muscle artifacts cannot be applied. More advanced analysis strategies have to be employed to successfully distinguish neural activity in the gamma range from artifactual activity, such as independent

component analysis (ICA) and source analysis. ICA can be used to separate artifactual components from components of neural origin. However, this method does not guarantee a complete separation of neural activity and artifact, i.e., an artifactual component might still contain some neural activity (removing it means you reduce the signal of interest), and equally a component primarily reflecting neural activity might still contain some artifactual activity too. Another approach is to use source analysis to identify the neural sources of gamma activity and in that way eliminate other sources of >30 Hz activity in the signal (Hipp & Siegel, 2013). Thus, although some analysis approaches are available to meet the challenge of successfully identifying gamma activity in EEG, caution should be exercised nonetheless when analysing and interpreting gamma activity.

To conclude, this PhD thesis does not include analysis of gamma activity. A literature-driven decision was made to specifically focus on pre-stimulus somatosensory alpha activity. Furthermore, analysis of gamma activity in EEG requires more advanced analysis skills and induces a larger risk of incorrect interpretation of findings (Hipp & Siegel, 2013). It was therefore felt that analysis of gamma activity would go beyond the scope of the thesis.

Finally, although the studies of this thesis focus on the power information of the time-frequency analysis, one can also use the phase information for further (statistical) analysis. This section gives a short account of these phase-based approaches. This type of analysis was not carried out in the studies of this thesis, but this section is designed to briefly clarify the meaning of outcome measures based on phase information, as some of the literature discussed in the thesis included phase-based analysis. Where for the power information one can simply use an average power value as an outcome measure (for example average power between 8-12Hz, from 0 to 1s after stimulus onset), for phase information you cannot simply average phase values over trials. Other analysis approaches have been developed though, to interpret phase information. Although a variety of specific analyses exist, in general they are designed to compute the consistency of phase values; the consistency in phase between two electrodes or neural locations at a given frequency. Phase consistency is a

measure of whether the difference in phase between one location and another (for example to electrodes) remains the same or very similar over time. It is not about whether the phase value of two sites is identical, but whether the difference in phase between the two sites remains the same over time (Bruns, 2004; Cohen, 2014). Phase consistency computations are also referred to in the literature as phase-based connectivity (Cohen, 2014), phase-locking value (PLV), or phase synchronisation (Bruns, 2004; Lachaux, Rodriguez, Martinerie, & Varela, 1999).

The phase of neural oscillations is related to the exact timing of neural activity, and phase consistency or synchronisation is thought to reflect the timing of communication between neural regions (Sauseng & Klimesch, 2008). Similarly, phase consistency has been proposed to reflect connectivity between neural regions, and as reflecting a mechanism of neural integration across neural networks (Bruns, 2004). As such, phase consistency has been pointed out as an essential process in the support of complex cognitive processing, which requires integration of activity in widespread neural networks (Engel & Singer, 2001; Fries, 2005; Lachaux et al., 1999).

### **3.5 Questionnaires**

A variety of psychological characteristics play a role in chronic pain. For instance, both anxiety and depression have been found to frequently co-occur with chronic pain conditions. Individuals with a chronic pain condition were found significantly more likely to have a mood disorder compared to pain-free individuals (21.7 versus 10 %), the same was found for anxiety disorders (35.1 versus 18.1 %) (McWilliams, Cox, & Enns, 2003). Also in both clinical and experimental pain settings associations between pain experience and depression and anxiety have been demonstrated. For instance, depression has been found to be significantly correlated with a number of measures of pain experience in chronic pain patients, including pain intensity, pain-related disability, and negative thoughts about pain (Geisser, Roth, Theisen, Robinson, & Riley, 2000). Also, pre-operative state anxiety (as measured using the State Trait Anxiety Inventory; STAI) one day before surgery, was significantly

correlated with post-operative reported pain intensity (Granot & Ferber, 2005). For experimental pain stimuli, higher levels of depressed mood were related to significantly higher reported pain intensity (Walsh, 1998), and finally participants with high trait anxiety were found to report significantly higher pain intensity than participants with low trait anxiety (Tang & Gibson, 2005). Two other psychological characteristics of importance are pain catastrophising and fear of pain. Pain catastrophising and fear of pain are key elements in the development and maintenance of chronic pain, as described in the fear-avoidance model of chronic pain (Leeuw et al., 2007; Vlaeyen et al., 1995). As these two factors are both considered important in the development of chronic pain it was decided to focus on the role of pain catastrophising and fear of pain and their influence on the reduction of pain by the three interventions primarily in the thesis. These two characteristics were measured using the FPQ-SF (McNeil & Rainwater, 1998) and the PCS (Sullivan, Bishop, & Pivik, 1995).

To assess individual levels of fear of pain the FPQ-SF was used. The FPQ-SF was constructed from the Fear of Pain Questionnaire-III (McNeil & Rainwater, 1998). The original FPQ-III was developed to assess fears about pain based on the assumption that fear is specific to a particular type of pain and setting. For this reason, items contain various types of pain and painful situations. Items reflect three factors; severe pain, minor pain and medical pain, as originally demonstrated by McNeil and Rainwater (1998) and confirmed by several other studies (Albaret, Muñoz Sastre, Cottencin, & Mullet, 2004; Osman, Breitenstein, Barrios, Gutierrez, & Kopper, 2002). For the present study, the short, 9-item version of the FPQ-III, the FPQ-SF was used. To fill in the FPQ-SF, participants were asked to rate how fearful they were (or expected they would be) of experiencing the pain associated with the painful experience described in each item, such as 'getting a paper-cut on your finger' and 'breaking your arm' on a 5-point scale ranging from 1-5, with 1 meaning 'not at all' and 5 'extreme'. The total score is ranged between 9 and 45, with a higher score indicating higher levels of fear of pain. The short version (FPQ-SF) demonstrated acceptable internal consistency values ranging from .83-.87 (Parr et al., 2012).

To assess individual levels of pain catastrophising, the PCS was used (Sullivan et al., 1995). Pain catastrophising has been described as reflecting a tendency for “exaggerated negative orientation” towards a painful event, with the PCS designed to cover three main factors of pain catastrophising: rumination, magnification, and helplessness. Rumination refers to increased thinking and worrying about the pain, an inability to divert attention away from pain-related thoughts. Magnification refers to exaggeration of the threat value of a painful event; higher levels of fear related to pain, and higher expectations of negative outcomes related to pain. Helplessness reflects a sense of pessimism with respect to the ability to cope with a painful experience, or feeling unable to deal effectively with pain (Sullivan et al., 2001; Sullivan et al., 1995). Factor analysis based on a sample of 425 undergraduate students supported the three sub-scales of rumination, magnification, and helplessness of the PCS (Osman, Barrios, Kopper, Hauptmann, Jones, & O’Neill, 1997). Moreover, the total scale internal consistency is good, with internal consistency values ranging from .89-.93 (Osman et al., 1997). The PCS contains 13 items describing thoughts and feelings related to pain. To fill in the PCS, participants are asked to rate how much they experience the thoughts or feelings described in the items when they experience pain, such as ‘when I’m in pain I worry all the time about whether the pain will end’ and ‘when I’m in pain I keep thinking about how much it hurts’, on a 5-point scale ranging from 0-4, with 0 meaning ‘not at all’ and 4 ‘all the time’. The total score on the scale ranges from 0-52, with a higher score indicating higher levels of pain catastrophising.

In summary, to examine the relationship between pre-stimulus somatosensory alpha activity and pain experience, this thesis includes four studies, that were designed to address: 1) if, and how pre-stimulus alpha activity might affect pain experience; 2) if the relationship between pre-stimulus somatosensory alpha activity and pain experience is influenced by uncertainty about pain intensity; and 3) if the relationship between pre-stimulus somatosensory alpha activity and pain experience is influenced by fear of pain and pain catastrophising. To address these objectives, the following methodology was applied:

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- To induce an experience of pain an experimental pain stimulus was used (pressure pain). The studies in this thesis investigated the impact of interventions that target alpha activity at an early stage of development and therefore it was considered important to use a standardised a controlled stimulus.
  - To assess pain experience two NRSs were used to measure perceived pain intensity and unpleasantness. This thesis uniquely examined the relationship between pre-stimulus somatosensory alpha activity and pain experience for both perceived pain intensity and pain unpleasantness.
  - To investigate the influence of a prolonged state of uncertainty about pain intensity a visual cue - pain stimulus paradigm was developed that allowed for a comparison of uncertain stimulus intensity (non-painful, pain threshold, moderately painful) to certain stimulus intensity for non-painful, pain threshold, and moderately painful stimuli.
  - EEG recordings were carried out to investigate somatosensory alpha activity during the anticipation of a painful stimulus, as EEG is a particularly suitable technique to answer questions about quick, dynamic changes in neural activity and to assess neural oscillatory activity specifically.
  - Finally, pain catastrophising and fear of pain are key elements in the development and maintenance of chronic pain, as described in the fear-avoidance model of chronic pain (Leeuw et al., 2007; Vlaeyen et al., 1995). Thus, this thesis also examined the influence of fear of pain and pain catastrophising on the relationship between pre-stimulus somatosensory alpha activity and pain experience. Fear of pain was measured with the FPQ-SF (McNeil & Rainwater, 1998) and pain catastrophising was measured with the PCS (Sullivan et al., 1995).



## **Chapter 4** Do different expectations of pain alter pre-stimulus alpha levels in the brain and does this influence pain experience?

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### **4.1 Introduction**

Alpha activity, activity in a frequency-band of around 8-12Hz, has an active role in neural processing. It directs the processing of incoming information through functional inhibition: processing in task-irrelevant neural regions is inhibited (increased alpha) and processing in task-relevant neural regions is facilitated (decreased alpha) (Foxye & Snyder, 2011; Jensen & Mazaheri, 2010; Klimesch, 2012). This functional inhibition mechanism has been demonstrated for a wide range of sensory and cognitive domains (e.g., Haegens, Luther, & Jensen, 2012; Van Diepen, Cohen, Denys, & Mazaheri, 2015; Van Dijk, Schoffelen, Oostenveld, & Jensen, 2008).

The involvement of alpha activity has also been considered for pain perception, with a body of studies focussing on changes in alpha activity during the experience of pain (e.g., Chang et al., 2001a, 2001b; Chang, Arendt-Nielsen, Graven-Nielsen, & Chen, 2003; Ferracuti et al., 1994) and also a small number of studies exploring changes in alpha activity before the onset of pain, i.e., pre-stimulus alpha activity (Babiloni et al., 2003, 2006; Franciotti et al., 2009; May et al., 2012). Crucially, a significant negative correlation between pre-stimulus alpha activity and pain experience has been found, higher pre-stimulus alpha is associated with lower perceived pain intensity (Babiloni et al., 2006). However, literature on the relationship between pre-stimulus alpha activity and pain experience is limited. A clear understanding of the role of pre-stimulus alpha activity in the processing of pain and its relationship with pain

experience is largely lacking. The aim of the present study was to further investigate the relationship between pre-stimulus somatosensory alpha activity in pain experience and the influence of uncertainty about pain intensity on this relationship.

#### **4.1.1 Pre-stimulus alpha activity and pain**

A number of studies have demonstrated changes in alpha activity during pain, establishing the involvement of alpha activity in pain perception, with a majority finding a decrease of alpha activity during painful stimulation (Chang et al., 2001a, 2001b; Chang et al., 2003; Ferracuti et al., 1994). Moreover, a significant negative correlation between alpha activity during pain and perceived pain intensity has been found (Chang et al., 2003; Nir, Sinai, Moont, Harari, & Yarnitsky, 2012; Shao, Shen, Yu, Wilder-Smith, & Li, 2012). This indicates that alpha activity is not only altered by the presence of pain but is also related to the experience of pain.

Alpha activity is not only modulated during pain, but also during the anticipation of pain before pain onset, in the absence of actual pain. Babiloni et al. (2003) demonstrated a larger decrease of pre-stimulus somatosensory alpha activity (at electrodes C3 and C4 based on the 10-20 system) for predictable painful compared to non-painful stimulation directly before pain onset (in the period of -1 to 0s before pain onset). This decrease of pre-stimulus somatosensory alpha activity reflects preparation for the anticipated pain through functional inhibition, as has been found across different sensory domains and likely reflects a domain-independent attentional mechanism (Fuxe & Snyder, 2011; Jensen & Mazaheri, 2010; Klimesch, 2012).

Moreover, a significant negative correlation between pre-stimulus somatosensory alpha activity and pain experience has been shown. Higher pre-stimulus alpha activity in the contralateral somatosensory region (electrode location CP3, from -1 to -.05s before pain onset) was associated with lower perceived pain intensity (Babiloni et al., 2006). This suggests that pre-stimulus somatosensory alpha activity is not only involved in the preparation for a painful stimulus but is also related to the subsequent experience of pain.

#### **4.1.2 Pain, pre-stimulus alpha activity and attentional modulation**

Although there is some initial evidence for the involvement of pre-stimulus somatosensory alpha activity in pain perception and an association with pain experience, further interpretation of the findings by Babiloni et al. (2003, 2006) is needed. What exactly takes place during this period of preparation before pain onset and what role does attention have? What are the factors affecting pre-stimulus somatosensory alpha activity and its relationship with pain experience?

An initial answer to these questions is provided by research on pre-stimulus somatosensory alpha activity and the perception of non-painful somatosensory stimuli. For non-painful somatosensory stimuli it has been demonstrated that pre-stimulus somatosensory alpha activity is modulated by how people attend to the upcoming stimulation. Van Ede, De Lange, Jensen, and Maris (2011) demonstrated an effect of spatial orientation of attention on pre-stimulus somatosensory alpha activity for tactile stimuli. Visual cues were used to direct attention to either the left or the right hand before the onset of a tactile stimulus on the hand. Somatosensory alpha activity contralateral to the attended hand was significantly lower than ipsilateral somatosensory alpha activity before stimulus onset. Jones et al. (2010) similarly found that in the somatosensory region representing the stimulated hand, pre-stimulus alpha activity was decreased when participants were cued to attend to the hand and increased when they were cued to attend to the foot. Thus, both of these studies demonstrate attentional modulation of pre-stimulus somatosensory alpha activity for non-painful somatosensory stimuli. In line with the principle of functional inhibition (Foxye & Snyder, 2011; Jensen & Mazaheri, 2010; Klimesch, 2012), an increase of alpha activity was present in task-irrelevant neural regions (ipsilateral somatosensory region) and a decrease of alpha activity in task-relevant neural regions (contralateral somatosensory region).

It is possible that a similar involvement of pre-stimulus somatosensory alpha activity is present for painful somatosensory alpha activity. Accordingly, we would expect to find a similar pattern of a contralateral decrease and an ipsilateral increase of pre-stimulus somatosensory alpha activity as a result of how we attend to pain. Attentional modulation of pre-stimulus somatosensory

alpha activity has indeed been demonstrated for painful stimuli too. May et al. (2012) found that pre-stimulus somatosensory alpha power over the contralateral region was lower when attention was directed to the location of stimulation compared to when stimulus location was unattended. In contrast, in the ipsilateral region pre-stimulus somatosensory alpha activity was higher when attention was directed to the stimulus location compared to when stimulus location was unattended. Del Percio et al. (2006) demonstrated that the event-related decrease in pre-stimulus alpha power was more prominent in the contralateral central region than the ipsilateral central region, with respect to the location of pain stimulation. Furthermore, they found that the decrease of pre-stimulus alpha power was significantly larger when participants attended to pain compared to when they were distraction from the pain. Together these two studies (Del Percio et al., 2006; May et al., 2012) confirm that a similar involvement of pre-stimulus somatosensory alpha activity via functional inhibition is present for painful somatosensory perception as for non-painful somatosensory perception, with an attentional modulation of pre-stimulus somatosensory alpha in preparation for an upcoming pain stimulus.

Finally, the studies by Babiloni et al. (2003, 2006) that examined pre-stimulus somatosensory alpha activity during the anticipation of a predictable pain stimulus also demonstrate some evidence for functional inhibition. The decrease of pre-stimulus somatosensory alpha activity at electrode locations C3 and C4 was more prominent at the C4 location, the contralateral region with respect to the stimulated hand (Babiloni et al., 2003). Moreover, the significant negative correlation between pre-stimulus somatosensory alpha activity and pain experience was found at electrode location CP3 specifically, the contralateral region with respect to the stimulated hand (Babiloni et al., 2006). As participants were aware of the location of stimulation, it seems likely their attention was drawn to that location. This suggests that the decrease of alpha activity (resulting in activation of the S1 region), might be guided by the direction of attention.

Although these studies supply some initial evidence to suggest that pre-stimulus somatosensory alpha activity for pain perception resembles an attentional mechanism, they have only addressed top-down attentional modulation of somatosensory alpha activity (Del Percio et al., 2006; May et al.,

2012) and fluctuations in pre-stimulus somatosensory alpha activity for predictable pain stimuli without an explicit manipulation of attention (Babiloni et al., 2003, 2006). However, they do not systematically address the involuntary capture of attention by pain, a bottom-up attentional process, also relevant to pain processing (Legrain et al., 2009).

Pain has an important function in warning us about potential threat of injury, or damage to the body. It interrupts ongoing behaviour, automatically captures our attention and motivates to act to escape the threat imposed by (anticipated) pain (Eccleston & Crombez, 1999; Legrain et al., 2009; Morley, 2008). It is not just pain that interrupts, but particularly pain that is uncertain or unpredictable, or more threatening (Morley, 2008). Uncertainty about pain is associated with enhanced capture of attention by pain. For example, the interruption of an ongoing task by pain, as demonstrated using the primary task paradigm, was found to be enhanced when participants were uncertain about pain onset or pain intensity (Crombez et al., 1994; Crombez et al., 1998). Uncertainty about pain intensity also influences pain experience. Pain experience is significantly higher when participants are uncertain about pain intensity compared to when pain intensity is known or certain (Lin et al., 2014; Ploghaus et al., 2001). Uncertainty about pain intensity is also associated with higher reported levels of anxiety (Ploghaus et al., 2001).

Where others demonstrated a top-down attentional modulation of pre-stimulus somatosensory alpha activity (Del Percio et al., 2006; May et al., 2012), enhanced bottom-up capture of attention when participants are uncertain about pain intensity might also have an influence on pre-stimulus somatosensory alpha activity (compared to when pain intensity is certain). However, to date, there is no investigation of the influence of uncertainty on pre-stimulus somatosensory alpha activity. The two studies by Babiloni et al. (2003, 2006) addressed pre-stimulus somatosensory alpha activity and its relationship with pain experience. But both studies only included a setting where pain intensity was known or certain. One other study on pre-stimulus alpha activity did look at uncertain expectation, however this study focussed on changes of alpha activity in the insula cortex specifically, using MEG. Here pre-stimulus alpha activity was compared for a condition where stimulus intensity was uncertain (painful or non-painful) and a condition where stimulus intensity

was certain (non-painful stimuli only). A significantly larger reduction of pre-stimulus alpha activity was found in the anterior insula when stimulus intensity was uncertain compared to certain (in the period of -550 to -50ms before pain onset). This difference could reflect stronger capture of attention in the uncertain condition due to the threat of a possible painful stimulation (Franciotti et al., 2009). Thus, there is some initial evidence for an influence of uncertainty about pain intensity on pre-stimulus alpha activity. However, it remains to be investigated if this applies to pre-stimulus alpha activity in the somatosensory cortex.

### **4.1.3 Study objectives**

The aim of the present study was to further investigate the relationship between pre-stimulus somatosensory alpha activity and pain experience and the influence of uncertainty about pain intensity on this relationship.

The first objective was to confirm that uncertainty about pain intensity influenced pain experience, measuring both perceived intensity and unpleasantness. Uncertainty about pain intensity (low intensity pain or high intensity pain) has been related to higher perceived pain intensity for painful stimuli (Lin et al., 2014; Ploghaus et al., 2001), and uncertainty about stimulus intensity (painful or non-painful) was related to higher perceived unpleasantness for non-painful stimuli (Sawamoto et al., 2000). Thus, in this study it was expected that both perceived pain intensity and unpleasantness would be increased for uncertain pain intensity compared to certain pain intensity.

The second objective was to assess if there was a difference in pre-stimulus somatosensory alpha activity during the anticipation of pain in the ipsilateral and contralateral somatosensory region and whether pre-stimulus somatosensory alpha activity was influenced by uncertainty about pain intensity. In general terms, irrespective of the certainty of expectation, it was expected that ipsilateral and contralateral somatosensory regions would display a difference in pre-stimulus alpha power, reflecting facilitation of processing in

the relevant neural region (contralateral) and inhibition of the irrelevant neural region (ipsilateral). As stimulation in the present study always took place on the left hand, we expected that pre-stimulus alpha activity in the contralateral somatosensory region, processing relevant information, would be lower compared to pre-stimulus alpha activity in the ipsilateral somatosensory region, processing irrelevant or distraction information.

A modulation of pre-stimulus somatosensory alpha activity has been found for top-down attentional influences (Del Percio et al., 2006; May et al., 2012). Uncertainty about pain intensity is related to enhanced bottom-up capture of attention by pain (Crombez et al., 1998; Morley, 2008). Furthermore, a significantly larger reduction of pre-stimulus alpha activity was found in the anterior insula when stimulus intensity was uncertain compared to the certain (Franciotti et al., 2009). Thus, it was expected that pre-stimulus somatosensory alpha activity might be influenced by uncertainty about pain intensity. Specifically, we expected that the difference in pre-stimulus somatosensory alpha power ipsilateral and contralateral (ipsilateral alpha > contralateral alpha), facilitating the processing of a painful stimulus, might be enhanced for uncertain pain intensity compared to certain pain intensity.

A third objective of the present study was to assess the relationship between pre-stimulus somatosensory alpha activity and pain experience. Babiloni et al. (2006) found a significant negative correlation between pre-stimulus somatosensory alpha activity and perceived pain intensity for the contralateral somatosensory region only. This study also assessed the presence of this relationship, not only for perceived pain intensity but also pain unpleasantness. Furthermore, it was explored if there was an influence of uncertainty about pain intensity on the presence of this relationship.

Finally, the influence of two psychometric measures on pre-stimulus somatosensory alpha activity and pain experience was examined: fear of pain and pain catastrophising. Both fear of pain and pain catastrophising play a significant role in pain perception. Fear of pain has been shown to significantly predict perceived pain intensity for experimentally induced pain (Hirsh et al., 2008; Parr et al., 2012) and has a significant positive relationship with pain-

related disability in patients with chronic pain (Zale et al., 2013). A significant positive relationship between pain catastrophising and reported pain intensity, pain-related distress and psychological distress has also been found for patients with chronic pain (Severeijns et al., 2001).

Furthermore, both fear of pain and pain catastrophising have been demonstrated to affect attention to pain. In a chronic pain setting, increased fearful thinking about pain was related to increased attention to pain (Crombez, Viane, Eccleston, Devulder, & Goubert, 2013), and both pain-related fear and pain catastrophising were positively related to vigilance to pain (Goubert, Crombez, & Van Damme, 2004). In an experimental pain setting, it was found that participants with high levels of pain catastrophising had problems with disengaging from a painful cue, resulting in impaired performance on a detection task. This suggests enhanced capture of attention by pain for high levels of pain catastrophising (Van Damme, Crombez, & Eccleston, 2004). In another study, participants with high levels of pain catastrophising also showed enhanced capture of attention by pain and stronger disruption of performance on a primary task. However, this was only the case in a threatening context, when participants had an uncertain expectation about the intensity of a painful stimulus (low or high intensity pain) (Crombez et al., 1998).

In the present study we expected an influence of uncertainty about pain intensity on both pain experience and pre-stimulus somatosensory alpha activity, possibly the result of enhanced capture of attention. As fear of pain and pain catastrophising also seem to influence both pain experience and attention to pain, it was decided to assess the role of these two factors as well. The fourth objective was to explore the relationship between fear of pain/pain catastrophising and pain experience and pre-stimulus somatosensory alpha activity.



## 4.2 Methods

### 4.2.1 Participants

This study was approved by the School of Psychology Research Ethics Committee, University of Leeds (reference number: 14-0334). All participants provided signed informed consent before participating in the study.

30 healthy participants were recruited, 23 female, 7 male; mean age 21.90 years  $\pm$  3.87 SD) through advertisements at the University of Leeds. All participants were aged 18 or older and met the inclusion criteria: they were all free from chronic pain, neurological conditions, skin conditions, not using any neurological/psychotropic medication, and not experiencing any pain at the time of testing.

### 4.2.2 Pressure stimuli

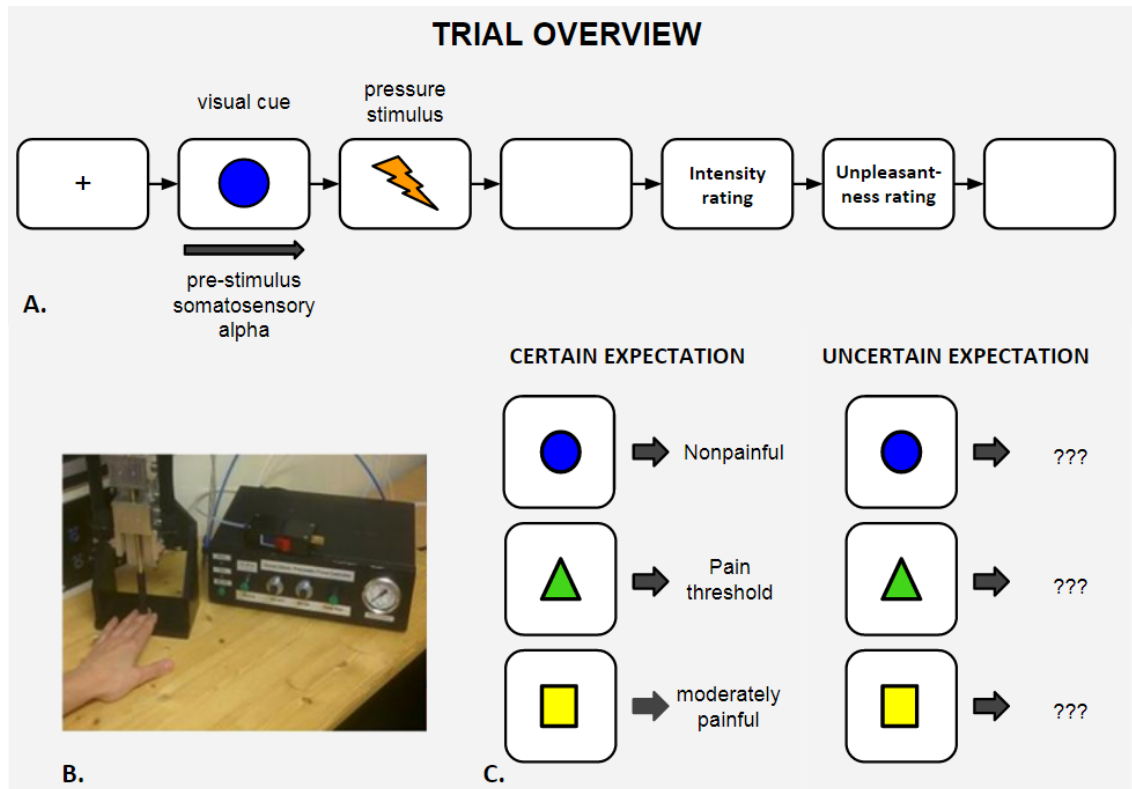
Pressure stimuli were delivered to the middle finger of the non-dominant hand using a custom-built MRI-compatible pressure pain stimulator (manufactured by DancerDesign, St. Helens, UK) (Figure 4.1). A circular probe was lowered onto the fingernail bed centrally placed to cover an equal area of nail and skin. Participants received pressure pain stimuli at three different intensities: 1) non-painful, light touch (rating of 2 on a 0-10 11-point numerical rating scale (NRS)); 2) pain threshold, the point where the pressure stimulation becomes painful for the first time (rating of 4 on NRS); and 3) moderately painful, but still tolerable (rating of 7 on NRS). These levels were set for each individual participant, using a ramping procedure (ascending method of limits), which was carried out twice. Stimulus duration was 4s for non-painful, 5s for pain threshold, and 6s for moderately painful pressure stimuli. These three different durations were used to control for the difference in length of the ramping-up period: the higher the pressure intensity, the longer the ramping-up period. Based on piloting, it was decided to use these durations to ensure similar durations of stimulation at maximum intensity for all three stimulus intensities. The average pressure applied during the experiment was  $.24 \text{ V} \pm 0.05$  for the non-painful stimuli,  $0.39 \text{ V} \pm 0.06$  for the pain threshold stimuli; and  $0.54 \text{ V} \pm 0.07$  for the moderately painful stimuli.

### **4.2.3 Visual cues**

To manipulate uncertainty, i.e. to create a condition where pain intensity was uncertain and a condition where pain intensity was known/certain, each pressure stimulus was preceded by a visual cue. Three different visual cues were used (a green triangle, a blue circle, and a yellow square). In the certain condition, each of the visual cues was paired with one particular pressure stimulus intensity, resulting in visual cues that were predictive of the pressure intensity of an upcoming stimulus. In the uncertain condition, the same three visual cues were used. However, here the visual cues were randomly combined with a pressure stimulus level, resulting in visual cues that were not predictive of the pressure intensity of an upcoming stimulus (Figure 4.1).

### **4.2.4 Pain experience**

To quantify pain experience, participants received two 11-point numerical rating scales (NRSs) on the computer after each stimulation (ranging from 0-10) to measure perceived intensity and unpleasantness (0 = not at all intense/unpleasant, 10 = extremely intense/unpleasant).



**Figure 4.1** A) Trial overview. Each trial consisted of a fixation cross (duration jittered, 750-1000ms), visual cue (duration jittered, 2000-2750ms), and a pressure stimulus (duration intensity depended; non-painful 4000ms, pain threshold 5000ms, and moderately painful 6000ms). A blank screen appeared after the pressure stimulus (duration jittered, 1000-1250ms), followed by the two rating scales, and finally another blank screen (1000ms); B) Manipulation of certainty of expectation. Visual cues were used to induce a certain and uncertain condition, with three visual cues predictive of the three different pressure intensities in the certain condition and the same three visual cues randomly combined with the three pressure intensities in the uncertain condition; C) Custom-built MRI-compatible pressure pain stimulator used to deliver pressure pain (manufactured by DancerDesign, St. Helens, UK). Pressure was applied to the middle finger of the non-dominant hand.

#### 4.2.5 EEG recordings

EEG was recorded during the experimental task using a 64-channel Quik-cell system (NeuroScan, El Paso, Texas, USA) according to the standard 10-20 system. Four additional electrodes were placed to record eye movement and blinks (horizontal electrooculogram (EOG): 2 electrodes placed at the outside of the left and right eye; vertical EOG: 2 electrodes placed above and below the left eye). Two minutes of resting state EEG was collected before the start of the experiment (1 minute eyes closed, 1 minute eyes open). A sampling rate of 1000Hz and a low-pass filter (200Hz) was used.

#### 4.2.6 Questionnaires

After finishing the experiment, participants were asked to complete a set of questionnaires. To measure fear of pain the Fear of Pain Questionnaire - Short Form (FPQ-SF) (Asmundson et al., 2008) was used. The FPQ-SF used in the present study, constructed from the Fear of Pain Questionnaire-III (McNeil & Rainwater, 1998), has 9 items describing a painful experience. Participants were asked to rate how fearful they were (or expected they would be) of experiencing the pain associated with the painful experience described in each item, such as 'getting a paper-cut on your finger' and 'breaking your arm', on a 5-point scale ranging from 1-5, with 1 meaning 'not at all' and 5 'extreme'.

To measure pain catastrophising the Pain Catastrophising Scale (PCS) was used (Sullivan et al., 1995). Pain catastrophising has been described as reflecting a tendency for "exaggerated negative orientation" towards a painful event (Sullivan et al., 1995). The PCS has 13 items describing thoughts and feelings related to pain. Participants are asked to rate how much they experience the thoughts or feelings described in the items when they experience pain, such as 'when I'm in pain I worry all the time about whether the pain will end' and 'when I'm in pain I keep thinking about how much it hurts', on a 5-point scale ranging from 0-4, with 0 meaning 'not at all' and 4 'all the time'.

#### 4.2.7 Design

This study has a 2 x 3 design with two within-subject factors: expectation (certain, uncertain); and pressure stimulation level (non-painful, pain threshold, moderately painful). The outcome measures are the intensity ratings, unpleasantness ratings, and alpha power. Alpha power changes will be assessed for two pre-stimulus time windows (-2 to -1s and -1 to 0s) and two somatosensory regions of interest, the ipsilateral somatosensory region and the contralateral somatosensory region (with respect to the stimulated hand).

## 4.2.8 Experimental procedure

After providing signed informed consent the ramping procedure was carried out to identify the three individual pressure stimulation intensities for each individual. Pressure intensity was increased with small, equal steps. The participant verbally rated each step on an 11-point NRS (0 = no pain, 10 = extremely painful). Prior to the start of the experimental task resting state EEG was recorded. All participants took part in both the certain and uncertain expectation conditions. The two expectation conditions were delivered in two separate blocks in a counterbalanced order. Before each block, participants completed a short practice to familiarise themselves with the task and the meaning of the visual cues in that particular block. Each of the two blocks contained 72 trials; 24 trials at each of the three pressure intensities, delivered in a random order. Each trial consisted of a fixation cross that was followed by a visual cue. The visual cue was immediately followed by a pressure stimulus. After each pressure stimulus the participants filled in two NRSs for perceived intensity and unpleasantness using the numbers on a computer key board.

## 4.2.9 EEG analysis

### 4.2.9.1 Pre-processing & artifact rejection

EEG recordings were analysed using Matlab version R2014a (Mathworks, Natick, MA, USA). The pre-processing and artifact detection steps were carried out using the Matlab toolbox EEGLAB (Delorme & Makeig, 2004). The continuous data was down-sampled (500Hz), re-referenced to an average-reference (all electrodes minus the two mastoid electrodes and the vertical and horizontal EOG), and high-pass filtered (cut-off frequency 0.1Hz, Hamming window FIR filter). Next epochs were extracted from the continuous recordings (-3.75-7.25s with respect to pressure stimulus onset). Finally, epochs were low-pass filtered (cut-off frequency 40Hz, Hamming window FIR filter).

Before Independent component analysis (ICA) was carried out, the FASTER EEGLAB plug-in function (Nolan, Whelan, & Reilly, 2010) was used to automatically interpolate generally contaminated channels and to mark (but not remove) epochs containing artifacts. The automatic detection was visually

checked to make a final decision on the trials that would be removed before the ICA. Only epochs with large steps or spikes, and other abnormalities not related to blinks, eye-movements and muscle activity were removed. Epochs containing blinks, eye-movements and muscle activity were kept at this point.

Next the ICA procedure was started using the `runica` function in EEGLAB. Principle components analysis (PCA) was applied before carrying out the ICA. PCA can be used as a data reduction technique to reduce dimensionality of high-dimensional data. In the context of EEG, an EEG recording can be considered as 64-dimensional data (in the case of 64 channels) (Cohen, 2014). All channels were included except the horizontal and vertical EOG, and the two mastoid electrodes. Components reflecting artifactual sources were removed.

The artifact detection procedure resulted in the inclusion of 19 datasets for further analysis. Each condition (certain and uncertain expectation) contained 72 trials originally, for the 19 datasets on average 56.47 trials were kept per condition after artifact correction. On average 2.74 components were removed per participant per condition.

#### **4.2.9.2 Frequency analysis**

To calculate the power of ongoing alpha activity the Matlab toolbox Fieldtrip (Oostenveld, Fries, Maris, & Schoffelen, 2011) was used. Power estimates were calculated for frequencies between 2 and 30Hz, for -2.75 to +2s with respect to the onset of the pressure stimulus. The convolution method was applied, using a single Hanning taper. An adaptive sliding time window, with 4 cycles for each frequency length with 25ms time steps was used.

#### **4.2.9.3 Data extraction**

For the statistical analysis the following data was extracted: average alpha-band power (8-12Hz) for two regions of interest, an ipsilateral and contralateral somatosensory region with respect to the stimulated hand, based on the average of C3, C5, CP3, and CP5 (ipsilateral) and C4, C6, CP4, CP6 (contralateral). This was done for two time windows: -2 to -1s and -1 to 0s with

respect to pressure stimulus onset. These particular pre-stimulus time windows were based on the time windows used by Babiloni et al. (2003, 2006). To date only a limited number of studies have directly assessed pre-stimulus somatosensory alpha activity the relationship between pre-stimulus somatosensory alpha activity and perceived pain intensity (Babiloni et al., 2003, 2006), offering little guidance in the selection of time windows in the present study. With research on the relationship between pre-stimulus somatosensory alpha and perceived pain at an early stage, the present study was exploratory in nature. Babiloni et al. (2003) investigated alpha activity before pain onset for a time window of -2 to -1s and a time window of -1 to 0s before pain onset. Babiloni et al. (2006) only assessed pre-stimulus alpha activity during the second directly before pain onset (-1 to 0s). In line with the exploratory nature of this study it was decided to adopt a broader scope and use the two time windows as were used in the study by Babiloni et al. (2003), i.e., a -2 to -1s and a -1 to 0s time window.

Finally, time-frequency representations (TFRs) were created with the grand average of the data of the 19 participants (averaged over the 8 electrodes of the two somatosensory regions). Six separate TFRs were created for each of the 3 pressure stimulus intensities and the certain and uncertain condition. In addition, topographies were created, based on the difference between the outcomes for uncertain and certain pain intensity.

#### **4.2.10 Statistical analysis**

Statistical analysis was performed using SPSS version 21. Two within-subject ANOVAs were carried out with the factors pressure stimulus intensity (non-painful, pain threshold and moderately painful) and expectation (certain and uncertain). One ANOVA was conducted for the independent variable intensity ratings and another for unpleasantness ratings.

For the pre-stimulus somatosensory alpha outcomes, a within-subject ANOVA was carried out with the factors pressure stimulus intensity (non-painful, pain threshold and moderately painful), expectation (certain and uncertain), region (ipsilateral and contralateral) and time (-2 to -1s before

pressure stimulus onset and -1 to 0s). Significance level was set at  $p < .05$ . In the case of a violation of sphericity the Greenhouse-Geisser corrected outcomes were used.

To investigate the relationship between perceived pain intensity and fear of pain and pain catastrophising, Pearson correlations between the intensity ratings and the FPQ-SF and PCS total scores were calculated (two-tailed significance) for the moderately painful stimulation, both for the certain and uncertain condition. To correct for multiple comparisons in the present study, the Holm-Bonferroni method was used (Holm, 1979). A commonly used method to correct for multiple comparisons is the Bonferroni method, where the significance level (0.05) is divided by the amount of comparisons or tests (N) to create the adjusted significance level ( $0.05 / N$ ). This offers protection against Type-I errors (false positives). However, there is also a loss of statistical power, i.e., an increased probability of rejecting an effect when a genuine effect is present (Type-II error) (Field, 2009). An alternative to the Bonferroni method is the Holm-Bonferroni method, which offers the same level of protection against type-I errors as the Bonferroni method. However, the Holm-Bonferroni method offers increased statistical power, it has a reduced risk of a Type-II error.

The Holm-Bonferroni method is a sequential or stepwise multiple test method, where N comparisons are sequentially tested against a certain adjusted significance level. To apply this method, first all statistical comparisons are performed. Next these comparisons are ordered based on their p-value, from lowest to highest p-value. Identical to the Bonferroni method, the first comparison in the sequence (i.e., the comparison with the lowest p-value) is tested against an adjusted significance level of  $0.05 / N$ . The second comparison in the sequence (with the second lowest p-value) is tested against an adjusted significance level of  $0.05 / (N-1)$ . In the same manner, a third comparison in the sequence would be tested against a significance level of  $0.05 / (N-2)$ . This procedure is terminated at the first non-significant comparison (all other comparisons following this non-significant comparison are automatically considered non-significant as well) or continued until the last comparison of the sequence has been reached (Abdi, 2010; Holm, 1979).



For the moderately painful stimulation, for the intensity ratings four hypotheses were tested: 2 (expectation: certain, uncertain) x 2 (questionnaires: fear of pain, pain catastrophising) against Holm-Bonferroni adjusted significance levels of .0125, .0167, .025 and .05 for each of the comparisons respectively (with the four comparisons ordered based on their p-values). The same procedure was repeated to investigate the relationship between perceived pain unpleasantness and fear of pain and pain catastrophising.

Moreover, Pearson correlations were calculated to assess the relationship between pre-stimulus somatosensory alpha activity (in the -2 to -1s and -1 to 0s time window) and pain experience (both intensity ratings and unpleasantness ratings, for the moderately painful stimulation). Finally, Pearson correlations were calculated to assess the relationship between pre-stimulus somatosensory alpha activity (in the -2 to -1s and -1 to 0s time window) and fear of pain and pain catastrophising.

For the relationship between pre-stimulus alpha activity and intensity ratings eight hypotheses were tested, 2 (expectation: certain, uncertain) x 2 (time window: -2 to -1s, -1 to 0s) x 2 (region of interest: ipsilateral, contralateral) against Holm-Bonferroni adjusted significance levels of .00625, .00714, .00833, .0100, .0125, .0167, .025 and .05. The same applied for the unpleasantness ratings.

For the relationship between pre-stimulus alpha activity and fear of pain eight hypotheses were tested, 2 (expectation: certain, uncertain) x 2 (time window: -2 to -1s, -1 to 0s) x 2 (region of interest: ipsilateral, contralateral) against Holm-Bonferroni adjusted significance levels of .00625, .00714, .00833, .0100, .0125, .0167, .025 and .05. The same was applied for pain catastrophising.

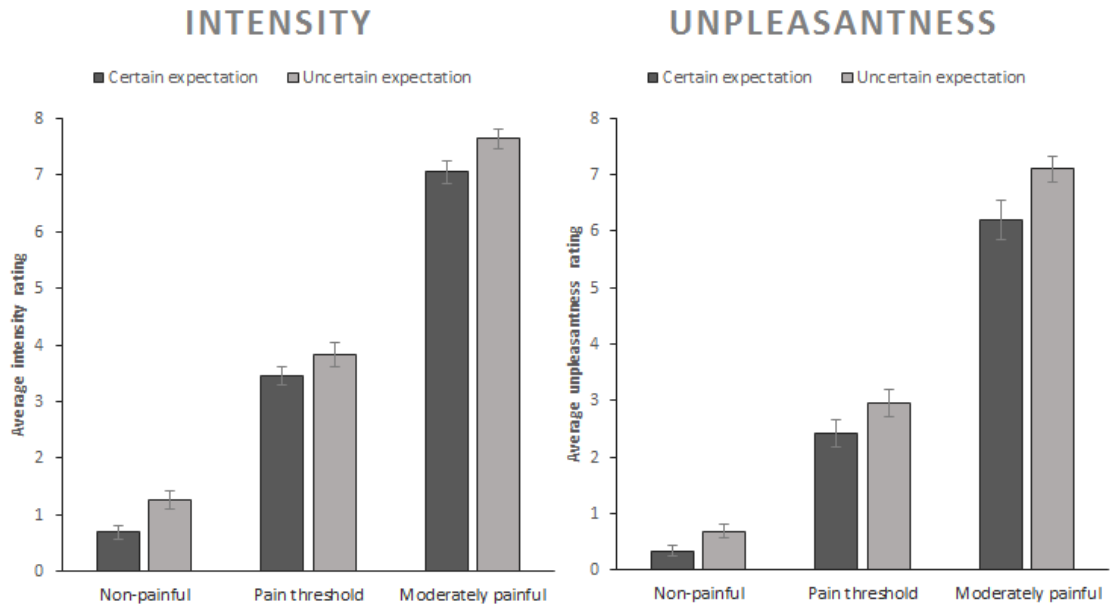
## **4.3 Results**

### **4.3.1 Pain experience**

For the intensity ratings a significant main effect of pressure intensity ( $F(2,28) = 964.731$ ;  $p < 0.001$ ; Partial  $\eta^2 = .971$ ) and a significant main effect

of expectation ( $F(1,29) = 9.588$ ;  $p = 0.004$ ;  $\text{Partial Eta}^2 = .248$ ) was found. No significant interaction between expectation and pressure intensity was found ( $F(2,28) = 1.409$ ;  $p = .252$ ;  $\text{Partial Eta}^2 = .046$ ). When pain intensity was certain, the intensity ratings (Mean (SD)) for the non-painful, pain threshold and moderately painful pressure stimuli were 0.69 (0.69), 3.45 (0.91) and 7.05 (1.12) respectively. When pain intensity was uncertain, the intensity ratings for the non-painful, pain threshold and moderately painful pressure stimuli were 1.27 (0.87), 3.82 (1.17) and 7.64 (0.96) respectively (Figure 4.2). Perceived intensity was significantly higher when pain intensity was uncertain compared to certain.

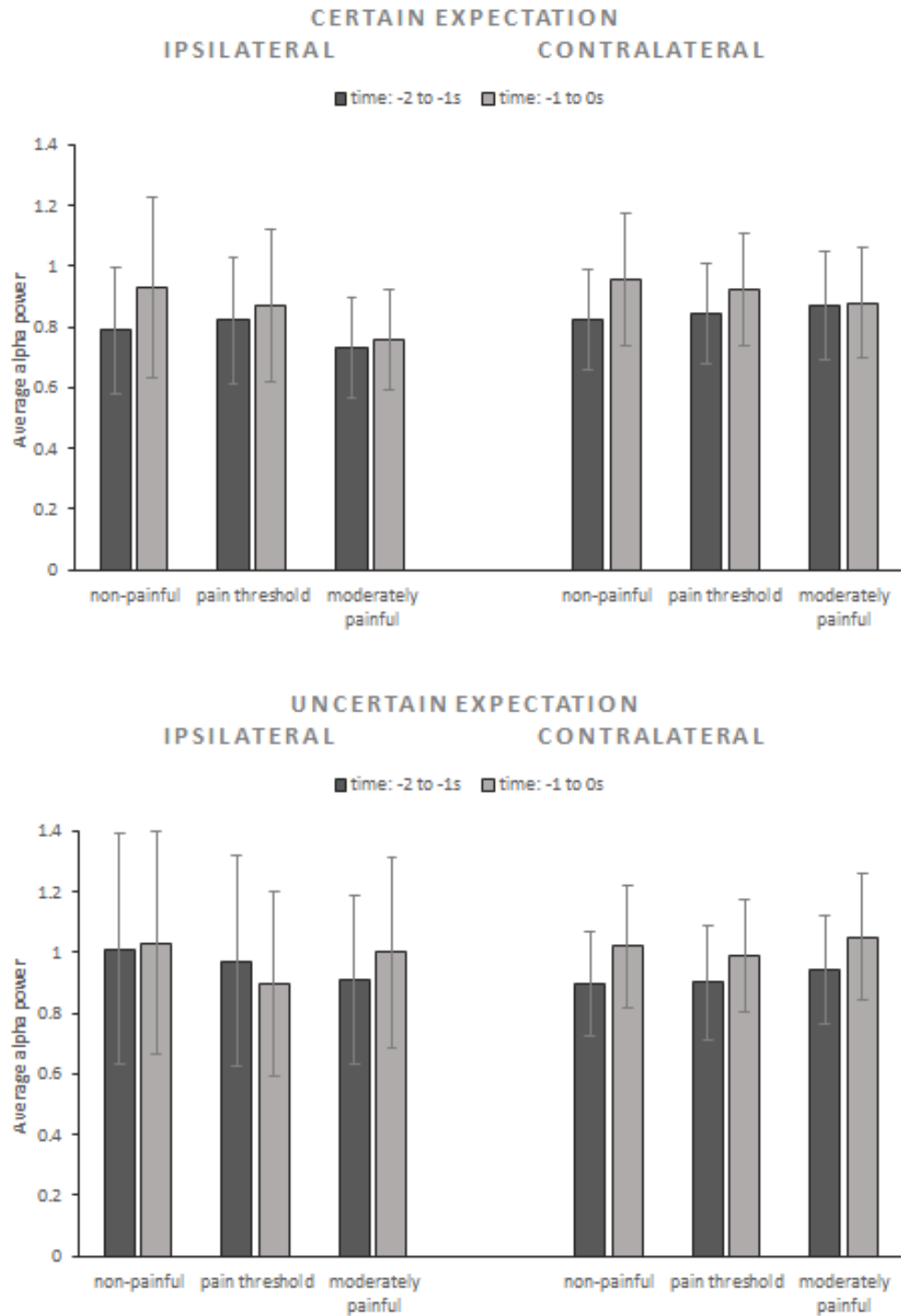
For the unpleasantness ratings a significant main effect of pressure intensity ( $F(2,28) = 303.598$ ;  $p < 0.001$ ;  $\text{Partial Eta}^2 = .956$ ), a significant main effect of expectation ( $F(1,29) = 12.111$ ;  $p = 0.002$ ;  $\text{Partial Eta}^2 = .295$ ), and a significant interaction between expectation and pressure intensity was found ( $F(2,28) = 4.617$ ;  $p = .028$ ;  $\text{Partial Eta}^2 = .137$ ). The unpleasantness ratings (Mean (SD)) for the non-painful, pain threshold and moderately painful pressure stimuli were 0.34 (0.47), 2.42 (1.30) and 6.20 (1.91) respectively, when pain intensity was certain. In the uncertain condition, the unpleasantness ratings for the non-painful, pain threshold and moderately painful pressure stimuli were 0.68 (0.65), 2.95 (1.30) and 7.10 (1.29) respectively (Figure 4.2). Perceived unpleasantness was significantly higher when participants were uncertain about pain intensity compared to certain. In addition, the difference in perceived unpleasantness for the uncertain and certain condition became larger with higher pressure stimulus intensity; the difference in unpleasantness ratings was 0.34 for the non-painful stimuli, 0.53 for the pain threshold stimuli, and 0.90 for the moderately painful stimuli.



**Figure 4.2** Average intensity and unpleasantness rating scores and standard error of means (SEM), for the certain and uncertain expectation condition separately. Both for the intensity ratings and the unpleasantness ratings a significant main effect of pressure intensity and expectation was found. Intensity and unpleasantness ratings were significantly higher when pain intensity was uncertain compared to certain.

### 4.3.2 Pre-stimulus somatosensory alpha activity

A within-subjects 2 x 3 x 2 x 2 ANOVA was calculated with the following factors: expectation (certain, uncertain), pressure stimulus intensity (non-painful, pain threshold, and moderately painful), time (-2 to -1s, -1 to 0s), and region (left somatosensory region, right somatosensory region). There was a significant main effect of time ( $F(1,18) = 5.21$ ;  $p = .035$ ; Partial  $\eta^2 = .23$ ). There were no other significant main effects, with expectation ( $F(1,18) = 1.094$ ;  $p = .31$ ; Partial  $\eta^2 = .057$ ), region ( $F(1,18) = .022$ ;  $p = .88$ ; Partial  $\eta^2 = .001$ ) and pressure intensity ( $F(2,17) = .10$ ;  $p = .57$ ; Partial  $\eta^2 = .022$ ). One marginally significant interaction was found for visual cue \* time \* ROI ( $F(1,18) = 4.07$ ;  $p = 0.059$ ; Partial  $\eta^2 = .16$ ) (Figure 4.3).



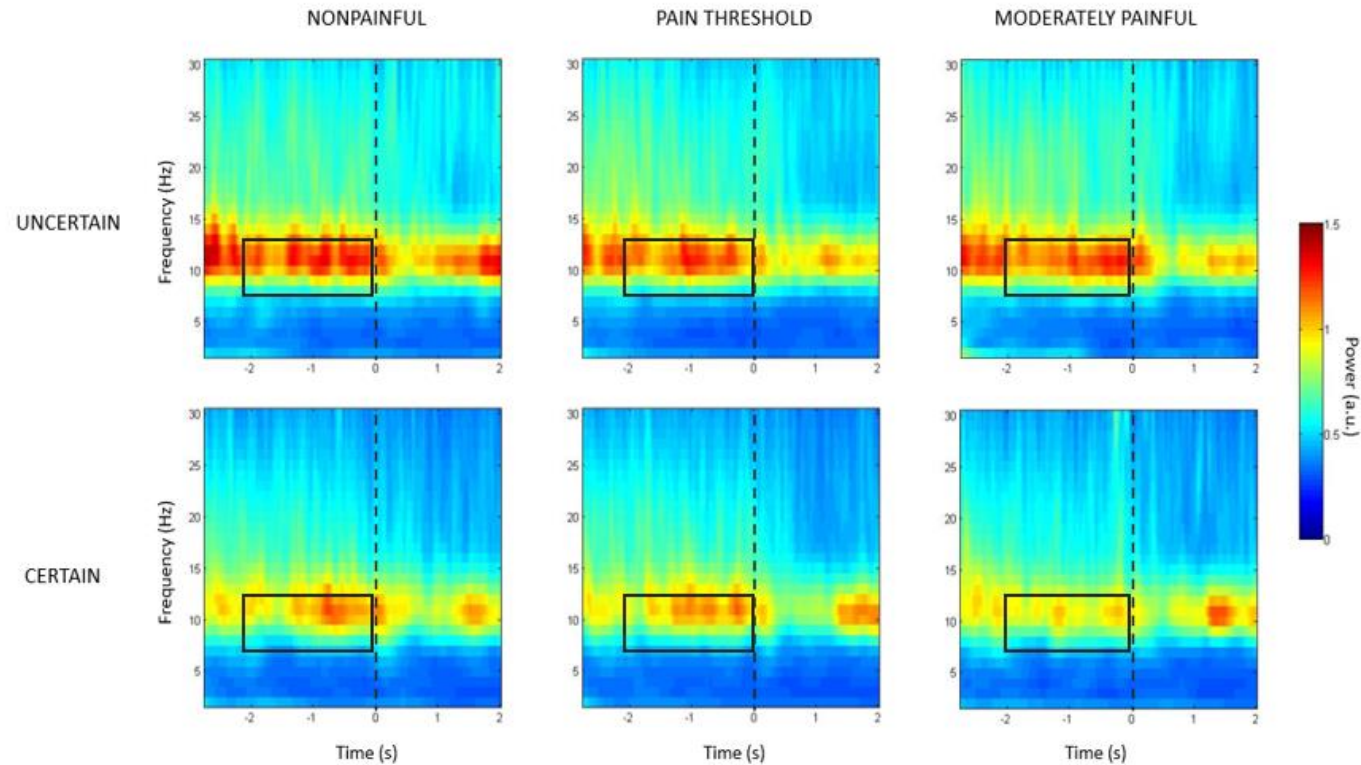
**Figure 4.3** Average alpha power and SEM comparing the two time windows -2 to -1s and -1 to 0s before pressure stimulus onset to illustrate changes in pre-stimulus somatosensory alpha activity over time, with the ipsilateral somatosensory ROI on the left and the contralateral somatosensory ROI on the right side, and the certain expectation condition in the top half and the uncertain expectation condition in the bottom half. Only a significant main effect of time was found, with alpha power building up over time before pain onset. No significant effect of pressure intensity, region (left/right somatosensory region), or expectation (certain/uncertain) was found.

#### **4.3.2.1 Time-Frequency representations (TFRs)**

The TFRs (averaged over the two somatosensory regions together) firstly illustrate the effect of time on alpha activity, showing a clear band of alpha activity present prior to pressure stimulus onset and a decrease of alpha activity shortly after pressure stimulus onset (see Figure 4.4). This was the case for painful and non-painful stimulation.

Visual inspection of the TFRs also suggests higher pre-stimulus somatosensory alpha activity for uncertain expectation compared to certain expectation. However no statistical significance was found based on the within-subject ANOVA.

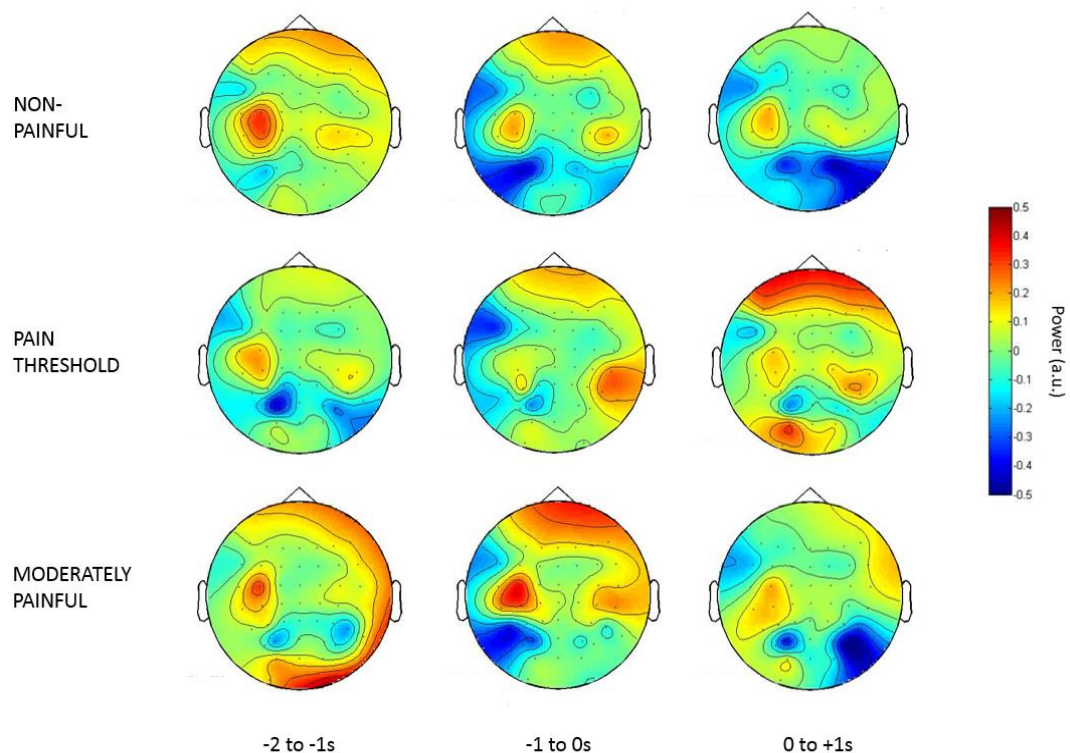
Finally, although no significant effect for pressure stimulus intensity was found overall, visual inspection of the TFRs for certain expectation does suggest an effect of pressure stimulus intensity, with higher pre-stimulus alpha activity for the non-painful stimulation than the painful stimulation. This was not the case in for uncertain expectation.



**Figure 4.4** TFRs of raw alpha power with time (s) on the x-axis and frequency on the y-axis. The representation was based on the average alpha power for all 19 participants over the two somatosensory ROIs, with three TFRs for uncertain expectation on the top row (for each pressure stimulus intensity) and three TFRs for certain expectation on the bottom row. Based on visual inspection a difference in alpha power before pain onset (from -2 to 0s) can be detected related to expectation about pain intensity, with higher pre-stimulus alpha power when participants were uncertain compared to certain about pain intensity.

### 4.3.2.2 Topographies

To further explore the differences in alpha power for uncertain and certain expectation, topographies were made from the alpha power distributions displaying the difference in alpha power between the uncertain and certain condition (average alpha power uncertain minus average alpha power certain) (Figure 4.5). Orange-red regions indicate regions where alpha power was higher in the uncertain compared to the certain condition.



**Figure 4.5** Topographies showing the difference in raw alpha power (8-12Hz) between the uncertain and certain condition (uncertain - certain), for the three pressure stimulus intensities across three time windows. Based on visual inspection, higher alpha power can be detected for uncertain pain intensity over central scalp regions. Higher alpha power for uncertain pain intensity is particularly prominent over the ipsilateral central scalp region.

Based on visual inspection, uncertainty about pain intensity seems to be associated with higher levels of alpha activity over bilateral central regions.

These higher levels seem to be particularly prominent in the ipsilateral central region with respect to the stimulated hand and less so in the contralateral region, most consistently in the non-painful and moderately painful condition. This could reflect more prominent ipsilateral de-activation for uncertain pain intensity.

### 4.3.3 Correlation results

To investigate the relationships between the different variables of the study - pain ratings, pre-stimulus somatosensory alpha power, fear of pain, and pain catastrophising – for moderate pain, correlation analyses were carried out.

A significant positive correlation was found for both self-reported fear of pain and pain catastrophising and the unpleasantness ratings, but only in the uncertain condition: unpleasantness ratings & PCS total score,  $r(29) = .55$ ,  $p = .002$  (adjusted significance level was .0125); and unpleasantness ratings & FoP total score,  $r(28) = .49$ ,  $p = .007$  (adjusted significance level was .0167). Higher levels of fear of pain and pain catastrophising were associated with higher levels of perceived unpleasantness.

For the intensity ratings a significant correlation was found only with pain catastrophising,  $r(29) = .42$ ,  $p = .022$ , again only in the uncertain expectation condition. However, this correlation was no longer significant after correction for multiple comparisons (adjusted significance level of was .0125).

A marginally significant positive correlation between pre-stimulus somatosensory alpha activity and pain intensity ratings was found, only when pain intensity was certain and only in the time window of -1 to 0s. This positive correlation between pre-stimulus somatosensory alpha (-1 to 0s) and intensity ratings was present both in the ipsilateral region ( $r(18) = .44$ ,  $p = .063$ ) and the contralateral region ( $r(18) = .43$ ,  $p = .064$ ). No (marginally) significant



correlations were found for the intensity ratings in the uncertain condition, nor for the unpleasantness ratings both in the certain and uncertain conditions.

Furthermore, a significant positive correlation between pre-stimulus somatosensory alpha activity and fear of pain was found, only when pain intensity was certain. A significant positive correlation between pre-stimulus somatosensory alpha and fear of pain was found for the -1 to 0s time window:  $r(18) = .643$ ,  $p = .003$  (adjusted significance level was .00625) for the ipsilateral region and  $r(18) = .584$ ,  $p = .009$  for the contralateral region (adjusted significance level was .0100). A significant positive correlation between pre-stimulus somatosensory alpha and fear of pain was also found for the -2 to -1s time window:  $r(18) = .60$ ,  $p = .007$  for the ipsilateral region (adjusted significance level was .00714) and  $r(18) = .60$ ,  $p = .007$  for the contralateral region (adjusted significance level was .00833).

In the uncertain expectation condition one significant positive correlation was found between pre-stimulus somatosensory alpha activity and fear of pain, for the -2 to -1s time window in the contralateral region:  $r(18) = .51$ ,  $p = .026$ . However, this did not survive correction for multiple comparisons at a significance level of .00625.

#### **4.4 Discussion**

The present study set out to investigate the relationship between uncertainty about pain intensity, pre-stimulus somatosensory alpha activity and pain experience, to allow for further interpretation of the role of pre-stimulus somatosensory alpha activity in pain experience. This study examined whether uncertainty about pain intensity influenced pain experience and pre-stimulus somatosensory alpha activity, by addressing three objectives: 1) whether uncertainty about pain intensity influenced pain experience (i.e., perceived pain intensity and unpleasantness); 2) if there was a relationship between pre-stimulus somatosensory alpha activity and pain experience; and 3) whether

uncertainty about pain intensity influenced pre-stimulus somatosensory alpha activity.

#### **4.4.1 Uncertainty about pain intensity and perceived pain**

This study demonstrated a significant effect of uncertainty about pain intensity on perceived pain intensity and unpleasantness. When people were uncertain about the intensity of an upcoming stimulation, their pain experience was enhanced; both intensity and unpleasantness ratings were significantly higher in the uncertain condition compared to the certain condition. This in line with previous findings (Lin et al., 2014; Ploghaus et al., 2001; Ploghaus et al., 2003) and demonstrates the effectiveness of the manipulation of uncertainty in the present study.

Higher perceived pain as a result of uncertainty could be related to differences in threat value for certain and uncertain pain intensity. Uncertainty about the intensity of an upcoming stimulus is thought to result in a higher threat value and higher reported levels of anxiety (Crombez et al., 1998; Ploghaus et al., 2001). This in turn affects the amount of attention to pain. Uncertain expectations have been associated with increased attention to the environment and body (Ploghaus et al., 2003). Uncertainty about pain intensity leads to enhanced capture of attention by pain, as reflected by a greater interruption of performance on a primary task when pain intensity is uncertain (Crombez et al., 1994; Crombez et al., 1998). A similar mechanism might apply to the findings of the present study, where a higher threat value in the uncertain condition resulted in increased attention to pain, leading to increased perceived pain intensity and unpleasantness.

Furthermore, a significant positive correlation between perceived pain and fear of pain/pain catastrophising was only found when pain intensity was uncertain. This suggests that higher fear of pain and pain catastrophising are associated with higher perceived pain particularly when pain intensity is uncertain, a setting related to higher threat value and a stronger capture of pain. Thus, the relationship between fear of pain/pain catastrophising and pain

experience might be influenced by the extent of capture of attention by pain. This is to some extent supported by the studies that demonstrated an association between fear of pain/pain catastrophising and attention to pain. In a chronic pain setting, increased fearful thinking about pain was associated with increased attention to pain (Crombez et al., 2013), and both pain-related fear and pain catastrophising were positively associated with vigilance to pain (Goubert et al., 2004). In an experimental pain setting, it was found that participants with high levels of pain catastrophising had problems with disengaging from a pain cue (Van Damme et al., 2004). Patients with high levels of pain catastrophising also showed enhanced capture of attention by pain and stronger disruption of performance on a primary task (Crombez et al., 1998).

Taken together, uncertainty about pain intensity results in higher perceived pain and this increase of perceived pain by uncertainty might be further amplified for individuals with higher fear of pain and/or pain catastrophising. This could be the result of exaggerated perceived threat value in the uncertain condition when people have higher levels of fear of pain and pain catastrophising.

#### **4.4.2 Pre-stimulus alpha activity and the experience of pain**

With respect to pain experience and pre-stimulus alpha activity, only in the certain condition some initial evidence for a relationship between pre-stimulus somatosensory alpha activity and pain experience was found: a marginally significant positive correlation between pre-stimulus somatosensory alpha activity and perceived pain intensity both in the ipsi- and contralateral region in the time window of -1 to 0s.

Although the present study provides further suggestion of a correlation between pre-stimulus somatosensory alpha activity and pain experience, there are some clear differences present compared to the study by Babiloni et al. (2006). Babiloni et al. (2006) found a significant correlation between pre-stimulus somatosensory alpha and perceived pain intensity for the contralateral

somatosensory region only, furthermore, they found a negative correlation, where the present study found a positive correlation. These differences might in part be explained by a different approach in calculation of the alpha activity outcome that was used for statistical analysis. In the present study, untransformed alpha power as measured at the electrode (sensor-level) was used. Average alpha power was calculated over two time windows (pre-stimulus: -2 to -1s and -1 to 0s) and over a certain set of electrodes (two somatosensory regions of interest both consisting of 4 electrodes). Babiloni et al. (2006) on the other hand, used laplacian-transformed alpha power outcomes for their statistical analysis, to improve spatial resolution of the alpha outcomes. In addition, they did not just use the average alpha power over a certain time window as the outcome. Instead they applied an event-related synchronisation/event-related desynchronisation (ERS/ERD) calculation to assess the change in alpha during the period of interest (E) compared to a baseline period, with two periods of interest: early pain anticipation (-1 to -0.5s before pain onset) and late pain anticipation (-0.5 to 0s). A negative value reflects ERD or an alpha decrease during the period of interest compared to baseline, a positive value reflects ERS or an alpha increase during the period of interest. This type of calculation allows for the interpretation of changes within a condition, e.g. during the expectation of predictable pain, alpha activity was significantly decreased compared to the baseline period. The present study in contrast, aimed to investigate differences in alpha activity between conditions, allowing for conclusions on whether alpha power is higher or lower comparing conditions, for example the certain expectation compared to the uncertain expectation condition. However, it did not answer whether alpha activity within a condition increased or decreased, for example if during uncertain expectation about an upcoming stimulation alpha activity was increased or decreased compared to a baseline period. In future studies a longer pre-stimulus period will be considered to allow for a sufficient baseline time window to carry out ERS/ERD calculation. Another difference between the two studies that might explain some of the variation between the two studies, is the different type of pain stimulation used. In the present study pressure pain stimulation with a duration of several seconds was used. Pressure pain has

been applied in the study of healthy and clinical populations and is the most commonly applied stimulus to assess the pain response in clinical pain populations (Plaghki & Mouraux, 2003). Furthermore, pressure pain with a larger blunt probe, as used in the present study, is thought to activate pain receptors in both the skin and deeper tissues (Treede et al., 2002). Babiloni et al. (2006) in contrast, used brief painful laser stimuli applied on the skin, with a duration of 10ms. Where the average pain intensity rating for the predictable moderately painful stimuli was 5.23 (SEM 0.32) in the study by Babiloni et al. (2006), the average pain intensity rating for the present study was 7.05 (SEM 0.21) in the certain condition and 7.64 (SEM 0.18) for the uncertain condition, both on a rating scale ranging from 0-10. Together this suggests that the pain experience for the two studies might be different. These different types of pain stimulation may have affected not only pain experience but may also expectations and neural activity during the pre-stimulus period.

To conclude, the findings of the present study and the study by Babiloni et al. (2006) together support the hypothesis of a correlation between pre-stimulus somatosensory alpha activity and pain experience. However, as differences exist between the findings of these two studies, further investigation is warranted to gain a better understanding of why this study found a positive correlation and Babiloni et al. (2006) a negative correlation.

#### **4.4.3 Uncertainty about pain intensity and pre-stimulus somatosensory alpha activity**

Firstly, in general terms, irrespective of the uncertain/certain pain intensity, it was expected that ipsilateral and contralateral somatosensory regions would display different amounts of pre-stimulus alpha activity, reflecting activation of relevant neural regions and de-activation of irrelevant neural regions. As stimulation in the present study always took place on the left hand, we expected that pre-stimulus somatosensory alpha activity in the contralateral region, processing relevant information, would be lower compared to pre-

stimulus somatosensory alpha activity in the ipsilateral region, processing irrelevant or distraction information. However, this study did not find a significant difference in pre-stimulus alpha activity for the ipsi- and contralateral region. Thus, looking at differences in ipsi- and contralateral pre-stimulus somatosensory alpha activity irrespective of certainty of expectation, did not provide enough evidence to confirm the presence of a mechanism functional inhibition for the perception of pain (Foxye & Snyder, 2011; Jensen & Mazaheri, 2010; Klimesch, 2012). This is surprising, as other studies did suggest different levels of ipsi- and contralateral pre-stimulus somatosensory alpha activity. Attentional modulation of pre-stimulus alpha activity has been demonstrated for painful stimulation. For instance, Del Percio et al. (2006) demonstrated an event-related decrease of pre-stimulus alpha power that was more prominent in the contralateral central region than the ipsilateral central region. Furthermore, they found that the decrease of pre-stimulus alpha power was significantly larger when participants attended to pain compared to when they were distraction from the pain. Babiloni et al. (2003) also found a more prominent decrease of pre-stimulus somatosensory alpha activity in the contralateral region than the ipsilateral region with respect to the stimulated hand.

Secondly, we also aimed to investigate the effects of uncertainty about pain intensity on pre-stimulus somatosensory alpha activity. Based on the outcomes of the within-subject ANOVA there was no evidence to suggest a main effect of uncertainty on pre-stimulus somatosensory alpha activity. However, visual inspection of the TFRs did show higher pre-stimulus somatosensory alpha activity (averaged over the two somatosensory regions) in the uncertain condition compared to the certain expectation condition. Moreover, the topographies of the differences in alpha power between the uncertain and certain condition further demonstrated that higher pre-stimulus somatosensory alpha activity in the uncertain condition was most prominent in the ipsilateral somatosensory region. This might reflect a mechanism of functional inhibition. Higher pre-stimulus somatosensory alpha activity ipsilateral when pain intensity was uncertain could reflect increased inhibition of this task-irrelevant region when pain intensity was uncertain. The enhanced inhibition of the ipsilateral somatosensory region in the uncertain condition

could be related to an attentional mechanism. Uncertain expectation is thought to result in higher threat value and has been related to enhanced capture of attention by pain (Crombez et al., 1998; Morley, 2008; Ploghaus et al., 2001).

In summary, statistical analysis did not show an effect of uncertainty about pain intensity on pre-stimulus somatosensory alpha activity. However, visual inspection of the TFRs and topographies does provide a strong suggestion of increased pre-stimulus somatosensory alpha activity when pain intensity is uncertain, particularly in the ipsilateral region, thought to be related to an enhanced bottom-up capture of attention.

Although the present study provided evidence for an effect of uncertainty on pain experience and some initial evidence to suggest an influence of uncertainty on pre-stimulus somatosensory alpha activity, more research is needed to better understand the influence of uncertainty on pre-stimulus somatosensory alpha activity and its relationship with pain experience. As both uncertainty about pain intensity and pre-stimulus somatosensory alpha activity have a relationship with the experience of pain, they could offer interesting options for non-pharmacological interventions for pain. Uncertainty about pain intensity has been associated with enhanced capture of attention (Crombez et al., 1998), suggesting that an influence of uncertainty on pre-stimulus alpha activity might reflect an attentional process. Thus, future studies should further investigate the influence of attention, especially bottom-up capture of attention, on pre-stimulus somatosensory alpha activity and pain experience.

#### **4.4.4 Conclusions**

To conclude, the present study investigated the effect of uncertainty about pain intensity on pre-stimulus somatosensory alpha activity and the experience of pain. Pain experience was enhanced by uncertainty about pain intensity. Furthermore, pre-stimulus somatosensory alpha activity seemed to be higher when pain intensity was uncertain compared to the certain, particularly

in the ipsilateral region. Finally, this study also suggested a relationship between pain experience and pre-stimulus somatosensory alpha activity, but only when pain intensity was certain. Previous studies have demonstrated changes in pre-stimulus alpha activity during the anticipation of pain (Babiloni et al., 2003) and a relationship between pre-stimulus somatosensory alpha activity and pain experience (Babiloni et al., 2006). However, these two studies both only applied predictable pain stimuli, and thus only investigated a condition of certainty about pain intensity. The present study was the first to investigate the influence of uncertainty about pain intensity on pre-stimulus somatosensory alpha activity and pain experience, allowing for further interpretation of the mechanisms behind the role of pre-stimulus somatosensory alpha activity in pain experience.



## **Chapter 5** Does listening to binaural beats at alpha frequency during pressure pain stimulation reduce the experience of pain?

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### **5.1 Introduction**

The summed activity of groups of neurons, as measured by EEG, contains oscillatory, or rhythmic activity. Oscillatory neural activity can be modified using external rhythmic stimulation (Cohen, 2014; Thut et al., 2011); for example rhythmic stimulation via sensory pathways, such as rhythmic visual or auditory stimulation. When presented with an external stimulation at a certain frequency, such as a flickering light at 10Hz, oscillatory neural activity at this same frequency tends to shift or synchronise in phase with respect to the external stimulation, resulting in alignment with the external stimulation. This leads to an increase of power specifically at the entrainment frequency, as reflected by a distinct peak in the frequency spectrum at the entrainment frequency (De Graaf et al., 2013; Spaak, De Lange, & Jensen, 2014). Interventions have been developed using the process of neural entrainment to modify oscillatory neural activity at a specific frequency (Thut et al., 2011), including alpha activity. As several studies have suggested a relationship between levels of alpha activity and pain experience (Babiloni et al., 2006; Nir et al., 2012; Tu et al., 2016), interventions altering levels of ongoing alpha activity can offer a promising perspective on pain management (Jensen et al., 2008). One type of rhythmic external stimulation to modulate alpha activity is listening to binaural beats at alpha frequency. An effect of listening to alpha binaural beats has been demonstrated for a variety of outcomes. For instance,

alpha binaural beats have been shown to improve auditory performance on a dichotic digit test (Solcà et al., 2016), but reduced performance on a visual-spatial memory task (Beauchene et al., 2016). Another study found an effect of both alpha and gamma binaural beats on creativity, reflected by improved performance on a divergent thinking task (Reedijk, Bolders, & Hommel, 2013). Finally, listening to alpha binaural beats reduced levels of pre-operative anxiety, blood pressure and heart rate in patients undergoing cataract surgery (Wiwatwongwana et al., 2016). This chapter will address the question of whether listening to binaural beats at alpha frequency can reduce pain experience.

### **5.1.1 Binaural beats**

Oscillatory neural activity can be modified using external rhythmic stimulation (Cohen, 2014; Thut et al., 2011), such as rhythmic stimulation via sensory pathways using visual or auditory stimuli. One approach to rhythmic auditory stimulation, is the use of binaural beats. Binaural beats are created by presenting two sinusoidal tones at slightly different frequencies to the left and right ear. As each ear receives a slightly different tone, this is perceived as a sound with fluctuations in loudness (Perrott & Nelson, 1969), as “a sound that waxes and wanes periodically” (Oster, 1973) or a perceived beat, which has a frequency that reflects the difference in frequency between the two sinusoidal tones. For example, a tone with a frequency of 445Hz presented at the left ear and a tone with a frequency of 455Hz presented at the right ear would result in a perceived binaural beat in the alpha band, with a frequency of 10Hz.

Listening to binaural beats has shown potential to change both oscillatory neural activity and behaviour, specifically, to increase oscillatory neural activity at a specific frequency (Karino et al., 2006; Schwarz & Taylor, 2005). The application of binaural beats to manipulate oscillatory activity at a specific frequency could be a promising approach in the study of the functional role of neural activity at a specific frequency, such as alpha activity. Rhythmic external stimulation is thought to alter oscillatory neural activity through a mechanism of neural entrainment (Cohen, 2014; Thut et al., 2011). Binaural

beat stimulation, as a form of rhythmic external stimulation, is thought to work through this same mechanism. The main components for neural entrainment are an external stimulation that is rhythmic or periodic and a neural population that exhibits oscillatory neural activity at the frequency of the external stimulation. Neural entrainment refers to a mechanism of phase synchronisation of oscillatory neural activity, such as alpha activity, to the frequency of the rhythmic external stimulation. As more and more neurons synchronise in phase an increase in power can be measured. The effect of the rhythmic external stimulation is frequency-specific, the external stimulation is maximally effective in increasing power in a neural population at the frequency of the stimulation (Thut et al., 2011). This means that the application of binaural beats at a certain frequency, inducing neural entrainment, has the potential to modify oscillatory neural activity in a controlled, frequency-specific manner.

Assessing both changes in neural activity and behaviour when people listen to binaural beats can lead to better understanding of the role of oscillatory neural activity in behaviour. This principle can be applied to pain experience, to address what the role of alpha activity is in the experience of pain. So far, evidence for the functional importance of alpha activity in pain perception largely depends on studies demonstrating a correlation between changes in alpha activity and pain experience, with a negative correlation between perceived pain intensity and both pre-stimulus somatosensory alpha activity (Babiloni et al., 2006; Tu et al., 2016) and alpha activity at rest (Nir et al., 2012). Using binaural beats at alpha frequency to increase alpha activity specifically, can provide further insight into the functional importance of alpha activity in pain experience. Finally, increasing alpha activity with alpha binaural beat stimulation could reduce pain experience, suggesting that alpha binaural beats might offer a promising approach to manage pain in a clinical setting.

### **5.1.2 Alpha binaural beat stimulation and changes in alpha activity**

Using alpha binaural beats to specifically increase levels of alpha activity, to, in turn, reduce pain experience, assumes that listening to alpha binaural beats increases alpha power. Indeed, a couple of studies have

demonstrated an increase in alpha power as a result of listening to alpha binaural beats. One study investigated the effect of binaural beats in the alpha frequency range at three different frequencies (8, 10 and 12Hz) on both alpha power and pain experience, compared to listening to white noise (Ecsy, 2014). Participants listened to alpha binaural beats for 10 minutes at each frequency. After the 10 minutes of auditory stimulation painful laser stimuli were applied to assess pain experience. Alpha power was calculated for the entrainment period (during the auditory stimulation) and found to be significantly higher (compared to white noise) only for the 10Hz and 12Hz frequency. For both 10Hz and 12Hz, the enhancement of alpha power in the binaural beat condition was most prominent in posterior regions and more prominent at left regions than right regions. In addition, comparing global alpha power across all electrodes resulted in significantly higher alpha power after 10Hz entrainment compared to 8Hz and 12Hz. A significant reduction in pain ratings was found after listening to alpha binaural beats at all three alpha frequencies compared to white noise (Ecsy, 2014). This suggests that listening to alpha binaural beats can result in both significantly higher levels of alpha power during the auditory stimulation period (online) and significantly lower pain ratings after the auditory stimulation period (offline), compared to listening to white noise. A second study by Ioannou et al. (2015) investigated changes in alpha power and phase synchronisation when listening to a variety of binaural beats with frequencies in the range of 1-48Hz. For each binaural beat frequency 20 seconds of silence were followed by 1 minute of binaural beats and 1 minute of a single, non-beat tone (200Hz). Alpha binaural beats were presented at 4 different frequencies: 9, 10, 11, and 12Hz, for 1 minute at each frequency. Normalised alpha-band power (9-12Hz) was calculated: alpha power in the binaural beat condition was normalised by alpha power in the single tone condition. For phase synchronisation (a measure of connectivity, see details Chapter 3), a number of outcomes were calculated, including the phase locking value (PLV). A significant increase of normalised alpha power (averaged across all electrodes) was found for alpha binaural beats and delta binaural beats. The increase of alpha power for binaural beats compared to a single tone, was largest for alpha binaural beats. A topography of normalised alpha power for alpha binaural

beats showed an increase that was most prominent in the posterior occipital region. The study included a large number of PLV outcomes, making a clear overall interpretation somewhat challenging. Only in the alpha-band significant changes in PLV were found. Both listening to alpha and delta binaural beats resulted in increased phase synchronisation in the alpha-band, compared to listening to a single tone. Together these findings provide further evidence supporting the potential of alpha binaural beats to increase alpha power. A third study found further evidence that listening to alpha binaural beats can modify alpha activity (Solcà et al., 2016). They did not find an increase in alpha power; they did, however, find other evidence to suggest neural entrainment as a result of listening to alpha binaural beats: a significant increase of phase synchronisation in the alpha-band. Alpha phase synchronisation between the two auditory cortices was compared for alpha binaural beats (10Hz), monaural beats (10Hz) and resting-state. Participants listened to each auditory condition for a duration of 4 minutes. Interhemispheric coherence between the two auditory cortices in the alpha-band was significantly increased in the alpha binaural beat condition, compared to monaural beats and resting-state. This reflects higher levels of phase synchrony of oscillatory neural activity in the alpha-band between the two hemispheres. Furthermore, both listening to alpha binaural beats (10Hz) and alpha monaural beats led to an improvement in performance on a dichotic digit test. No significant difference in performance was found between listening to alpha binaural beats and monaural beats.

Although there is evidence to suggest that alpha binaural beats affect alpha activity and specifically increase alpha power, not all studies are in support of this. A study investigating changes in phase synchronisation by Gao et al. (2014) studied the effects of binaural beat stimulation at delta (1Hz), theta (5Hz), alpha (10Hz), and beta (20Hz) frequency. Binaural beats were embedded in pink noise. Stimulus duration for each of the binaural beat conditions was 5 minutes with 2-minute breaks between conditions. Phase synchrony was assessed using the PLV. No evidence was found for an effect of alpha binaural beats on phase synchronisation in the alpha-band. Only in the theta-band, and in the last minute of binaural beat stimulation, a significant increase of the PLV was found (electrode sites FP1-O2). In addition, no

convincing evidence for an increase in alpha power was found. Thus, no evidence in favour of frequency-specific changes in rhythmic neural activity in the alpha band as a result of listening to alpha binaural beats was present. Another study, by Beauchene et al. (2016), also assessed changes in PLV outcomes. They studied the effects of binaural beats at theta, alpha, and beta frequency on visual-spatial memory and phase synchronisation. These effects were compared to a classical music, single tone, and no tone condition. Participants carried out a visual-spatial working memory task for 30 minutes, while listening to 5 minutes of each auditory condition. Where listening to beta binaural beats (15Hz) led to an improvement in performance on the visual-spatial memory task, listening to alpha binaural beats led to a reduction in performance on the task. With respect to the PLV no significant increase in the alpha band was found for listening to alpha binaural beats, the only changes in PLV in this study were found in the theta band. So although listening to alpha binaural beats affected memory performance, this was not related to any significant change in phase synchronisation in the alpha-band. Finally, a study investigating the effects of alpha binaural beats on alpha power also did not find strong evidence to suggest an entrainment effect of alpha binaural beats. Alpha binaural beat stimulation (10Hz) consisted of ten 1-minute binaural beat segments, with 1-minute segments of a single constant tone in-between (400Hz). The alpha binaural beats were based on one tone at 395Hz and one at 405Hz. No significant increase of alpha power was found when listening to alpha binaural beats compared to a single tone (Vernon et al., 2014).

Overall, it is difficult to provide a conclusive answer on whether listening to alpha binaural beats can increase alpha activity; at best, findings are mixed. Although there are some studies supporting the idea of neural entrainment as a result of listening to binaural beats at alpha frequency (Ecsy, 2014; Ioannou et al., 2015; Solcà et al., 2016), this was not confirmed by three other studies (Beauchene et al., 2016; Gao et al., 2014; Vernon et al., 2014). It should be stressed however, that the number of studies investigating the neural effects of alpha binaural beats is rather low and study designs variable, which might in part add to the difficulty of interpreting the findings. There is potential for alpha binaural beats to increase alpha activity, but more work on the specific effects

of listening to alpha binaural beats on alpha activity and optimal stimulation settings is needed, to be able to conclude on the matter with more certainty.

### 5.1.3 Binaural beats at alpha frequency and pain experience

The present study focussed on the use of binaural beats at alpha frequency to not only increase levels of ongoing alpha activity, but also reduce levels of pain experience. Besides assessing the potential of alpha binaural beats to modify alpha activity, it is equally relevant to find out whether listening to alpha binaural beats is capable of modifying pain experience. So far, only a few studies have investigated the effect of listening to alpha binaural beats on pain experience. If listening to alpha binaural beats is effective in reducing pain experience it would have the potential to be a relatively inexpensive and accessible intervention that deserves further investigation.

Two studies investigating the effect of binaural beats at alpha frequency on pain experience showed a decrease in reported pain levels (Ecsy et al., 2016; Ecsy, 2014). Both studies investigated the change in pain experience by assessing pain ratings after 10 minutes of listening to alpha binaural beats at 8, 10 and 12Hz (10 minutes for each frequency) compared to pain ratings after three lots of 10 minutes of listening to white noise. Participants received 30 brief moderately painful laser stimuli, applied to the skin of the right forearm, after every 10 minutes of auditory stimulation. The painful stimuli were set at a moderately painful level for each participant separately (a rating of 7 on a 0-10 numeric rating scale). In Ecsy et al. (2016) a significant reduction in pain ratings was found for all three alpha binaural beat conditions compared to a white noise control (with baseline pain ratings as a covariate) (8Hz:  $t(31) = 4.90$ ,  $p < .001$ ; 10Hz:  $t(31) = 5.61$ ,  $p < .001$ ; 12Hz:  $t(31) = 4.85$ ,  $p < .001$ ), with a reduction of adjusted average pain rating (taking into account baseline pain ratings as a covariate) ranging from 0.50-0.58 (SE 0.10). The largest reduction of pain ratings was found for alpha binaural beats at 10Hz, where the unadjusted average rating for the moderately painful stimulus at baseline was 6.74, and 6.05 after listening to the 10Hz binaural beats. In Ecsy (2014) a significant increase in alpha activity was found for alpha binaural beats at 10

and 12Hz. This increase of alpha activity during listening to binaural beats at 10 and 12Hz was accompanied by a significant reduction in average pain rating (with baseline pain ratings as a covariate) (8Hz:  $t(31) = 4.90$ ,  $p < .001$ ; 10Hz:  $t(31) = 5.61$ ,  $p < .001$ ; 12Hz:  $t(31) = 4.85$ ,  $p < .001$ ), with a reduction in adjusted average rating of 0.58 (SE 0.10) for the 10Hz binaural beat condition and a reduction of 0.50 (SE 0.10) for the 12Hz binaural beat condition. Furthermore, although no significant increase of alpha power was found for the 8Hz binaural beat condition compared to white noise, a significant reduction in average pain rating was found still, with a reduction in adjusted average pain rating of 0.51 (SE 0.10). As only two studies have explored the effect of alpha binaural beats on pain experience so far, using brief painful stimuli and measuring pain experience after the exposure to alpha binaural beats (offline), further investigation to confirm and further explore the relationship between alpha binaural beats and pain experience is warranted.

#### **5.1.4 Study objectives**

The aim of this study was to investigate the effects of listening to binaural beats at alpha frequency (10Hz) on the experience of pain, as indexed by changes in both perceived pain intensity and unpleasantness. A small number of studies suggest that listening to alpha binaural beats could lead to entrainment of ongoing alpha activity, leading to an increase of alpha power (Ecsy, 2014; Ioannou et al., 2015). As higher levels of alpha activity at rest and in the pre-stimulus period before pain onset have previously been related to lower levels of reported pain intensity (Babiloni et al., 2006; Nir et al., 2012), it was expected that pain experience would be decreased as a result of an increase of alpha activity, resulting from the alpha binaural beat stimulation.

A reduction of pain experience as a result of listening to alpha binaural beats would be in line with the findings of two studies by Ecsy and colleagues (Ecsy et al., 2016; Ecsy, 2014). However, there is an important difference between these two studies and the present study with respect to the timing of pain experience assessment. The assessment of pain experience in two studies by Ecsy and colleagues (Ecsy et al., 2016; Ecsy, 2014) took place after



listening to the binaural beats, assessing an aftereffect of entrainment of alpha activity on pain experience outlasting the alpha binaural beat stimulation (offline effect). The present study uniquely aimed to investigate whether listening to alpha binaural beats could reduce the amount of pain experienced online, with participants rating pain stimuli during the binaural beat stimulation, assessing whether alpha entrainment directly influenced pain experience. There is little data available to make a clear prediction on whether or not the effects of alpha binaural beats on pain experience differ during and after alpha binaural beat listening. So far, the effects of alpha binaural beats on pain experience have been based on pain assessment after alpha binaural beats only. In addition, changes in alpha activity as a result of alpha binaural beats have only been assessed online, no studies have specifically assessed changes in alpha activity offline, after alpha binaural beats. The present study will help to find out whether listening to alpha binaural beats leads to a similar reduction in pain experience online as offline. Thus, the present study could offer further support to the findings of the two studies by Ecsy and colleagues (Ecsy et al., 2016; Ecsy, 2014) and moreover allows for further exploration of the effects of alpha binaural beats on pain experience.

The present study differed from the two existing studies on alpha binaural beats and pain perception (Ecsy et al., 2016; Ecsy, 2014) in two other main ways. First, in the present study, the influence of uncertainty on the reduction in pain experience during alpha binaural beat stimulation was assessed. A condition where the intensity of an upcoming stimulus was uncertain was compared to when stimulus intensity was certain or known. Uncertainty about the intensity of an upcoming stimulus has been found to result in higher levels of perceived pain intensity (Lin et al., 2014; Ploghaus et al., 2001). Furthermore, expectations about pain intensity have been demonstrated to affect both pre-stimulus alpha activity and alpha activity at rest (Franciotti et al., 2009; Huneke et al., 2013). As uncertainty about pain intensity seems to affect pain experience and possibly also alpha activity before pain onset, this suggests that uncertainty about pain intensity might also influence the increase of alpha and reduction of pain experience by alpha binaural beats.

Second, the present study used a different type of pain stimulation with a longer duration. Pressure stimulation was applied for a duration of several seconds at three different intensities, non-painful, pain threshold and moderately painful, whereas the studies by Ecsy and colleagues (Ecsy et al., 2016; Ecsy, 2014) used brief laser stimuli (150ms) on the skin at a moderately painful intensity only. Thus, the present study allowed for further investigation of the potential of alpha binaural beats to alter experience of, not only moderately painful stimuli, but also pain threshold stimuli. In addition, as perceived intensity and unpleasantness were also assessed for non-painful pressure stimulation, this could inform us whether the effects of the alpha binaural beats are restricted to painful stimulation or have a more generic effect on non-painful somatosensory perception as well. A benefit of applying pressure pain as an experimental pain stimulus is that it is used both in the study of healthy and clinical populations and is the most commonly applied stimulus to assess the pain response in clinical pain populations (Plaghki & Mouraux, 2003). Pressure pain has been used in the diagnosis of several pain syndromes such as fibromyalgia, tension-type headache, and temporomandibular disorder, demonstrating its clinical relevance (Treede et al., 2002). Thus, applying pressure pain as the experimental pain stimulus in the studies of the thesis might facilitate the translation of the findings to a clinical pain population (to some extent).

Binaural beats are best perceived at lower frequencies in a 400-500Hz range, with optimal binaural beat around 440Hz (Oster, 1973) and maximum detection of binaural beats at 500Hz (Perrott & Nelson, 1969). A decline in the probability of perceiving a binaural beat occurs when the frequencies are higher, with no clear binaural beat perceivable over 1000Hz (Oster, 1973; Perrott & Nelson, 1969). Comparing the neural response for 390 and 430Hz binaural beats to 810 and 850Hz binaural beats showed a larger frequency following response for the binaural beats at the lower frequency (Grose & Mamo, 2012). Thus, in the present study it was decided to use tone frequencies within this optimal frequency range of 400-500Hz. Furthermore, as one of the objectives of the present study was to confirm the findings by Ecsy and colleagues (Ecsy et al., 2016; Ecsy, 2014) who used alpha binaural beats

within this frequency range, in this study it was decided to use alpha binaural beats with a frequency of 10Hz using the same two tones as Ecsy and colleagues used: a sinusoidal tone with a frequency of 445Hz was presented to the left ear and 455Hz to the right ear.

Similar to Ecsy and colleagues (Ecsy et al., 2016; Ecsy, 2014), pain experience was compared for an alpha binaural beats condition and a white noise condition in the present study. Comparing alpha binaural beats to white noise allows for the assessment of whether listening to alpha binaural beats (and their rhythmic nature) is more effective in reducing perceived pain than listening to white noise. Listening to white noise has been demonstrated to reduce levels of experienced pain. Boyle, Bentley, Watson, and Jones (2006) found a significant decrease in unpleasantness ratings for listening to white noise, the average unpleasantness rating (Mean (SD)) in the control condition (no noise) was 5.1 (1.6), which was reduced to 4.6 (1.6) in the white noise condition. Another study also found a significant reduction of unpleasantness ratings for moderately painful laser stimuli, with an average unpleasantness rating of 4.9 (1.2) for the control condition and 4.2 (1.3) for the white noise condition. The effects of listening to white noise on pain unpleasantness were considered to be the result of distraction by listening to white noise (Boyle, Elderedy, Martinez Montes, Bentley, & Jones, 2008). Based on the findings by Ecsy et al. (Ecsy et al., 2016; Ecsy, 2014), we expect a larger reduction of pain experience for listening to alpha binaural beats than white noise. This would indicate that alpha binaural beats have a unique effect, that goes beyond the effect of distraction, as is present for listening to (non-beat) auditory stimulation, like white noise, in general.

Finally, in the present study two psychometric measures were assessed in relation to the effect of binaural beats on the pain experience: fear of pain and pain catastrophising. Both fear of pain and pain catastrophising have been implicated as important factors in the development and maintenance of chronic pain, as part of the fear-avoidance model of chronic pain (Leeuw et al., 2007; Vlaeyen et al., 1995). Fear of pain and pain catastrophising affect pain experience for both experimental pain (Hirsh et al., 2008; Parr et al., 2012) and

chronic pain (Severeijns et al., 2001; Zale et al., 2013). Moreover, pain catastrophising can affect the outcomes of pain treatment (Riddle et al., 2010; Wertli et al., 2014). These individual characteristics of fear of pain and pain catastrophising might, therefore, have an influence on the effectiveness of listening to alpha binaural beats in the reduction of pain. Thus, in the present study it was explored whether there was an influence of fear of pain and pain catastrophising on the reduction of perceived pain intensity and unpleasantness during the listening to alpha binaural beats.

## **5.2 Methods**

### **5.2.1 Participants**

This study was approved by the School of Psychology Research Ethics Committee, University of Leeds (reference number: 16-0167). All participants provided signed informed consent before participating in the study.

Eighteen healthy pain-free participants were recruited, 13 female and 5 male with an average age of  $25.44 \pm 10.05$  years (range 19-54 years), 14 right-handed and 4 left-handed. Participants were screened for any hearing problems that would significantly affect their capability to listen to the auditory stimulation and for any pain at the time of measurement. All participants were aged 18 years or older and all but two had no hearing problems or pain at the time of testing. The remaining two reported minor hearing problems that did not significantly affect them at the time of the experiment. One participant also reported experiencing some pain from time to time as a result of recent surgery, but the participant was pain-free at the time of the experiment.

One participant was removed from the final analysis, as in this case the participant did report pain at the time of measurement and moreover some of the rating scores were significant outliers, with an average unpleasantness rating  $>5.6$  for the non-painful stimuli, where the average unpleasantness rating for the non-painful stimuli for the remaining 17 participants was 0.24. Furthermore, due to technical problems the rating scores for one condition

(binaural beats, uncertain expectation) were not saved for one participant. To be able to use the dataset of this participant (the data of the other three conditions that was intact), it was decided to use mean replacement for the missing data. This resulted in an N of 17 for the final analysis. Outliers were defined according to the “outlier labelling rule”, with a cut off of 2.2 interquartile range (IQR) (Hoaglin & Iglewicz, 1987; Hoaglin & Iglewicz, 1986); i.e., a score of 2.2 interquartile range below the 1<sup>st</sup> quartile or above the 3<sup>rd</sup> quartile was considered to be an outlier.

Each participant took part in two separate experimental sessions, receiving the binaural beat stimulation in one session and white noise stimulation in the other (Figure 5.1). All measurements were carried out by two Master Students (C. Harney and B. Davison) as detailed on p. ii, who were trained by L. Arendsen and instructed to carry out the two sessions on separate days. However, due to time constraints with respect to the students’ project deadline, it was decided to allow a number of participants to complete the two sessions on the same day to try and obtain as large a sample of participants possible within the time available. Of the 17 participants included in the analysis, twelve completed the two sessions on separate days. The other five participants took part in the two sessions on the same day, two participants with a break of one hour or more and three with a break of less than an hour between sessions.

### **5.2.2 Auditory stimuli**

To entrain alpha activity and alter pain experience all participants listened to alpha binaural beats for the duration of the experimental task. A sinusoidal tone with a frequency of 445Hz was presented to the left ear and 455Hz to the right ear, resulting in an alpha binaural beat at 10Hz, in accordance with the 10Hz binaural beat setting used by Ecsy and colleagues (Ecsy et al., 2016; Ecsy, 2014). In a separate session, participants listened to white noise for the duration of the experimental task (order counterbalanced across participants). Participants listened to the two types of auditory simulation

with noise-cancelling over-ear headphones (brand: Beats by Dr Dre; model: Beats solo 2), at their preferred volume. The binaural beat and white noise audio files were created using Audacity software version 2.1.2 (Audacity®, open-source audio software, <http://www.audacityteam.org/>) and the sounds were delivered using the VLC media player version 2.1.5 (VideoLAN, open source cross-platform multimedia player <http://www.videolan.org/videolan/>) on an experimental computer.

### **5.2.3 Pressure stimuli**

The pressure stimuli were delivered to the middle finger of the non-dominant hand using a custom-built MRI-compatible pressure pain stimulator (manufactured by DancerDesign, St. Helens, UK). Pressure stimuli were applied following the same procedure as in the other three studies of the PhD thesis (Chapters 4, 6, and 7), as explained in detail in Chapter 4 (p. 75). Pressure stimuli were applied at three different intensities: non-painful, pain threshold, and moderately painful. These three levels were established for each participant individually before the start of the experimental task, using a ramping procedure.

### **5.2.4 Visual cues**

To manipulate uncertainty, i.e. to create a condition where pain intensity was uncertain and a condition where pain intensity was known/certain, visual cues were used. In the certain condition, each of the visual cues was paired with one particular pressure stimulation intensity, resulting in visual cues that were predictive of the pressure intensity of an upcoming stimulus. In the uncertain expectation condition the same three visual cues were used. However, in this condition the visual cues were randomly combined with a pressure stimulus intensity, resulting in visual cues that were not predictive of the upcoming pain stimulus.

### 5.2.5 Pain experience

To quantify pain experience, participants received two 11-point numerical rating scales (NRSs) on the computer screen after each stimulation (ranging from 0-10) to measure perceived intensity and unpleasantness (0 = not at all intense/unpleasant, 10 = extremely intense/unpleasant). They were asked to rate these scales by typing in the number using the keyboard.

### 5.2.6 Questionnaires

As part of this study participants were asked to complete a set of questionnaires: the Fear of Pain Questionnaire – Short Form (FPQ-SF) (McNeil & Rainwater, 1998); and the Pain Catastrophising Scale (PCS) (Sullivan et al., 1995). Participants were asked to complete these questionnaires at the end of both of the experimental sessions.

To measure fear of pain the FPQ-SF was used. The FPQ-SF was constructed from the Fear of Pain Questionnaire-III (McNeil & Rainwater, 1998). Items reflect 3 factors; severe pain, minor pain and medical pain. To complete the FPQ-SF, participants were asked to rate how fearful they were (or expected they would be) of experiencing the pain associated with the painful experience described in each item, such as 'getting a paper-cut on your finger' and 'breaking your arm' on a 5-point scale ranging from 1-5, with 1 meaning 'not at all' and 5 'extreme'. The total score ranged between 9 and 45, with a higher score indicating higher levels of fear of pain.

To measure pain catastrophising the PCS was used (Sullivan et al., 1995). The PCS contains 13 items describing thoughts and feelings related to pain. Participants were asked to rate how much they experience the thoughts or feelings described in the items when they experience pain, such as 'when I'm in pain I worry all the time about whether the pain will end' and 'when I'm in pain I keep thinking about how much it hurts', on a 5-point scale ranging from 0-4, with 0 meaning 'not at all' and 4 'all the time'. The total score on the scale

ranges from 0-52, with a higher score indicating higher levels of pain catastrophising.

### **5.2.7 Study design**

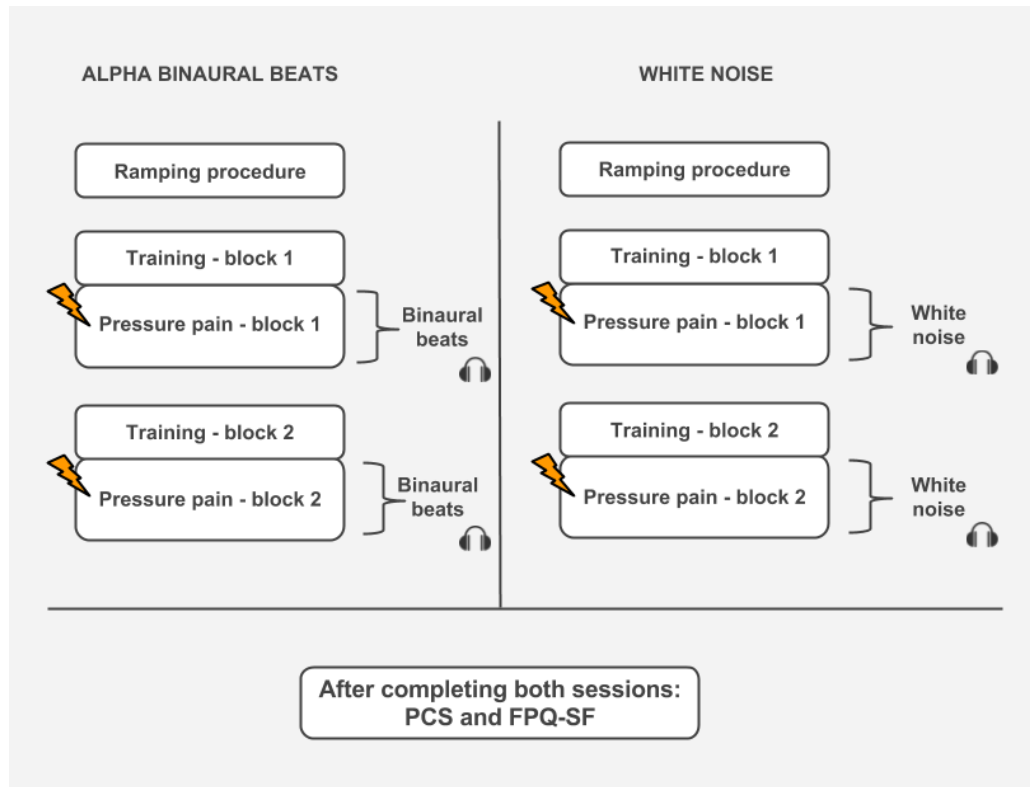
The present study used a 2x2x3 design with three within-subject factors: auditory stimulation (alpha binaural beats, white noise), expectation (certain, uncertain) and pressure stimulus intensity (non-painful, pain threshold, moderately painful). The outcome measures were the intensity and unpleasantness ratings and scores on the questionnaires.

### **5.2.8 Experimental procedure**

Each participant took part in two separate experimental sessions, receiving the binaural beat stimulation in one session and white noise stimulation in the other (Figure 5.1). Order of auditory stimulation conditions was counterbalanced. The ramping procedure was carried out at the beginning of each of the two sessions, to ensure that the pressure stimuli were applied at the intensities representing the participants experience of non-painful, pain threshold and moderately painful stimulation at the time of testing. In each session the participants completed the same experimental task. The task included two expectation conditions; certain expectation and uncertain expectation, that were delivered in two separate blocks. Each block contained 72 trials (24 at each of the three pressure stimulus intensities). Every trial started with the presentation of a fixation cross (duration jittered, 750-1000 ms) followed by a visual cue (duration jittered, 2000-2750 ms). The visual cue was followed by a pressure stimulation. After each pressure stimulation, the participants were presented with the two rating scales to assess perceived intensity and unpleasantness for the preceding pressure stimulus. Participants received regular short breaks throughout the experiment. Each block was preceded by a short practice to familiarise the participant with the task in general and the function of the visual cues in each block in particular. During the practice the participants did not receive any actual pressure stimuli. Total



duration of the experimental task was variable, depending on the time individual participants took to rate intensity and unpleasantness and durations of the breaks, but usually between 15 to 20 minutes for each block (one block certain, one block uncertain), adding up to 30-40 minutes in total.



**Figure 5.1** Overview of experimental procedure. The two auditory conditions (alpha binaural beats and white noise) were delivered during the pressure pain task in two separate sessions. The order of auditory conditions was counterbalanced over participants. The pressure pain task consisted of two blocks, each block containing a different expectation condition (certain and uncertain). The order of the certain and uncertain condition was the same for session 1 and session 2 for each participant but the order was counterbalanced between participants.

### 5.2.9 Statistical analysis

Statistical analysis was carried out using SPSS version 21. To investigate the effect of the auditory stimulation on pain experience and the influence of uncertainty about pain intensity two 2x2x3 within-subject ANOVAs were calculated with the factors auditory stimulation (alpha binaural beats,

white noise), expectation (certain, uncertain) and pressure stimulus intensity (non-painful, pain threshold, moderately painful); one for the intensity ratings and one for the unpleasantness ratings. Significance level was set at  $p < .05$ . In case of a violation of sphericity the Greenhouse-Geisser corrected outcomes were used.

To investigate the relationship between change in perceived pain intensity during listening to alpha binaural beats and fear of pain/pain catastrophising, Pearson correlations were calculated between fear of pain/pain catastrophising and the difference in perceived pain intensity comparing white noise and binaural beats (score white noise – score binaural beats). The focus was on perceived pain intensity for moderately painful stimuli, and the correlations were calculated for both the certain and uncertain condition. To correct for multiple comparisons the Holm-Bonferroni method was used (Holm, 1979), as explained in detail in Chapter 4 (p. 82). Four hypotheses were tested for the moderately painful stimuli: 2 (expectation: certain, uncertain) x 2 (questionnaires: fear of pain, pain catastrophising) against significance levels of .0125, .0167, .025 and .05. The same procedure was carried out for the unpleasantness ratings.

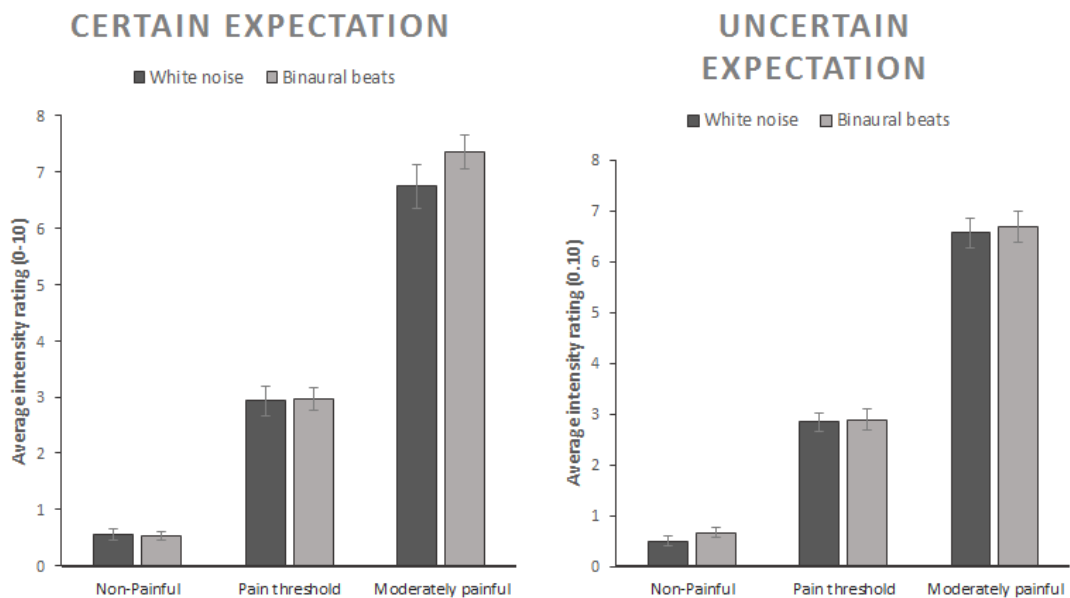
## 5.3 Results

### 5.3.1 Alpha binaural beats

A 2x2x3 within-subject ANOVA with the factors auditory stimulation (alpha binaural beats, white noise), expectation (certain, uncertain) and pressure stimulus intensity (non-painful, pain threshold, moderately painful) revealed no evidence to suggest a reduction of perceived pain intensity during the listening to alpha binaural beats compared to listening to white noise. A significant main effect of pressure intensity (non-painful, pain threshold, moderately painful) was found ( $F(2,32) = 381.18$ ;  $p < .001$ ; Partial  $\eta^2 = .96$ ), but no significant main effect of auditory stimulation ( $F(1,16) = 0.996$ ;  $p = .33$ ; Partial  $\eta^2 = .059$ ), no significant interaction between auditory stimulation and

expectation ( $F(1,16) = 0.22$ ;  $p = .65$ ; Partial  $\eta^2 = .013$ ), and no significant auditory stimulation \* pressure intensity interaction ( $F(2,32) = 2.10$ ;  $p = .14$ ; Partial  $\eta^2 = .12$ ).

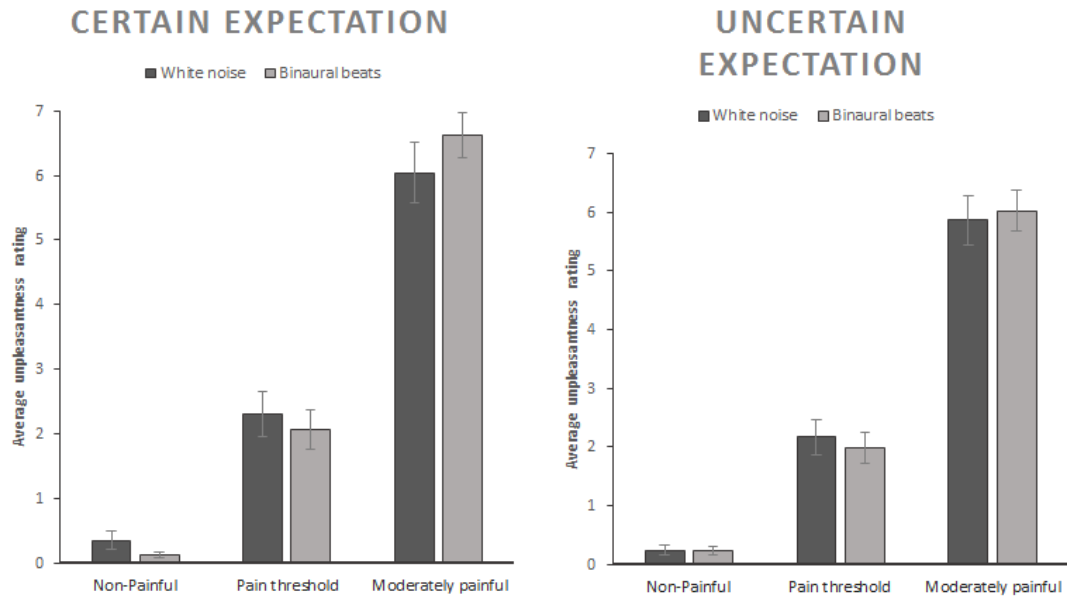
When pain intensity was certain, intensity ratings (mean (SD)) for alpha binaural beats and white noise respectively, were: 0.54 (0.35) and 0.55 (0.43) for non-painful pressure stimuli; 2.96 (0.82) and 2.94 (1.08) for pain threshold pressure stimuli; and 7.35 (1.26) and 6.75 (1.61) for moderately painful pressure stimuli. When pain intensity was uncertain, intensity ratings for alpha binaural beats and white noise respectively, were: 0.66 (0.41) and 0.49 (0.39) for non-painful pressure stimuli; 2.88 (0.85) and 2.84 (0.74) for pain threshold pressure stimuli; and 6.68 (1.28) and 6.56 (1.17) for moderately painful pressure stimuli (Figure 5.2).



**Figure 5.2** Average intensity rating scores and standard error of means (SEM) for the three pressure intensities, comparing listening to white noise (green) and listening to alpha binaural beats (blue) for the certain and uncertain expectation condition separately. No evidence for a significant effect of listening to alpha binaural beats compared to white noise on perceived pain intensity was found.

For the unpleasantness ratings, a 2x2x3 within-subject ANOVA with the factors auditory stimulation (alpha binaural beats, white noise), expectation (certain, uncertain) and pressure stimulus intensity (non-painful, pain threshold, moderately painful) also revealed no evidence to suggest a reduction in experienced unpleasantness as a result of listening to alpha binaural beats compared to listening to white noise. A significant main effect of pressure level was found ( $F(2,32) = 280.23$ ;  $p < .001$ ; Partial  $\eta^2 = .95$ ), but no significant main effect of auditory stimulation ( $F(1,16) = 0.004$ ;  $p = .95$ ; Partial  $\eta^2 = .00$ ) and no significant interaction of auditory stimulation and expectation ( $F(1,16) = .075$ ;  $p = .79$ ; partial  $\eta^2 = .005$ ) (Figure 5.3).

When pain intensity was certain, unpleasantness ratings (mean (SD)) for alpha binaural beats and white noise respectively, were: 0.12 (0.16) and 0.35 (0.58) for non-painful pressure stimuli; 2.07 (1.23) and 2.30 (1.43) for pain threshold pressure stimuli; and 6.63 (1.43) and 6.04 (1.93) for moderately painful pressure stimuli. When pain intensity was uncertain, unpleasantness ratings (mean (SD)) for alpha binaural beats and white noise respectively, were: 0.23 (0.41) and 0.24 (0.36) for non-painful pressure stimuli; 1.98 (0.85) and 2.17 (1.26) for pain threshold pressure stimuli; and 6.02 (1.28) and 5.86 (1.73) for moderately painful pressure stimuli.



**Figure 5.3** Average unpleasantness rating scores and standard error of means (SEM) for the three pressure intensities, comparing listening to white noise (green) and alpha binaural beats (blue) for the certain and uncertain expectation condition separately. No evidence for a significant effect of listening to alpha binaural beats compared to white noise on perceived pain unpleasantness was found.

Finally, a trend towards significance was present for the auditory stimulation \* pressure intensity interaction ( $F(1.45, 23.14) = 3.28$ ;  $p = .070$ , partial  $\eta^2 = .17$ ). This suggested that the effect of listening to alpha binaural beats compared to white noise on perceived pain unpleasantness might have been different depending on pressure stimulus intensity. The averages in Table 5.1 show that the unpleasantness ratings for non-painful and pain threshold stimuli were slightly lower for binaural beats compared to white noise, whereas unpleasantness ratings for moderately painful stimuli were higher; ratings were 0.12 lower for the non-painful stimuli, 0.21 lower for the pain threshold stimuli, and .38 higher for the moderately painful stimuli. Post-hoc paired-samples t-tests comparing the unpleasantness ratings for alpha binaural beats and white noise for each pressure level and each expectation condition separately, did not demonstrate any significant differences however.

**Table 5.1** Average unpleasantness ratings (Mean(SD)) for each pressure intensity and each auditory condition separately, averaged over the two expectation conditions.

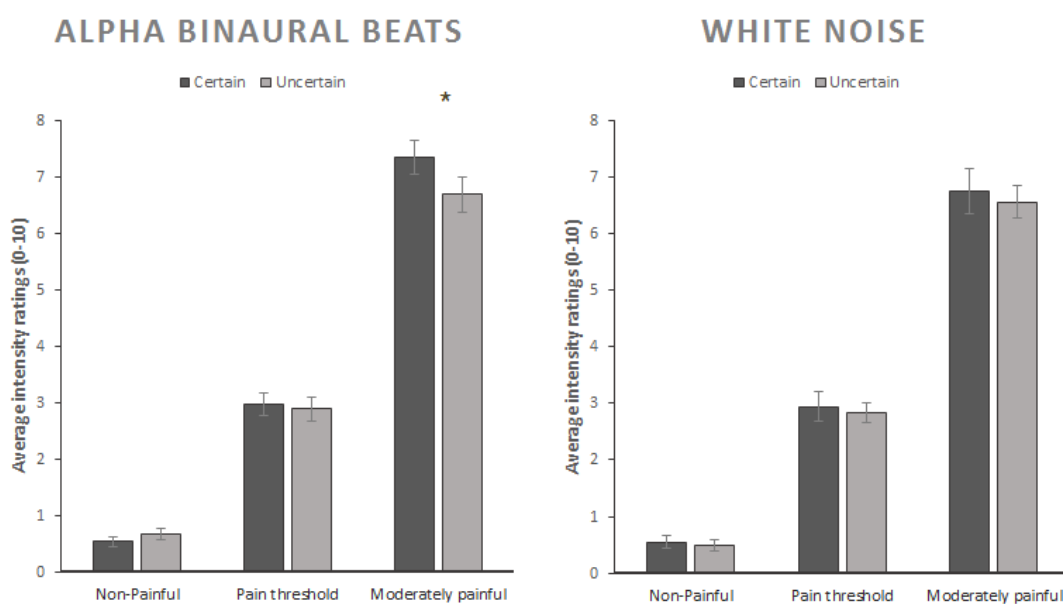
	Alpha binaural beats	White noise
Non-painful	0.18 (0.21)	0.30 (0.43)
Pain threshold	2.02 (1.08)	2.23 (1.29)
Moderately painful	6.33 (1.34)	5.95 (1.74)

### 5.3.2 Expectation

There was no significant main effect of expectation ( $F(1,16) = 2.09$ ;  $p = .17$ ; Partial  $\eta^2 = .12$ ). However, a significant interaction of expectation \* pressure intensity was found ( $F(2,15) = 4.42$ ;  $p = .03$ ; Partial  $\eta^2 = .37$ ) (Figure 5.4). As can be seen in Table 5.2, overall the intensity ratings for non-painful stimuli were similar for uncertain compared to certain expectation; intensity ratings were 0.04 higher in the uncertain condition. For the pain threshold stimuli they were slightly lower however; intensity ratings were 0.12 lower in the uncertain condition. The largest difference was between uncertain and certain expectation was present for the moderately painful stimuli, again with lower intensity ratings in the uncertain condition; intensity ratings were 0.43 lower. Post hoc paired-samples t-tests comparing the intensity ratings in the certain and uncertain condition for each stimulus intensity and each auditory stimulation condition, demonstrated a significant difference in perceived pain intensity for the moderately painful stimuli in the alpha binaural beat condition only ( $t(16) = 2.66$ ;  $p = .017$ ).

**Table 5.2** Average intensity ratings (Mean(SD)) for each pressure intensity and each expectation condition separately, averaged over the two auditory conditions.

	Certain expectation	Uncertain expectation
Non-painful	0.54 (0.33)	0.58 (0.33)
Pain threshold	2.95 (0.82)	2.83 (0.73)
Moderately painful	7.05 (1.17)	6.62 (1.14)



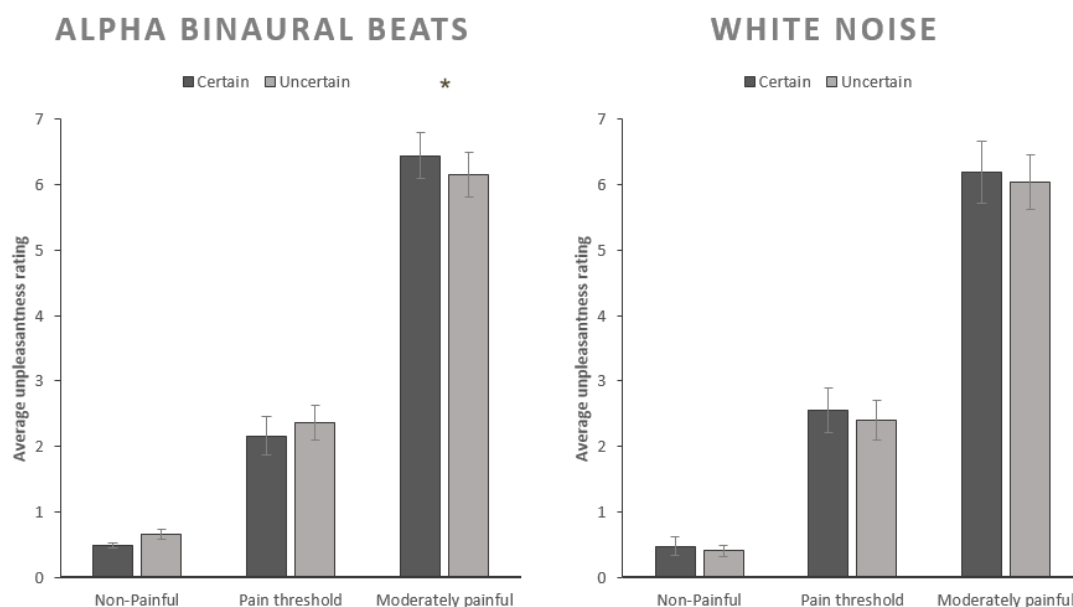
**Figure 5.4** Average intensity rating scores and standard error of means (SEM) for the three pressure intensities, comparing certain (green) and uncertain expectation (blue), for listening to white noise and alpha binaural beats separately. Post-hoc t-tests demonstrated significantly lower perceived pain intensity for uncertain compared to certain expectation in the binaural beat condition, for the moderately painful stimuli.

Similarly, for the unpleasantness ratings no main effect of expectation was found ( $F(1,16) = 2.89$ ;  $p = .11$ ; partial  $\eta^2 = .15$ ) but the expectation \* pressure intensity interaction was significant ( $F(2,32) = 3.35$ ;  $p = .048$ ; partial  $\eta^2 = .17$ ) (Figure 5.5). As can be seen in Table 5.3, overall no difference in unpleasantness ratings was present for the non-painful pressure stimuli, comparing certain and uncertain expectation. For the pain threshold stimuli, unpleasantness ratings were slightly lower in the uncertain condition; unpleasantness ratings were 0.11 lower. The largest difference was present for the moderately painful stimuli, where unpleasantness ratings were 0.39 lower in the uncertain condition. Post hoc paired-samples t-tests comparing certain and uncertain expectation for each pressure stimulus intensity and each auditory stimulation condition demonstrated a significant difference in unpleasantness ratings in the alpha binaural beat condition only, with a significant difference for the moderately painful pressure stimuli ( $t(16) = 2.45$ ;  $p = .026$ ), and a trend towards significance for non-painful pressure stimuli ( $t(16) = 2.06$ ;  $p = .056$ ).

**Table 5.3** Average unpleasantness ratings (Mean(SD)) for each pressure intensity and each expectation condition separately, averaged over the two auditory conditions.

	Certain expectation	Uncertain expectation
Non-painful	0.23 (0.34)	0.23 (0.28)
Pain threshold	2.18 (1.13)	2.07 (1.03)
Moderately painful	6.33 (1.37)	5.94 (1.42)





**Figure 5.5** Average unpleasantness rating scores and standard error of means (SEM) for the three pressure intensities, comparing certain (green) and uncertain expectation (blue), for listening to white noise and alpha binaural beats separately. Post-hoc t-tests demonstrated significantly lower perceived pain unpleasantness for uncertain compared to certain expectation in the binaural beat condition, for the moderately painful stimuli.

### 5.3.3 Questionnaire data

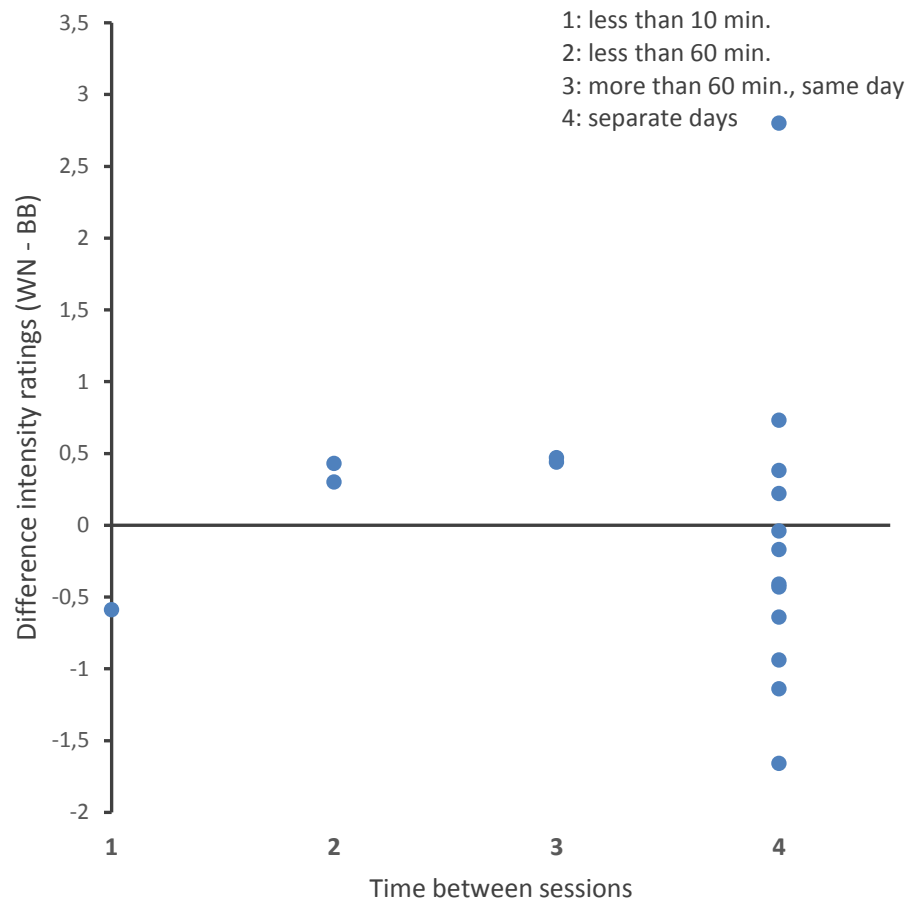
Finally, the relationship between change in perceived pain intensity during listening to alpha binaural beats and fear of pain/pain catastrophising was assessed, both when pain intensity was certain and uncertain. For the moderately painful stimuli, no significant correlations between the difference in intensity rating (rating white noise - rating binaural beats) and the levels of self-reported fear of pain were found (certain expectation:  $r = -.34$ ;  $p = .19$ ; uncertain expectation:  $r = -.31$ ;  $p = .22$ ;  $N = 17$ ). No significant correlations between the difference in intensity rating for white noise and binaural beats and the levels of self-reported pain catastrophising were found either (certain expectation:  $r = -.053$ ;  $p = .84$ ; uncertain expectation:  $r = -.26$ ;  $p = .31$ ;  $N = 17$ ).

The same correlation analysis was carried out for the unpleasantness ratings. Similarly, no significant correlations were found between the difference

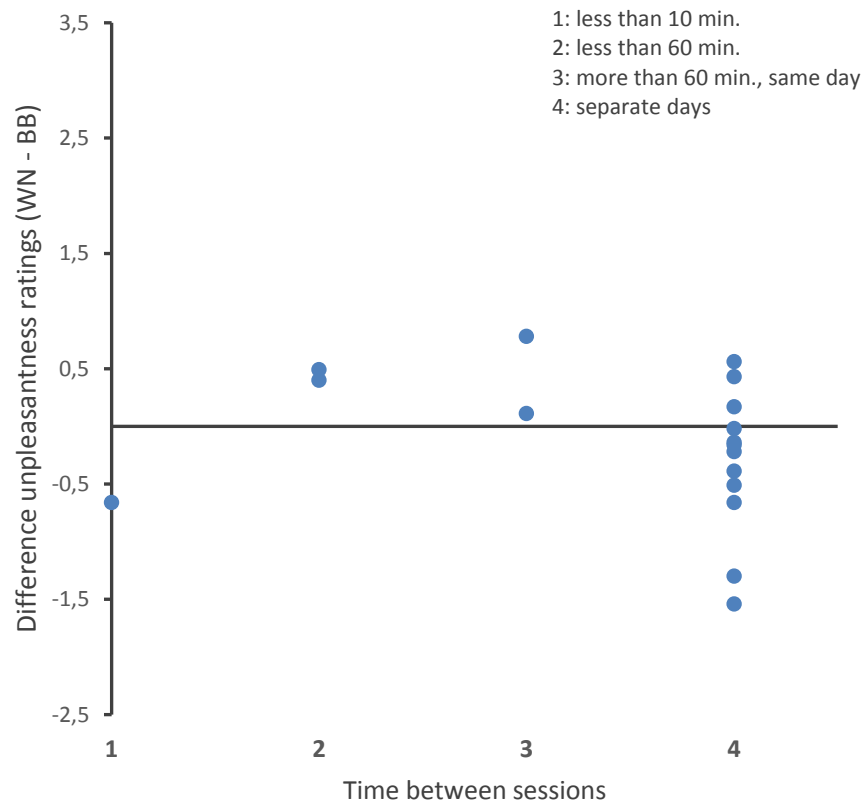
in unpleasantness rating (rating white noise – rating binaural beats) and the levels of self-reported fear of pain for the moderately painful stimuli (certain expectation: ,  $r = -.29$ ;  $p = .26$ ; uncertain expectation:  $r = -.27$ ;  $p = .30$ ;  $N = 17$ ). No significant correlations between the difference in unpleasantness rating and the levels of self-reported pain catastrophising were found either (certain expectation:  $r = -.063$ ;  $p = .81$ ; uncertain expectation:  $r = -.22$ ;  $p = .40$ ;  $N = 17$ ).

### **5.3.4 Control analysis carry-over effects auditory stimulation**

Although the majority of participants took part in the two sessions (alpha binaural beat and white noise session) on separate days, five participants took part in the two sessions on the same day. To check for the possibility of an carry-over effect of the auditory stimulation from one session to the next, scatterplots were created plotting the difference in intensity rating for alpha binaural beats and white noise and the time between sessions (Figure 5.6). The same was done for the unpleasantness ratings (Figure 5.7). For the group of participants ( $N = 12$ ) that took part in the two sessions on different days, the difference in rating scores between alpha binaural beats and white noise are spread out with both positive and negative values (reflecting lower and higher ratings for alpha binaural beats compared to white noise, respectively), for both the intensity and unpleasantness ratings. The difference in intensity and unpleasantness ratings for the participants that had the two sessions on the same day ( $N = 5$ ) fell within the same range of scores at those of the group that had the sessions on different days, suggesting that there is no particular case for a carry-over effect for the participants that had the two sessions on the same day.



**Figure 5.6** Scatterplot with the average difference in intensity rating comparing white noise and binaural beats (white noise ratings – binaural beats ratings, averaged over the three pressure intensity levels and the two expectation conditions) on the y-axis, and the time between measurement on the x-axis. The difference in intensity ratings (white noise – binaural beats) for the participants that had the two sessions on the same day fell within the same range as the difference scores that were found for the participants that had the two sessions on separate days. Thus, there is no indication for a carry-over effect.



**Figure 5.7** Scatterplot with the average difference in unpleasantness rating comparing white noise and binaural beats (white noise ratings – binaural beats ratings, averaged over the three pressure intensity levels and the two expectation conditions) on the y-axis, and the time between measurement on the x-axis. The difference in unpleasantness ratings (white noise – binaural beats) for the participants that had the two sessions on the same day fell within the same range as the difference scores that were found for the participants that had the two sessions on separate days. Thus, there is no indication for a carry-over effect.

## 5.4 Discussion

The present study investigated whether listening to alpha binaural beats during pain would reduce pain experience (by increasing alpha activity), compared to listening to white noise. No evidence was found to suggest that listening to alpha binaural beats for a total of 30 minutes reduced pain experience; no significant reduction of pain intensity or unpleasantness ratings was present for alpha binaural beats compared to white noise. This is in contrast with the findings of two existing studies (Ecsy et al., 2016; Ecsy, 2014)

that found a significant increase of alpha power during alpha binaural beat stimulation at 10 and 12Hz (Ecsy, 2014), and a significant reduction of pain ratings after three times 10 minutes of binaural beat stimulation at 8, 10, and 12Hz compared to white noise (Ecsy et al., 2016; Ecsy, 2014). The two studies by Ecsy and colleagues provided some initial evidence for a reduction of pain experience after listening to alpha binaural beats via a modulation alpha activity. The present study did not provide further evidence to support this.

#### **5.4.1 Online versus offline effects of alpha binaural beats**

As the findings of the present study did not confirm the findings of Ecsy and colleagues (Ecsy et al., 2016; Ecsy, 2014), this puts to question the effectiveness of listening to alpha binaural beats to reduce pain experience, more so than listening to white noise. The effect of rhythmic external stimulation, such as binaural beat stimulation, is dependent on a number of factors, such as stimulation frequency and duration (Thut et al., 2011). Assessing the similarities and differences between the present study and two existing studies on alpha binaural beats and pain experience (Ecsy et al., 2016; Ecsy, 2014) could therefore assist in trying to explain the difference in findings. With respect to alpha binaural beat settings and total alpha binaural beat stimulation duration, the present study and two existing studies are comparable. The same two sinusoidal tones to create the alpha binaural beats at 10Hz were used in the present study, as in the two studies by Ecsy and colleagues (Ecsy et al., 2016; Ecsy, 2014). Stimulus duration was 10 minutes at each alpha frequency (8, 10, 12Hz) in the studies by Ecsy et al. (Ecsy et al., 2016; Ecsy, 2014), adding up to a total alpha binaural beat duration of 30 minutes. In this study participants listened to alpha binaural beats for the entire duration of the experimental task, including two separate blocks for the certain and uncertain expectation condition each with a duration of around 15 minutes, adding up to a total of 30 minutes of alpha binaural beat stimulation. However, a clear difference between the studies is present with respect to when pain experience was assessed. Where the present study investigated changes in pain experience during alpha binaural beat stimulation (online effects of

listening to alpha binaural beats) the studies by Ecsy et al. (Ecsy et al., 2016; Ecsy, 2014) investigated changes in pain experience in the period directly after alpha binaural beat stimulation offset (offline effects or aftereffects). Thus, the lack of an effect on pain experience in the present study might be explained by a difference in timing of assessment of pain experience.

Unfortunately, it remains unclear why an effect on pain experience is present after, but not during alpha binaural beat stimulation. Little is known about the mechanism through which an aftereffect - offline changes in pain perception after alpha binaural beats offset - comes about as a result of neural entrainment during listening to alpha binaural beats. The two studies that found an effect for alpha binaural beats measured a reduction in pain ratings after binaural beat stimulation (offline) (Ecsy et al., 2016; Ecsy, 2014) but the significant increase of alpha power was measured during alpha binaural beat stimulation (online) (Ecsy, 2014). It is not clear whether alpha power is still increased in the period after listening to alpha binaural beats. As changes in alpha activity for listening to alpha binaural beats have only been measured during binaural beat stimulation, what mechanism of neural change was responsible for the reduction in pain experience after binaural beat offset remains to be confirmed.

An example illustrating that neural changes found during rhythmic stimulation do not necessarily reflect the same underlying mechanism as changes found after rhythmic stimulation is provided by another type of rhythmic stimulation, transcranial alternating current stimulation (tACS). Vossen, Gross, and Thut (2015) specifically investigating whether aftereffects of tACS at alpha frequency were the direct result of neural entrainment or reflected another mechanism. They found a significant increase of alpha power after tACS offset (= alpha tACS aftereffect of increased alpha power). However, they did not find evidence to support that this aftereffect reflected neural entrainment. As neural entrainment takes place through a process of phase synchronisation, this can only take place when the tACS is delivered in a phase-congruent manner. To create a phase-congruent and phase-incongruent condition, alpha tACS was delivered intermittently using trains of tACS (80

cycles duration) with periods of no stimulation in-between. In the phase-congruent condition a new train of tACS was in-phase with the previous train of tACS, in the phase-incongruent condition this was not the case. A significant aftereffect of increased alpha power was found in both the phase-congruent and phase-incongruent condition. Therefore, the authors concluded that the aftereffects found after tACS were not the result of entrainment. In a review on the underlying mechanisms of offline changes in neural activity after tACS it was suggested that aftereffects of tACS are the result of changes in neural plasticity (Herrmann, Rach, Neuling, & Strüber, 2013). This suggest that only finding a reduction of pain experience after listening to binaural beats and not during, might also be related to the involvement of a different neural mechanism in the modulation of alpha activity after and during binaural beat stimulation.

It should be stressed though that the two (tACS and binaural beats) are not necessarily directly comparable. The mechanisms involved in binaural beats and tACS are likely to be different, as they are different types of rhythmic stimulation. Where binaural beats are a type of sensory rhythmic stimulation, influencing neural activity via sensory pathways, tACS as a type of electrical stimulation directly influences neural activity. To explain why changes in pain experience as a result of alpha binaural beat stimulation were found offline, but not online, further investigation is needed. Specifically, investigation of the modulation of alpha activity during *and* after binaural beat listening, and how they are different. This should ultimately lead to a better understanding of the specific circumstances that are related to a positive outcome with respect to pain experience, allowing for an improvement of the application of alpha binaural beats as an intervention for pain.

#### **5.4.2 Alpha binaural beats and type of pain stimulus**

Another difference between the present study and the studies by Ecsy and colleagues (Ecsy et al., 2016; Ecsy, 2014) was the type of experimental pain stimulus that was used. In the present study pressure pain stimuli with a duration of several seconds were applied, in the studies by Ecsy and

colleagues brief laser pain stimuli (150ms) were applied. Laser pain stimuli are considered a well-controlled pain stimulation technique that selectively activates pain receptors (nociceptive A $\delta$  and C fibers) without activating touch receptors (A $\beta$  mechanoreceptive fibers) (Plaghki & Mouraux, 2003). Pressure pain stimuli on the other hand are not selective, they activate both pain receptors and touch receptors (Plaghki & Mouraux, 2003), and are thought to not only affect the skin but also deeper tissue layers (Treede et al., 2002). Thus, pain stimulation in this study differs from the stimulation by Ecsy et al. (Ecsy et al., 2016; Ecsy, 2014), with respect to stimulus duration and the tissues and receptors that were affected.

Different experimental pain stimuli have been shown to relate to different outcomes when investigating the effectiveness of pharmacological interventions to reduce pain. Two comprehensive reviews assessed the effectiveness of several types of pain medication to reduce pain for a variety of experimental pain stimuli (Olesen, Andresen, Staahl, & Drewes, 2012; Staahl, Olesen, Andresen, Arendt-Nielsen, & Drewes, 2009). In both reviews it was pointed out that a reduction in pain was not always found for all types of experimental pain stimuli or to a lesser extent for some types of pain stimuli. For example, opioids were effective in reducing pain for a wide variety of experimental pain stimuli, but tended to attenuate experimental pain of a higher intensity and a longer duration in particular, more so than for short-lasting pain stimuli. Thus, this suggests that if (or to what extent) a reduction in pain is found for an intervention is influenced by the experimental pain method applied. It should be stressed that these findings were based on pharmacological interventions only. We cannot directly generalise this to non-pharmacological interventions, such as binaural beats. However, it is worth considering that type of pain stimulus might influence the effect of alpha binaural beats to some extent. If we want to consider using alpha binaural beats as an intervention/treatment to reduce pain, an essential step would be to reproduce the findings by Ecsy et al. (Ecsy et al., 2016; Ecsy, 2014), a significant offline reduction of pain, for other types of experimental pain and clinical pain states as well.



### 5.4.3 Evaluation of the potential of alpha binaural beats to reduce pain

This study did not find a significant reduction in perceived pain intensity and unpleasantness during the listening to alpha binaural beats. This suggests that alpha binaural beats might not be an effective approach to manage pain. Specifically, the present study did not find a significant reduction for listening to alpha binaural beats compared to listening to white noise. As white noise has also been demonstrated to reduce pain experience (Boyle et al., 2006; Boyle et al., 2008), this suggests the binaural beats with their rhythmic nature (entraining alpha activity) are not more effective in reducing pain than other non-rhythmic auditory stimuli such as white noise.

The reduction of perceived pain for listening to white noise was considered to be the result of distraction (Boyle et al., 2006; Boyle et al., 2008). This fits with other findings showing that attending to something else than pain, directing attention to another task or stimulus, reduces pain experience (Legrain et al., 2009; Miron et al., 1989; Tracey et al., 2002). Not finding a stronger reduction of pain experience for alpha binaural beats compared to white noise in this study, suggests that any effects of listening to alpha binaural beats might not so much be related to the rhythmic nature of binaural beats specifically, but instead reflect a more generic distraction effect of listening to auditory stimulation.

It should be noted that the two studies by Ecsy et al. (Ecsy et al., 2016; Ecsy, 2014) did find a significant reduction of pain ratings after listening to alpha binaural beats, compared to white noise. However, if we look at other studies that compared the effects of binaural beats to non-beat auditory stimuli (such as white noise or a single tone) a unique effect for binaural beats was not often found either. Unfortunately, the literature with respect to pain perception is limited, but several studies have investigated the effects of listening to binaural beats on anxiety. Three studies found a reduction of anxiety after listening to binaural beats, but these effects were usually not different from listening to non-beat auditory stimulation. A study by Weiland et al. (2011) investigated the effects on levels of anxiety in patients attending the emergency

department, for four different audio tracks with and without binaural beats, with a duration of 20 minutes: (1) an electro-acoustic composition; (2) sounds from natural settings; (3) sounds from natural settings with an embedded binaural beat; and (4) ambient noise. The binaural beat frequency was decreased from 10Hz to 4Hz in steps of 2Hz over the time course of the track and in the end increased back to 10Hz again. A significant reduction of anxiety was present after listening to the electro-acoustic composition, the natural sounds, and the natural sounds plus binaural beats. The track with binaural beats did not result in a significantly larger reduction of anxiety. Wiwatwongwana et al. (2016) investigated anxiety in patients undergoing surgery, measuring anxiety with the STAI, blood pressure, and heart rate. Binaural beats were embedded in a music track, and compared to the same music track without binaural beats (duration 60 minutes) and a condition of no auditory stimulation. Again, the frequency of the binaural beats varied over time: participants listened to 20Hz binaural beats for 5 minutes, then beat frequency was gradually declined to 10Hz over 5 minutes, in the following 50 minutes the binaural beat frequency was kept at 10Hz. A similar reduction in state anxiety and blood pressure was found for the music with binaural beats and without binaural beats; there was no significant difference between music with binaural beats and music without binaural beats. However, only for the music with binaural beats a significant decrease of heart rate was found. One further study on binaural beats and anxiety was the only that did find a stronger suggestion for a unique effect for binaural beats. Padmanabhan et al. (2005) investigated the effects of listening to binaural beats on levels of pre-operative anxiety. The same audio recording with and without binaural beats, with a duration of 30 minutes, was compared to a control condition where no auditory stimulation took place. Binaural beat frequency changed over the time course of the track, the last 10 minutes of the track had a binaural beat at delta frequency (unfortunately no further details on the audio recordings were given). The binaural beat group demonstrated a larger reduction (26.3%) of anxiety than the non-beat audio group (11.1%). This difference between groups approached significance ( $p=.053$ ).

In other areas of research on alpha binaural beats, a unique effect for alpha binaural beats was not always present either. For example, Beauchene

et al. (2016) assessed performance on a visual-spatial working memory task, comparing binaural beats at theta, alpha, and beta frequency to several non-beat control conditions (classical music, single tone, and no tone). Participants carried out the task for 30 minutes, while listening to 5 minutes of each auditory condition. The three control conditions and the 5Hz and 10Hz binaural beats all led to reduced performance on the task. The effects of alpha binaural beats were not different from listening to non-beat stimulation, pure tone, classical music though. Finally, a study investigating the effects of binaural beats at alpha (10Hz) and gamma (40Hz) frequency on attentional control, also did not find a specific effect of listening to binaural beats alpha frequency compared to the control condition (constant tone) (Reedijk, Bolders, Colzato, & Hommel, 2015). Only the gamma binaural beats had a significant effect on performance on the attentional blink task, with gamma binaural beats leading to increased attentional control (Reedijk et al., 2015). Even though the studies described above did not investigate the effects of alpha binaural beats on pain experience specifically, they provide further support that listening to alpha binaural beats does not necessarily result in different outcomes than listening to non-beat auditory stimulation. Thus, together with the findings of the present study they are not in support of an unique potential of alpha binaural beats compared to other types of non-beat auditory stimulation in the modulation of pain experience.

Not finding a significant reduction of pain in this study also puts to question whether the alpha binaural beats were effective in increasing alpha activity, as we expected a reduction of pain experience by alpha binaural beats via an increase of alpha power. However, as the present study did not include EEG recordings we cannot conclude on this with any certainty. Assessing the literature on alpha binaural beats and their effect on alpha activity does show that alpha binaural beats were not consistently effective in increasing alpha power. Only a small number of studies on the effects of alpha binaural beats on alpha power are available, and the results are mixed. Two studies (Ecsy, 2014; Ioannou et al., 2015) did find that alpha binaural beats increase alpha power. Both found a significant online increase of alpha power for alpha binaural beats (most prominent in posterior regions), compared to non-beat control auditory

stimulation. Two other studies did not find such an increase of alpha power (Gao et al., 2014; Vernon et al., 2014). Thus, the evidence for an increase of alpha activity by alpha binaural beats is inconclusive.

Furthermore, neither of the two studies that found an effect of binaural beats on alpha activity (Ecsy, 2014; Ioannou et al., 2015) focussed on somatosensory alpha activity. Both studies identified an increase of alpha activity that was most prominent in posterior regions. However, a significant negative correlation between pre-stimulus alpha activity and perceived pain has been found for the somatosensory region specifically (Babiloni et al., 2006; Tu et al., 2016), suggesting that in particular an increase of somatosensory alpha activity would lead to a reduction of pain. Thus, not finding a reduction of pain experience could also be related to whether somatosensory alpha activity specifically was increased or not. Further investigation of the effect of alpha binaural beats on somatosensory alpha activity specifically could offer insight in whether or not alpha binaural beats have potential in the modulation of pain experience.

#### **5.4.4 Alpha binaural beats and expectation**

The main objective of the present study was to assess the effects of alpha binaural beat stimulation on pain experience. In addition, it was considered whether the effects of alpha binaural beats were affected by type of expectation before pain onset. It was established that no general effect of alpha binaural beats on pain experience was present. No interaction between auditory stimulation and expectation was present either. However, one significant interaction was found for expectation: a significant interaction between expectation and pressure intensity. Both intensity and unpleasantness ratings showed the same pattern. Overall (averaged over the two auditory conditions), the ratings were reduced in the uncertain condition compared to the certain condition, this reduction was more prominent for a higher pressure stimulus intensity. When participants were uncertain about pressure intensity of an upcoming pressure pain stimulus, pain experience was reduced, mostly so for moderately painful pressure stimuli.

Although this was not the main objective of the study, it is a finding of some interest, for the following reason: a reduction of pain experience for uncertain expectation compared to certain expectation, is the opposite of what we found in the Study 1 (Chapter 4). Both in Study 1 of this thesis and in other studies investigating the effects of uncertainty about pain intensity, pain experience tended to be increased when participants were uncertain (Lin et al., 2014; Ploghaus et al., 2001; Sawamoto et al., 2000). If we compare the average ratings for this study (averaged over the two auditory conditions) to the ratings of Study 1, a clear difference in ratings seems to be present in the uncertain condition only. When pain intensity was certain, the average intensity rating (Mean(SD)) for the moderately painful stimuli was 7.05 (1.12) and 7.05 (1.17) for Study 1 and the present study respectively, and the average unpleasantness rating 6.20 (1.91) and 6.33 (1.37). However, in the uncertain condition, the ratings were considerably lower in the present study. The average intensity rating was 7.64 (0.96) and 6.62 (1.14) for Study 1 and the present study respectively, and the average unpleasantness ratings 7.10 (1.29) and 5.94 (1.42), for the moderately painful stimuli. This suggests that the opposite pattern of difference in pain experience for certain versus uncertain pain intensity, in these two studies, is particularly the result of a difference in pain experience in the uncertain condition. Both studies used the same paradigm with the same visual cues to manipulate expectation, and the same pressure pain stimuli. The only clear difference between the present study and Study 1 is the auditory stimulation. Thus, this suggest that, although no difference between alpha binaural beats and white noise was found in their effect on pain experience in this study (no significant mean effect of auditory stimulation), auditory stimulation overall might have had an effect on pain experience particularly in the uncertain condition. Uncertainty about the intensity of an upcoming stimulus is characterised by higher reported levels of anxiety (Ploghaus et al., 2001). Several studies have demonstrated that listening to binaural beats and other auditory stimuli was effective in reducing anxiety (Padmanabhan et al., 2005; Weiland et al., 2011; Wiwatwongwana et al., 2016). Thus, perhaps in the present study, auditory stimulation resulted in

lower levels of perceived pain particularly in the uncertain condition by reducing levels of anxiety.

#### **5.4.5 Study limitations and future directions**

The results of the present study, together with other studies comparing the effects of binaural beat stimulation and non-beat auditory stimulation, suggest that the effects of alpha binaural beats are not stronger than the effects of non-binaural beat auditory stimuli, such as white noise, a single tone, or music (Beauchene et al., 2016; Reedijk et al., 2015; Weiland et al., 2011; Wiwatwongwana et al., 2016). This suggests that the effects of alpha binaural beats therefore might not so much reflect the specific rhythmic nature of the alpha binaural beats (and neural entrainment), but more a general effect of listening to auditory stimulation, such as distraction. Furthermore, there was some suggestion that auditory stimulation in general (binaural beats and white noise) might have a particularly influence on pain experience when pain intensity is uncertain, associated with higher reported levels of anxiety (Ploghaus et al., 2001). However, the present study did not include measurement of a change in state anxiety over the time course of the experiment. To get a better insight in how alpha binaural beats, and auditory stimuli in general, modulate pain experience, inclusion of a measure of state anxiety before and after listening to the auditory stimulation could be a useful addition for future studies.

A second point of consideration is the amount of time between sessions. The alpha binaural beats and white noise were delivered in two separate sessions, similar to the studies by Ecsy et al. (Ecsy et al., 2016; Ecsy, 2014). In the present study, the majority of participants (12 participants) took part in these two sessions on two different days, but the other five participants took part in the two sessions on the same day. Of the five participants that had their two sessions on the same day, four had at least a half hour break between sessions, on participant only had a five-minute break. The effects on pain experience of listening to alpha binaural beats have so far have been demonstrated after binaural beat stimulation offset (Ecsy et al., 2016; Ecsy,

2014). How long changes in pain experience stay present after alpha binaural beat stimulation is not known. Therefore, especially when time between sessions was short, there was a change of carry-over effects of the auditory stimulation. Two scatterplots, plotting the difference in rating scores for white noise and alpha binaural beats and time between sessions, for the intensity ratings (Figure 4.6) and the unpleasantness ratings (Figure 4.7), did not demonstrate a clear indication of a carry-over effect. The difference in pain experience between white noise and alpha binaural beats, for the participants that had the sessions on the same day, fell within the same range as the difference scores of the participants that had the sessions on different days. However, in general it would still be better practice to have a less variable inter-session period, with sessions on different days for all participants, to improve consistency and reduce the risk of carry-over effects.

#### **5.4.6 Conclusions**

Listening to alpha binaural beats did not result in a significant online reduction of pain experience, compared to listening to white noise. Overall the findings of the present study support a notion of uncertainty about the potential of alpha binaural beats to affect alpha activity and pain experience. Research on the effects of alpha binaural beats (in pain) is limited, and the existing findings are mixed. Although Ecsy and colleagues found a reduction of pain experience after listening to alpha binaural beats (offline effect) (Ecsy et al., 2016; Ecsy, 2014), a reduction of pain experience during alpha binaural beats (online effect) was not found in this study. Furthermore, although two studies (Ecsy, 2014; Ioannou et al., 2015) demonstrated an increase alpha power for alpha binaural beats, two other studies did not find an increase of alpha power (Gao et al., 2014; Vernon et al., 2014). Finally, it is not clear if the effects of listening to binaural beats are specifically related to the rhythmic nature of binaural beats, or whether they are much more related to effects of listening to auditory stimulation in general, such as distraction. Overall, the evidence in favour of alpha binaural beats as an intervention to alter alpha activity and reduce pain experience is not very substantial. As the present study added to

the number of studies suggesting that alpha binaural beats are not necessarily capable of reducing levels of pain experience more so than listening to non-binaural beat auditory stimulation (white noise), critical assessment of the effectiveness of binaural beat stimulation is warranted.



## **Chapter 6** Does the application of transcranial alternating current stimulation (tACS) at alpha frequency reduce the experience of pain?

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### **6.1 Introduction**

Alpha activity has been implicated in pain experience, not only during pain but also before pain onset. Two studies found changes in alpha activity in the period directly before pain onset, during the expectation of a predictable experimental pain stimulus, which has been termed pre-stimulus alpha activity. Babiloni et al. (2003) reported a significant reduction of pre-stimulus alpha power in the bilateral primary somatosensory region (electrode C3 and C4, based on the 10-20 system). Babiloni et al. (2006) detected the same alpha power reduction in the contralateral somatosensory cortex with respect to stimulated hand (electrode location CP3). Importantly, this reduction of somatosensory pre-stimulus alpha power was significantly negatively correlated with levels of perceived pain intensity, as reported directly after each pain stimulus. Nir et al. (2012) also found a significant negative correlation between alpha power and perceived pain intensity, but for alpha activity during rest over bilateral temporal regions (electrode T7 and T8), measured 30 minutes before a 5-minute tonic painful heat stimulation. Thus, higher pre-stimulus somatosensory alpha activity directly before pain and higher alpha activity at rest (non-task-related background activity) are both associated with lower pain experience. This suggests that manipulation of alpha activity might

be effective in changing pain experience. Specifically, increasing levels of alpha power might reduce the intensity of pain experienced.

Alpha activity has not only been related to pain experience, but also to expectations about pain intensity. Expectations about the intensity of an upcoming pain stimulus can affect both pre-stimulus alpha power and alpha power at rest. A magnetoencephalography (MEG) study by Franciotti et al. (2009) focussed on the influence of uncertainty about pain intensity on pre-stimulus alpha activity in the insula. When participants were uncertain about the intensity of an upcoming stimulus (painful or non-painful), a larger reduction of pre-stimulus alpha power was found in the anterior insula than when they were certain about the intensity of the upcoming stimulus (which was non-painful). Huneke et al. (2013) found that an expectation of pain relief or reduced pain influenced alpha activity at rest. Placebo treatment, inducing an expectation of pain relief was found to significantly increase alpha power at rest in the placebo group only. Source localisation estimated that the increase of alpha originated from other components of the pain network, the left insula and bilateral medial prefrontal cortex. These two neural regions have previously been found activated during the anticipation of pain (Ploghaus et al., 1999). Furthermore, activity in these regions has been associated with expected pain intensity as reported by participants (Koyama et al., 2005) and perceived threat during the anticipation of pain (Wiech et al., 2010).

Thus, there is some evidence to suggest that 1) pre-stimulus and resting-state alpha activity can be modified by the participants' expectation about pain intensity; and 2) that higher pre-stimulus and resting-state alpha activity is related to reduced pain experience. Yet, to date, evidence for a relationship between alpha activity and pain experience is largely correlational, and evidence for a causal relationship between alpha activity and pain experience is limited. A promising approach to establish a causal role of alpha activity in pain experience is experimental modulation of alpha activity with the application of transcranial alternating current stimulation at alpha frequency (alpha tACS) (Herrmann, Rach, Neuling, & Strüber, 2013; Herrmann, Strüber, Helfrich, & Engel, 2016). The application of alpha tACS offers the opportunity to

increase alpha activity in a frequency-specific manner, and is a relatively affordable, non-invasive technique (Abd Hamid, Gall, Speck, Antal, & Sabel, 2015). This chapter will address the question whether alpha tACS applied over the somatosensory cortex can reduce pain experience in an experimental pain setting, and whether this is influenced by uncertainty about the intensity of an upcoming stimulus.

### **6.1.1 The application of tACS**

TACS is a type of non-invasive transcranial electrical stimulation (tES) used to directly modulate oscillatory neural activity. TACS involves the application of an oscillating electrical current (an electrical current that alternates around a set point over time) at a low intensity, usually through two electrodes placed on the scalp, over the brain region of interest (Cohen Kadosh, 2015). An important attribute of tACS for the present study is that it affects oscillatory neural activity in a frequency-specific manner. Oscillatory neural activity is modulated predominantly at the tACS frequency (Herrmann et al., 2016). Therefore, stimulating with tACS at a frequency within the alpha frequency range (e.g., 10Hz) allows for the modulation of oscillatory neural activity in the alpha-band specifically. Two main mechanisms have been suggested to explain the frequency-specific effects of tACS on oscillatory neural activity: neural entrainment and a mechanism of synaptic plasticity (Abd Hamid et al., 2015; Antal & Paulus, 2013; Herrmann et al., 2013). Neural entrainment is implicated during the application of tACS (online) in particular (Helfrich et al., 2014), whereas the changes in synaptic plasticity focus more on effects found after tACS offset (offline), i.e. aftereffects (Vossen et al., 2015).

In general terms, neural entrainment refers to the phenomenon that oscillatory neural activity can be modulated by an external rhythmic stimulation through a process of phase synchronisation (Cohen, 2014; Thut et al., 2011), tACS is an example of such an external rhythmic stimulation. When tACS is applied on the scalp, oscillatory neural activity is thought to adjust or shift its phase to synchronise with the tACS signal. When more and more neurons shift their phase and synchronise (with the external source and each other), an

increase in power can be measured for a population of neurons (Thut et al., 2011). Importantly, tACS, applied at one particular frequency, results in entrainment of oscillatory neural activity at this particular frequency and an increase in power at that particular frequency. This was demonstrated for alpha tACS and alpha activity by Helfrich et al. (2014) in a simultaneous tACS-EEG study. During the application of alpha tACS (10Hz) for 20 minutes, they found both a significant increase of phase synchronisation in the alpha-band and a significant increase of alpha power. No increase in phase synchronisation or power was found in adjacent frequency bands (delta/theta and beta-band).

Finally, the extent to which entrainment takes place as a result of tACS also depends on the frequency characteristics of the neural network of interest. Neurons within neural networks display intrinsic frequency preferences, i.e., neurons demonstrate oscillatory activity that is strongest or dominant at a particular frequency (or a narrow frequency band), and neurons respond most strongly to input at a specific frequency (Hutcheon & Yarom, 2000). It is thought that entrainment as a result of tACS is strongest/most effective when the frequency of tACS matches the dominant frequency of the neural network of interest. Oscillatory neural activity within a frequency range of 8-12Hz (alpha frequency range) is the dominant rhythm in the somatosensory cortex (Kuhlman, 1978; Tiihonen, Kajola, & Hari, 1989). Therefore, applying tACS at alpha frequency over somatosensory regions should result in optimal entrainment of somatosensory alpha activity.

The study by Helfrich et al. (2014) demonstrated an online entrainment effect of alpha tACS. To our knowledge, this is the only EEG study that assessed the online effects of alpha tACS on alpha power to date. There are several other EEG studies that have investigated changes in alpha activity as a result of alpha tACS, but these focussed on offline changes after alpha tACS, or aftereffects (Kasten, Dowsett, & Herrmann, 2016; Vossen et al., 2015; Zaehle, Rach, & Herrmann, 2010). Thus, these studies might involve a mechanism of synaptic plasticity rather than neural entrainment. When alpha tACS was applied for a considerable duration (around 10-20 minutes), significant aftereffects were found, i.e., a significant increase of alpha power

(Kasten et al., 2016; Vossen et al., 2015; Zaehle et al., 2010). However, this aftereffect of increased alpha power is not necessarily the result of neural entrainment. Vossen, Gross, and Thut (2015) specifically investigated whether the offline effects of alpha tACS were reflecting neural entrainment or not. By using an intermittent pattern of alpha tACS (periods of alpha tACS with a duration of 80 cycles, with periods of no-tACS in-between), they demonstrated that an aftereffect of alpha tACS (a significant increase of alpha power) was present even when the periods of alpha tACS were phase-incongruent. Because the phase of the stimulation was changed for every period of tACS in the phase-incongruent alpha tACS condition, consistent neural entrainment could not take place. Thus, the significant increase of alpha power after alpha tACS could not be the result of neural entrainment. Instead, the offline result of alpha tACS was suggested to result from a mechanism of synaptic plasticity. Specifically, the increase of alpha power offline has been suggested to be the result of a strengthening of synapses through a process of spike-time-dependent-plasticity (STDP) (Herrmann et al., 2013; Zaehle et al., 2010).

In general terms, plasticity means that the function of a neural network can be modulated by activity or experience: the specific spatial and temporal pattern of incoming activity (or information) shapes the strength of synapses or connections in a neural network. Synaptic plasticity specifically refers to the phenomenon that the strength of synapses or efficacy of synaptic transmission can be modulated by incoming activity (Citri & Malenka, 2008). STDP is a type of synaptic plasticity that relies in particular on the temporal pattern of incoming and outgoing activity (action potentials and post-synaptic potentials). When action potentials precede post-synaptic potentials, the result is a strengthening of synapses. When the opposite takes place, the result is a weakening of synapses. For repetitive or rhythmic input, synapses in a neural network with their intrinsic frequency preference close to that of the repetitive input will be strengthened (Zaehle et al., 2010).

Alpha tACS, which involves stimulation of a neural network at a certain temporal pattern, is thought to strengthen synapses through the process of STDP, specifically in neural networks with their intrinsic frequency preference

close to that of the tACS frequency (Herrmann et al., 2013; Zaehle et al., 2010). This strengthening of synapses as a result of alpha tACS is what ultimately leads to the increase in alpha power that persists after tACS offset (Zaehle et al., 2010). Although two different mechanisms have been suggested to explain the effects of tACS, one focussing in particular on the changes during alpha tACS and one focussing on the changes after alpha tACS, they have some features in common. Both mechanisms ultimately point to an increase in alpha power as a result of alpha tACS. Also, both mechanisms describe the effects of alpha tACS as frequency-specific and particularly effective when there is a match between the tACS frequency and the frequency characteristics of the neural network of interest. It is these two features that are essential to the present study, in which alpha tACS was applied over the somatosensory cortex, to investigate the role of oscillatory neural activity in the alpha frequency range in the experience of pain. Oscillatory neural activity within the alpha frequency range is the dominant rhythm in the somatosensory cortex (Kuhlman, 1978; Tiihonen et al., 1989). Thus, we expected that the application of alpha tACS over the somatosensory scalp region would result in an optimal effect of alpha tACS, i.e., an increase of alpha power.

### **6.1.2 The effectiveness of tACS in altering neural oscillatory activity**

Although models to explain the effect of tACS have been developed, and there is initial evidence to support the effectiveness of alpha tACS in increasing alpha power (Helfrich et al., 2014; Kasten et al., 2016; Vossen et al., 2015; Zaehle et al., 2010), controversies exist around the effectiveness of tACS and transcranial electrical stimulation (tES) in general. Applying alpha tACS to enhance alpha activity and reduce pain experience is based on the assumption that tACS applied on the scalp is capable of directly modulating oscillatory neural activity. However, there is ongoing debate in the scientific community that revolves around two main questions: 1) How much of tES, applied on the scalp at a low current intensity, actually penetrates the skin and skull to reach the cortex?; and 2) are the low levels of tES that reach the cortex sufficient to modulate oscillatory neural activity?

One marked occasion that resulted in strong scepticism about the effectiveness of tES was the annual meeting of the Cognitive Neuroscience Society in 2016 (Cognitive Neuroscience Meeting, New York 2016). As described on [sciencemag.org](http://sciencemag.org) by Underwood (2016), György Buzsáki of New York University (NYU) presented data gathered together with Antal Berényi of the University of Szeged in Hungary, demonstrating that most of the alternating current applied on the scalp did not reach the cortex through the skin and skull (90% loss of current). They came to this conclusion based on measurements with more than 200 electrodes inserted in the brain of a human cadaver. This would mean that typical tES in humans, at current intensities of 1-2mA, would result in very low levels of current reaching the cortex to affect neural activity. Other evidence against the effectiveness of tES (specifically transcranial direct current stimulation, tDCS), emerged from a systematic review and meta-analysis by Horvath, Forte, and Carter (2015). Their main conclusion, based on the input from experimental tDCS studies that included 30 different neurophysiological outcome measures (for example, transcranial magnetic stimulation induced motor evoked potential (TMS-MEP), other ERP outcomes, EEG power spectrum, fMRI) was that overall tDCS did not demonstrate effectiveness in modulating neural activity. They only found a significant effect of tDCS for the MEP outcomes.

Although these findings resulted in scepticism about the application of tES, they were also met with critique. Strong criticism was expressed on the execution and reasoning in the systematic review and meta-analysis (Horvath et al., 2015). For example Antal, Keeser, and Padberg (2015) detailed the problems with the methodological approach of the review and meta-analysis, and errors in data inclusion/exclusion, data description, data extraction, and pooling of data. They concluded that the strong negative conclusions about the effectiveness of tDCS by Horvath et al. (2015) were not justified.

With respect to the main point demonstrated by Buzsáki and Berényi, that only a very low current of tACS applied on the scalp actually reaches the cortex, it has been suggested that this small current might still be sufficient to affect neural activity. Whereas the low levels of tACS current are not enough to

directly evoke an action potential, this is also not what the main models on the working of tACS suggest. Instead, the low levels of current are thought to affect neural activity by interacting with the neural network's intrinsic activity, resulting in a change in the likelihood of neurons to fire, or the modification of neuronal synaptic efficiency (Fertonani & Miniussi, 2016). However, it should be noted that, even though there are clear theoretical models available to explain the mechanisms through which low current intensity tACS could still affect ongoing oscillatory neural activity, there is very little experimental data available that directly tests these models (Fertonani & Miniussi, 2016).

Despite the scepticism about the effectiveness of tES (in particular tDCS) in modulating neural activity, tACS has been proposed as a neuromodulation technique with considerable potential to affect both neural activity and several behavioural domains, such as the motor and visual domain (e.g., Antal & Paulus, 2013; Cohen Kadosh, 2015; Herrmann et al., 2013). Furthermore, a recent meta-analysis and review (Schutter & Wischniewski, 2016) supported the effectiveness of tACS. The effects of tACS at a variety of frequencies and on performance in a variety of perceptual and cognitive domains (such as contrast discrimination, working memory, and auditory perception) was assessed, spanning 51 experiments from 24 studies. The authors concluded that, even though effect sizes were small to moderate, tACS reliably improved cognitive and perceptual performance, compared to sham stimulation. Another review of the literature on tACS, including studies in motor function, visual perception, and somatosensory perception by Abd Hamid et al. (2015) also concluded that the existing literature on tACS was promising with respect to the effectiveness of tACS in general. They pointed out that evidence for an effect of tACS seemed to be particularly present in the motor domain, as the largest number of tACS studies focussed on motor performance. However, there is also evidence for an effect of tACS in the visual domain and on the performance on a variety of cognitive tasks, including a memory task, a test on non-verbal intelligence (Raven's Advanced Progressive Matrices), and a test on creative thinking (Torrance Test of Creative Thinking).



There are a number of experimental studies demonstrating the effects of alpha tACS on alpha activity. For example, Helfrich et al. (2014) showed that application of alpha tACS for a duration of 20 minutes, with tACS electrodes at electrode locations Cz and Oz, resulted in a significant increase of alpha power, compared to the sham condition. Also, further support for neural entrainment of alpha activity as a result of alpha tACS came from the phase-locking values (PLVs), calculated for the alpha tACS signal and neural activity, to investigate phase synchronisation. A significant increase in phase synchronisation was found in the alpha-band, but not in the delta/theta-band or the beta-band. An online effect of alpha tACS on oscillatory neural activity was present specifically in the alpha-band, for both EEG power and phase synchronisation.

A number of EEG studies have investigated the offline effects of alpha tACS on alpha activity. Two studies assessed aftereffects of alpha tACS in the first few minutes, directly after alpha tACS offset (Vossen et al., 2015; Zaehle et al., 2010). Vossen et al. (2015) used an intermittent pattern of alpha tACS (adding up to a total alpha tACS duration between 11-15 minutes), with alpha tACS applied over PO7/PO9 and PO8/PO10 electrode locations. A significant aftereffect of alpha tACS was found, where alpha power was significantly increased after alpha tACS compared to sham, but only in the 8-second intermittent alpha tACS condition, not the 3-second intermittent condition. Thus, suggesting that for an aftereffect of alpha tACS to take place the stimulation duration (in an intermittent stimulation protocol) needs to be of a sufficient length. Similarly, Zaehle et al. (2010) found a significant aftereffect of alpha tACS. Alpha tACS was applied for 10 minutes at PO9 and PO10 electrode locations. A significant offline increase in alpha power in was found in the alpha tACS group only. Together these studies suggest that an aftereffect of increased alpha is present directly after alpha tACS onset, but that tACS duration might be of influence.

Two other studies have investigated alpha tACS aftereffects over a longer period after tACS offset (Kasten et al., 2016; Neuling et al., 2013). After application of alpha tACS over electrode location Cz and Oz for 20 minutes,

alpha power was significantly increased up to 30 minutes after alpha tACS offset compared to sham, but only in a state of low endogenous alpha power (when participants had their eyes open), but not high endogenous alpha power (when participants had their eyes closed) (Neuling et al., 2013). Thus, although alpha tACS appeared capable of increasing alpha power, this seems to depend on the state of the neural system. Kasten et al. (2016) investigated how long aftereffects of increased alpha power were present after alpha tACS offset. For alpha tACS applied at electrode locations Cz and Oz, for a duration of 20 minutes, alpha power was significantly increased compared to baseline for alpha tACS only, not for sham. Alpha power remained significantly higher in the alpha tACS group compared to the sham group up to 70 minutes after stimulation. Finally, not all studies found a significant aftereffect for alpha tACS. A study, using a very short period of tACS (1s), compared alpha power in the 1.5s before and directly after each 1s of alpha tACS. Alpha tACS was delivered at electrode locations Cz and Oz. They found that 1-second periods of alpha tACS were not sufficient to induce an increase of alpha power in the 1.5s directly after the 1s of alpha tACS (Strüber, Rach, Neuling, & Herrmann, 2015).

Taken together, these studies provide evidence for an increase of alpha power as a result of alpha tACS both offline and online, but mostly offline. They also suggest that the effects of alpha tACS might depend on the duration of alpha tACS, 11-20 minutes of stimulation did result in an aftereffect of increased alpha power (Kasten et al., 2016; Neuling et al., 2013; Vossen et al., 2015; Zaehle et al., 2010), whereas 1s trains of alpha tACS and 3s trains of alpha tACS did not (Strüber et al., 2015; Vossen et al., 2015).

Although there is evidence to suggest that alpha tACS has the potential to increase alpha power, the evidence for an effect of alpha tACS on pain perception, and somatosensory perception in general, is limited. Studies demonstrating behavioural/perceptual effects of alpha tACS so far have predominantly focused on the motor and visual domain. For example, in the motor domain, when alpha tACS was applied over the motor cortex, a significant improvement of implicit motor learning was found during 7 minutes of alpha tACS (Antal et al., 2008). Pollok, Boysen, and Krause (2015) reported

that motor sequence learning was significantly improved during the application of alpha tACS compared to sham (average alpha tACS duration of 12 minutes and 12s), and Wach et al. (2013) found that 10 minutes of alpha tACS significantly affected offline performance on a fast finger tapping task, compared to sham. Within the visual domain, Hopfinger, Parsons, and Fröhlich (2016) assessed changes in performance on an exogenous and endogenous visual attention task during alpha tACS, applied over electrode location P6 and Pz. Alpha tACS only affected performance in the exogenous attention task, compared to sham. In the study by Helfrich et al. (2014) alpha tACS applied over electrode location Cz and Oz (for 20 minutes), which led to an online improvement of accuracy on a visual detection task.

In summary, there are studies demonstrating that alpha tACS can increase alpha power and affect behaviour, particularly for motor and visual performance. However, to date, no studies have investigated the effects of alpha tACS on the perception of pain. Two studies have found effects of alpha tACS applied over the somatosensory region on non-painful somatosensory perception though. Feurra et al. (2011) investigated whether tACS applied over the right somatosensory hand area (as located using TMS) could induce a tactile sensation in the left hand, and whether this was affected by tACS frequency. TACS was delivered in a range of frequencies between 2-70 Hz, for a duration of 5s at each frequency, and with a peak-to-peak current intensity of 1.5mA. Participants were asked to rate the strength of tactile sensation from 0-3, with 0 meaning no sensation at all and 3 meaning a clear and strong sensation. Alpha tACS over the somatosensory hand area led to the strongest tactile sensations; reported tactile sensations for alpha tACS were stronger than for delta, theta, and mid gamma tACS. This study provides a first indication that alpha tACS over the somatosensory region could have an effect on tactile perception. Another study (Gundlach et al., 2016) investigated the effect of alpha tACS applied over bilateral somatosensory regions (CP3 and CP4), on the detection of near-threshold tactile stimuli. Alpha tACS was applied at 1mA peak-to-peak current intensity for a duration of 5 minutes, during a near-threshold somatosensory detection task. In a separate session, participants carried out the same task whilst receiving sham stimulation.

Comparing average somatosensory perception threshold over a 5-minute period before, during and after alpha tACS, did not result in any significant differences. However, there was an effect of alpha tACS online (during alpha tACS), depending on the phase of alpha tACS. When the somatosensory threshold data was split up into different alpha tACS phase bins, it was found that somatosensory perception thresholds changed as a function of alpha tACS phase. There was a significant increase in perception threshold compared to baseline in the phase bin of  $-180^\circ$ . Furthermore, when the same somatosensory detection task was carried out, but with alpha tACS applied over the visual cortex (a task-irrelevant region), this effect was not found. Thus, although alpha tACS did not result in any significant changes in overall mean somatosensory detection thresholds, the study did demonstrate a phase-dependent modulation of somatosensory thresholds, but only when alpha tACS was applied over task-relevant (somatosensory) scalp regions. These two studies together (Feurra et al., 2011; Gundlach et al., 2016) provide some initial evidence to suggest that alpha tACS applied over the somatosensory scalp region could affect somatosensory perception, including pain.

To my knowledge the present study is the first to investigate the effect of alpha tACS over bilateral somatosensory scalp regions on pain experience. This investigation is felt to have merit as it could lead to 1) a better understanding of the role of somatosensory alpha activity in pain experience, and an initial behavioural assessment of a causal relationship between alpha and pain experience specifically; and 2) add to a limited number of studies investigating the application of alpha tACS over somatosensory regions, leading to further knowledge on the effectiveness of somatosensory alpha tACS in general.

### **6.1.3 Study objectives**

The aim of the present study was to investigate whether alpha tACS applied during pressure pain, over bilateral somatosensory scalp regions, modulated pain experience. To investigate the effects of alpha tACS, pain experience during alpha tACS was compared to pain experience during sham

stimulation. Alpha tACS was applied over bilateral somatosensory scalp regions (electrode location CP3 and CP4) adopted from the study by Gundlach et al. (2016). As higher pre-stimulus somatosensory alpha power has been related to lower perceived pain intensity (Babiloni et al., 2006; Tu et al., 2016), we expected that the application of somatosensory alpha tACS, leading to an increase of alpha power, would result in a reduction of pain experience, i.e., lower perceived pain intensity and pain unpleasantness as measured on a numerical rating scale (NRS).

A further aim of the study was to explore whether the effect of alpha tACS on pain experience was influenced by uncertainty about the intensity of an upcoming stimulus. Both pain experience, and pre-stimulus and resting-state alpha activity, have been found to be affected by expectations about pain intensity (Franciotti et al., 2009; Huneke et al., 2013; Lin et al., 2014; Ploghaus et al., 2001). Uncertainty about the intensity of an upcoming stimulus has been found to result in higher levels of perceived pain intensity (Lin et al., 2014; Ploghaus et al., 2001). Also, uncertainty about stimulus intensity was found to result in a larger reduction of pre-stimulus alpha activity, compared to when stimulus intensity was certain (Franciotti et al., 2009). Together these findings suggest that the effect of somatosensory alpha tACS on pain experience (through an increase of alpha) might be influenced by uncertainty about pain intensity.

Finally, pressure stimuli were applied at three different intensities (non-painful, pain threshold and moderately painful). This allowed us to explore whether the effects of somatosensory alpha tACS on somatosensory perception were more general, resulting in a reduction of perceived intensity and unpleasantness for both painful and non-painful stimuli, or specific to pain perception, resulting in a reduction for the painful stimuli only.

Similar to the alpha binaural beat study (Chapter 5), in the present study the impact of two individual pain-related characteristics, fear of pain and pain catastrophising, on the effects of somatosensory alpha tACS was assessed. It has been demonstrated both in healthy volunteers and patients with chronic pain that fear of pain and pain catastrophising are related to levels of pain

experienced and pain-related symptoms: higher levels of fear of pain and pain catastrophising tend to be related to higher levels of reported pain both for experimental pain in healthy volunteers and higher levels of pain and pain related disability in patients with chronic pain (Hirsh et al., 2008; Parr et al., 2012; Severeijns et al., 2001; Zale et al., 2013). These individual characteristics might therefore have an influence on the effects of somatosensory alpha tACS on pain experience and for that reason were measured in the present study.

## **6.2 Methods**

### **6.2.1 Participants**

This study was approved by the School of Psychology Research Ethics Committee, University of Leeds (reference number: 16-0302). All participants provided signed informed consent before participating in the study.

Twenty six healthy right-handed volunteers took part in the study; 22 females and 4 males with an average age of  $21.42 \pm 4.68$  years (range 18-36 years). All participants met the inclusion criteria of being: aged 18 or older, free of any pain at the time of testing, and not using any psychopharmacological agents. Participants were screened using a medical history questionnaire before taking part, to ensure safe and ethical application of tACS and pressure pain. They were free of any medical conditions or wounds on the scalp and hands, and any medical conditions that would make stimulation inappropriate (e.g. cardio-vascular conditions, epilepsy, severe headaches/migraine), and free of any metallic foreign bodies or any type of medical implant.

Three participants were removed from the final analysis, as they only completed one of the two sessions. Where two of these participants failed to attend the second session, the third participant did attend the second session but requested for the alpha tACS to be turned off within the first minutes of the pressure pain task, as the participant was experiencing an itchy sensation on the skin. This resulted in an N of 23 for the final analysis.

### 6.2.2 Alpha tACS

tACS was administered for the entire duration of the pressure pain task, using a battery-driven constant current stimulator (DC Stimulator PLUS, NeuroConn GmbH, Ilmenau, Germany) and two 5x5 cm rubber electrodes, placed in saline-soaked sponges and attached with a rubber band. The alpha tACS consisted of a sinusoidal waveform with a frequency of 10Hz, and a peak-to-peak current intensity of 1mA. Impedance was kept below 55 k $\Omega$ . The two tACS electrodes were placed bilaterally over the somatosensory scalp region, at electrode location CP3 and CP4 (based on EEG 10-20 electrode placement system), as adapted from Gundlach et al. (2016). The alpha tACS was ramped up for 10s and was turned off when the pressure pain task was completed. For the sham condition random noise stimulation (RNS) was applied. RNS was ramped up over a period of 10s, followed by 10s of RNS, and finally ramped down again over a period of 10s. This sham protocol with a brief period of stimulation at the start of the experiment was aimed to make the tACS and sham session indistinguishable for the participants. Furthermore, it was decided to apply RNS, stimulation that included a wide range of frequencies, to minimise any potential effects of RNS of somatosensory alpha activity (Gundlach et al., 2016).

### 6.2.3 Pressure stimuli

Pressure stimuli were applied following the same procedure as in the other three studies of this PhD thesis (Chapters 4, 6, and 7), as explained in detail in Chapter 4 (p. 75). Pressure stimuli were applied to the middle finger of the left (non-dominant) hand at three different intensities: 1) non-painful, light touch (rating of 2/10 on a 11-point numerical rating scale (NRS)); 2) pain threshold; i.e., the point where the pressure stimulation becomes painful for the first time (rating of 4/10 on NRS); and 3) moderately painful, but still tolerable (rating of 7/10 on NRS). These levels were set for each individual participant, using a ramping procedure (ascending method of limits), which was carried out twice. The average was used for the experiment. The ramping procedure was

carried out at the start of each of the two sessions. The average pressure (Mean (SD)) applied during the first session was 0.27(0.04)V for the non-painful stimuli, 0.41(0.05)V for the pain threshold stimuli; and 0.53(0.06)V for the moderately painful stimuli. The average pressure applied during the second session was 0.29(0.03)V for the non-painful stimuli, 0.42(0.05)V for the pain threshold stimuli; and 0.56(0.05)V for the moderately painful stimuli.

#### **6.2.4 Visual cues**

To manipulate uncertainty, i.e. to create a condition where pain intensity was uncertain and a condition where pain intensity was known/certain, each pressure stimulus was preceded by a visual cue. Three different visual cues were used (a green triangle, a blue circle, and a yellow square). In the certain condition, each of the visual cues was paired with one particular pressure stimulus intensity, resulting in visual cues that were predictive of the pressure intensity of an upcoming stimulus. In the uncertain condition, the same three visual cues were used. However, here the visual cues were randomly combined with a pressure stimulus level, resulting in visual cues that were not predictive of the pressure intensity of an upcoming stimulus.

#### **6.2.5 Pain experience**

To quantify pain experience, participants received two 11-point numerical rating scales (NRSs) on the computer screen after each stimulation (ranging from 0-10) to measure perceived intensity and unpleasantness (0 = not at all intense/unpleasant, 10 = extremely intense/unpleasant). They were asked to rate these scales by typing a number using the keyboard.

#### **6.2.6 Questionnaires**

As part of this study participants were asked to complete a set of questionnaires: the Fear of Pain Questionnaire – Short Form (FPQ-SF) (McNeil & Rainwater, 1998); and the Pain Catastrophising Scale (PCS) (Sullivan et al.,



1995). A detailed description of the FPQ-SF and PCS can be found in the methodology chapter (Chapter 3, p. 63). Participants were asked to complete these questionnaires at the end of both of the experimental sessions.

As part of the study participants also completed some additional questionnaires to assess anxiety and depression: the State Trait Anxiety Scale (STAI) (Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983); and the Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983). Both anxiety and depression have been found to frequently co-occur with chronic pain conditions. Individuals with a chronic pain condition were found significantly more likely to have a mood disorder compared to pain-free individuals (21.7 versus 10 %), the same was found for anxiety disorders (35.1 versus 18.1 %) (McWilliams, Cox, & Enns, 2003). Also in both clinical and experimental pain settings associations between pain experience and depression and anxiety have been demonstrated. For instance, depression has been found to be significantly correlated with a number of measures of pain experience in chronic pain patients, including pain intensity, pain-related disability, and negative thoughts about pain (Geisser, Roth, Theisen, Robinson, & Riley, 2000). Also, pre-operative state anxiety (as measured using the State Trait Anxiety Inventory; STAI) one day before surgery, was significantly correlated with post-operative reported pain intensity (Granot & Ferber, 2005). For experimental pain stimuli, higher levels of depressed mood were related to significantly higher reported pain intensity (Walsh, 1998), and finally participants with high trait anxiety were found to report significantly higher pain intensity than participants with low trait anxiety (Tang & Gibson, 2005).

As both depression and anxiety play a role in pain experience, in this study, anxiety and depression were also assessed. Boxplots of the total scores on the STAI and HADS were checked for outliers. Significant outliers were defined according to the "outlier labelling rule", with a cut off of 2.2 interquartile range (IQR) (Hoaglin & Iglewicz, 1987; Hoaglin DC, Iglewicz B, 1986); i.e., a score of 2.2 interquartile range below the 1st quartile or above the 3rd quartile was considered to be a significant outlier.

The STAI consists of two subscales measuring state anxiety and trait anxiety. Spielberger and colleagues defined state anxiety as an emotional state of anxious thoughts and feelings that fluctuates over time (feelings of nervousness, worry, tension), whereas trait anxiety was considered to reflect a more stable, general proneness to anxiety. For the state anxiety subscale, participants were asked to rate how they felt right now, at this moment, with their answers reflecting their present feelings. The trait anxiety subscale contained the same items as the state anxiety subscale; however, this time participants were asked to rate how they generally felt. Examples of normal/direct items reflecting the presence of anxiety are: 'I feel indecisive' and 'I feel nervous'. Examples of reversed items reflecting the absence of anxiety are: 'I feel calm' and 'I feel pleasant'. In the present study the STAI form Y was used, the revised version of the original STAI form X with improved psychometric properties (Spielberger et al., 1983). The STAI was demonstrated to be a reliable measure across a broad range of studies and populations (Barnes, Harp, & Jung, 2002). The state and trait subscale each contain 20 items, of which 10 are reversed items. Participants are asked to rate how much they feel as described in the item on a scale from 1-4 (1 = not at all; 4 = very much so), resulting in a total score per subscale ranging from 20-80. A higher score on each subscale indicates higher levels of anxiety. In each experimental session participants were asked to fill in the STAI state and trait subscale, at the end of the session.

To measure depression and anxiety the HADS was used (Zigmond & Snaith, 1983). A review by Herrmann (1997) confirmed the factor validity of its two subscales (measuring anxiety and depression). Furthermore, the HADS was demonstrated to be a reliable and valid measure, with good internal consistency (Crawford, Henry, Crombie, & Taylor, 2001; Herrmann, 1997; Zigmond & Snaith, 1983).

The two subscales contain 7 items each. For each item there are four answer options that each have a particular rating ranging from 0 to 3 points. Participants were asked to choose the answer that closest represented how they had been feeling in the past week for each item. For example 'Worrying

thoughts go through my mind': 1.) a great deal of the time; 2.) a lot of the time; 3.) from time to time, but not too often; 4.) only occasionally. The maximum score for each subscale is 21. A higher score indicates a higher level of depression/anxiety. Participants were asked to complete the HADS at the end of session 2.

Finally, in both sessions, just before the start and immediately after the end of the pressure pain task, participants were asked to report their levels of tiredness and attention on a 10-cm visual analogue scale (VAS). The tiredness VAS asked: "How tired do you feel at the moment?" (0 = energetic, not tired at all; 10 = extremely tired). The attention VAS asked: "How focused/alert do you feel at the moment?" (0 = distracted, not focused at all; 10 = extremely focused/alert).

### **6.2.7 Design**

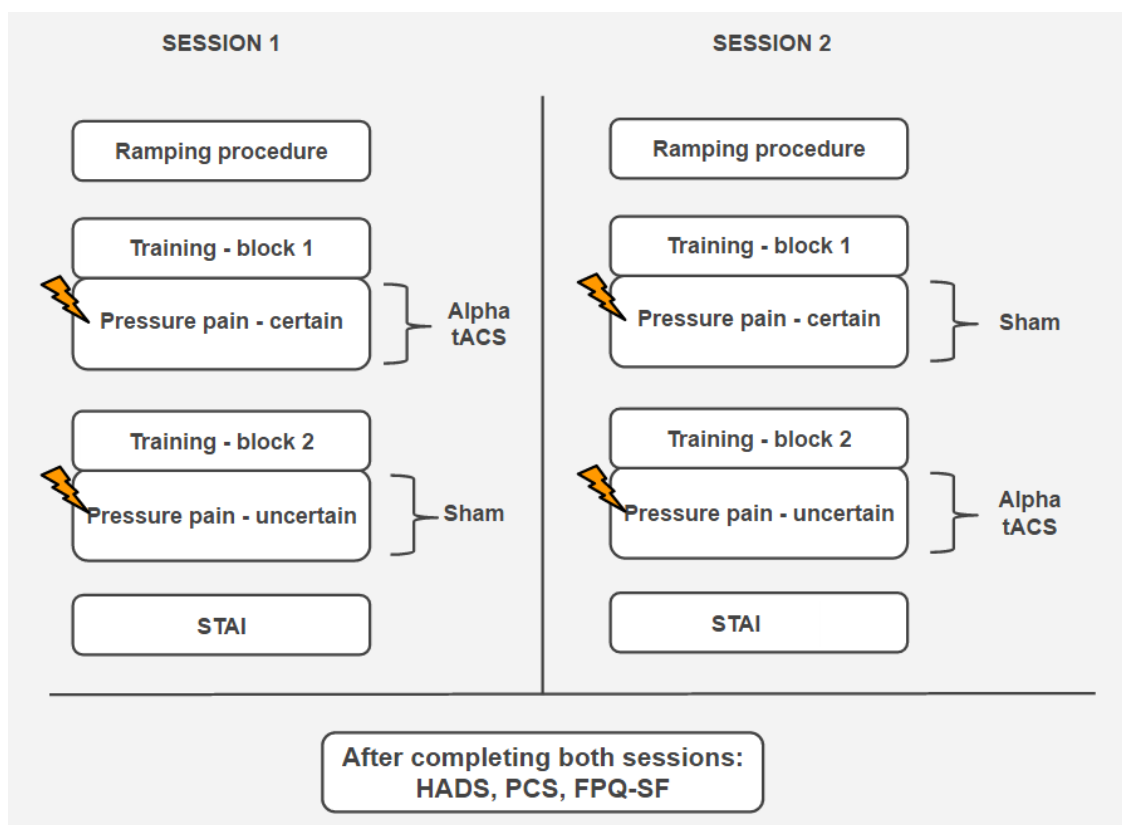
The present study used a 2x2x3 design with three within-subject factors: stimulation condition (alpha tACS, sham), expectation (certain, uncertain) and pressure stimulus intensity (non-painful, pain threshold, moderately painful). To assess pain experience, intensity ratings and unpleasantness ratings were used.

### **6.2.8 Experimental procedure**

The experiment consisted of four pressure pain blocks in total: 1) alpha tACS and certain expectation; 2) alpha tACS and uncertain expectation; 3) sham and certain expectation; and 4) sham and uncertain expectation. These four blocks were split over two sessions. Each session contained one tACS and one sham block, one of which was combined with certain and the other with uncertain expectation (Figure 6.1). Order of alpha tACS and sham was counterbalanced over the two sessions per participant; each participant received alpha tACS first in one of the sessions and sham first in the other session. The order of certain and uncertain expectation was kept the same for each individual participant over the two sessions, but was counterbalanced

between participants: half of the participants did the certain condition first for both sessions, the other half did the uncertain condition first. The two sessions were scheduled with at least one week in-between to avoid any carry-over effects of tACS, and around the same time of day. Participants were not made aware of the two different tACS conditions (alpha tACS and sham) throughout the experiment but were debriefed after completion of the study.

For each session the general procedure was the same. At the start of the session the ramping procedure was carried out to identify the three individual levels of pressure intensity. Each session included two separate blocks, one where participants were certain about pressure stimulus intensity and one where participants were uncertain about pressure stimulus intensity before pressure onset. During one of these blocks alpha tACS was administered, during the other sham stimulation. Each block contained 72 trials (24 trials for each of the three pressure stimulus intensities). Every trial started with the presentation of a fixation cross (with a jittered duration of 750-1000 ms) followed by a visual cue (with a jittered duration of 2000-2750 ms). The visual cue was followed by a pressure stimulation at one of the three intensities (non-painful, pain threshold, and moderately painful). After each pressure stimulation, the participants were asked to rate their experience using two 11-point NRSs, reporting their experienced intensity and unpleasantness for the preceding pressure stimulus. Participants received regular short breaks throughout the experiment. Each block was preceded by a short practice to familiarise the participant with the task in general and the function of the visual cues in each block in particular. Total duration of the experimental task was variable, depending on the time individual participants took to rate intensity and unpleasantness and duration of breaks, but was between 15 to 20 minutes for each block, adding up to 30-40 minutes in total.



**Figure 6.1** Overview of experimental procedure. The two tACS conditions (alpha tACS and sham) were delivered during the pressure pain task in two separate sessions. The order of tACS conditions was counterbalanced for each participant over the two sessions. The pressure pain task consisted of two blocks, each block containing a different expectation condition (certain and uncertain). The order of the certain and uncertain condition was the same for session 1 and session 2 for each participant. The order was counterbalanced between participants.

### 6.2.9 Statistical analysis

Statistical analysis was carried out using SPSS version 21. The rating data was first checked for outliers. Significant outliers were defined according to the “outlier labelling rule”, with a cut off of 2.2 interquartile range (IQR) (Hoaglin & Iglewicz, 1987; Hoaglin & Iglewicz, 1986); i.e., a score of 2.2 interquartile range below the 1st quartile or above the 3rd quartile was considered to be a significant outlier. No participants were found to consistently be an outlier with respect to their intensity and unpleasantness ratings, i.e., no participant demonstrated an outlier for more than one rating score outcome,

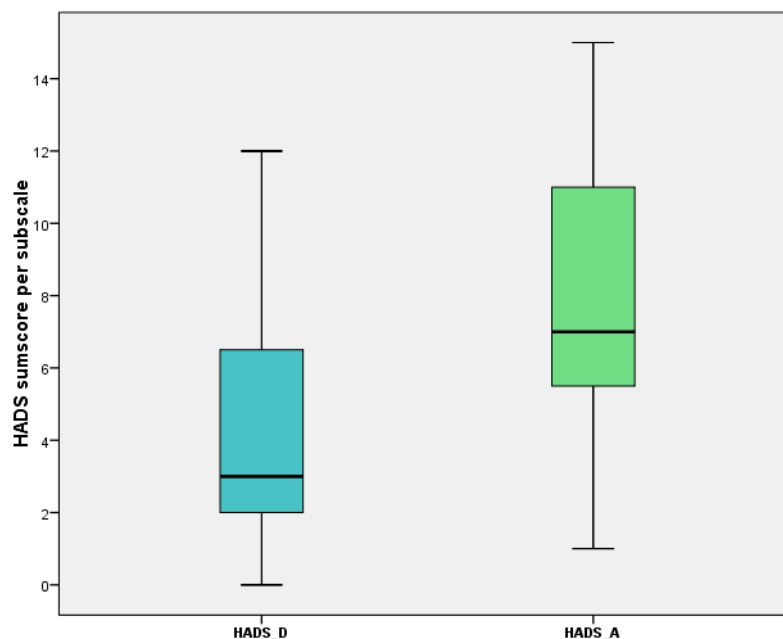
therefore no further steps were taken. The significance level was set at  $p < .05$ . In the case of a violation of sphericity the Greenhouse-Geisser corrected outcomes were used. To investigate the effect of tACS on pain experience and the influence of uncertainty about pain intensity, two 2x2x3 within-subject ANOVAs were calculated with the factors tACS (alpha tACS, sham), expectation (certain, uncertain) and pressure stimulus intensity (non-painful, pain threshold, moderately painful); one for the intensity ratings and one for the unpleasantness ratings.

To investigate the relationship between the change in reported pain intensity for moderately painful stimulation as a result of alpha tACS (sham intensity rating - alpha tACS intensity rating) and self-reported fear of pain and pain catastrophising Pearson correlations between the change in intensity ratings and the fear of pain and pain catastrophising scores were calculated (two-tailed significance), both for the certain and uncertain condition. To correct for multiple comparisons the Holm-Bonferroni method was applied (Holm, 1979), as explained in detail in Chapter 4 (p. 82). Four hypotheses were tested for the moderately painful pressure stimuli: 2 (expectation: certain, uncertain) x 2 (questionnaires: fear of pain, pain catastrophising) against corrected significance levels of .0125, .0167, .025 and .05. The same procedure was carried out for the unpleasantness ratings.

As a set of control analyses the scores on the HADS and the STAI state and trait subscale were inspected for significant outliers following the same procedure as described for the rating scores, to check whether any of the participants had an extreme score for depression or anxiety. Finally, for the tiredness and attention VAS outcomes, assessed at the beginning and end of the pressure pain task in both sessions, two 2x2 within-subject ANOVAs were calculated with the factors time (before and after pressure pain task) and session (session 1, session 2) to assess if there were any changes in tiredness and attention over the time course of a session and whether this was different for session 1 and 2.

### 6.2.10 Control analyses

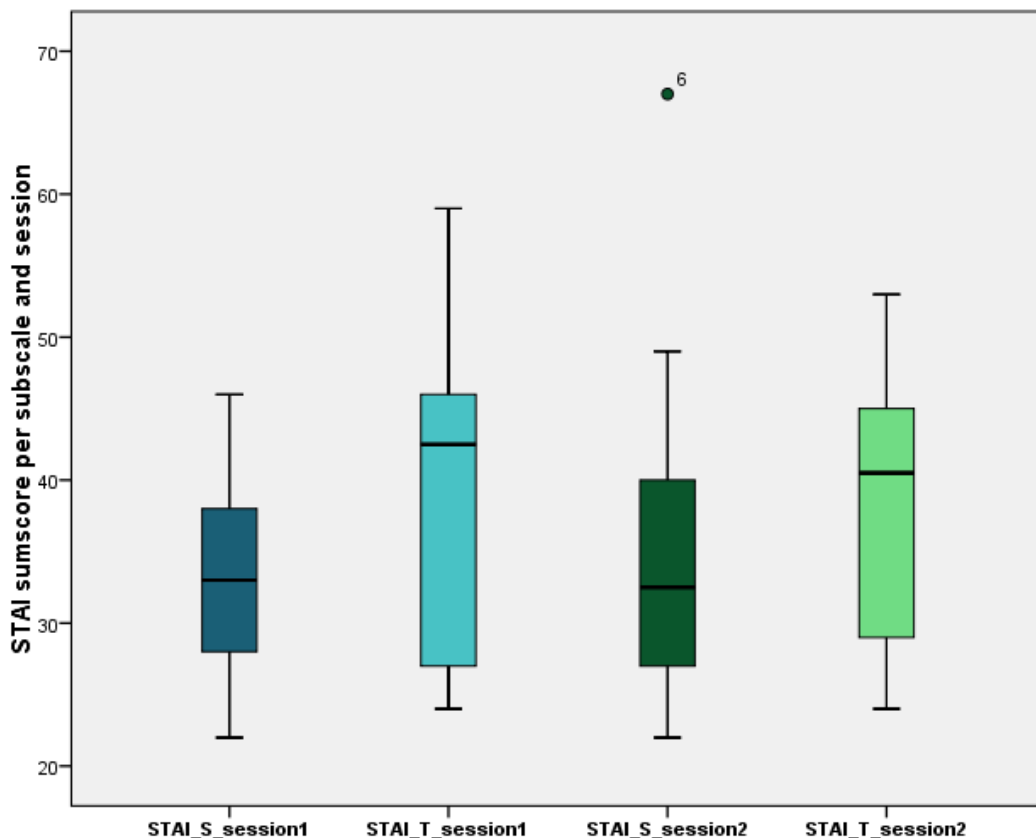
The two HADS subscales (anxiety and depression) each contain 7 items with four answer options (ranging from 0-3 points), adding up to a total score for each subscale ranging from 0-21. A higher score indicates a higher level of depression/anxiety. In this study, for the HADS-depression subscale the total score ranged from 0-12, with an average score (Mean (SD)) of 4.04 (3.38). For the HADS-anxiety subscale the total score ranged from 1-15, with an average score of 8.13 (3.91). There were no significant outliers for both subscales (N = 23) (Figure 6.2).



**Figure 6.2** Boxplots of the total score per subscale, for the HADS-depression ('HADS-D', left) and HADS-anxiety subscale ('HADS-A', right) (N = 23).

The STAI state and trait subscale each contain 20 items, of which 10 are reversed items. Participants were asked to rate how much they feel as described in the item on a scale from 1-4 (1 = not at all; 4 = very much so), resulting in a total score per subscale ranging from 20-80. Higher scores on each subscale indicate higher levels of anxiety. At end of the first session, the STAI-state subscale scores ranges from 22-46, with an average score of 33.18 (6.65). At end of the second session, the STAI-state subscale scores ranges

from 22-67, with an average score of 34.65 (10.30) (N = 23). The wider range of scores for the STAI-state subscale in the second session was caused by one score that showed up as an outlier in the boxplot (score of 67), applying the outlier labelling rule (Hoaglin & Iglewicz, 1987; Hoaglin & Iglewicz, 1986) demonstrated that this score was not a significant outlier however. For the STAI-trait subscale scores ranged from 22-67 in the first session, with an average score of 38.05 (11.10). For the second session, the STAI-trait subscale scores ranged from 24-53, with an average score of 39.39 (9.10) (N = 22). No significant outliers were present.

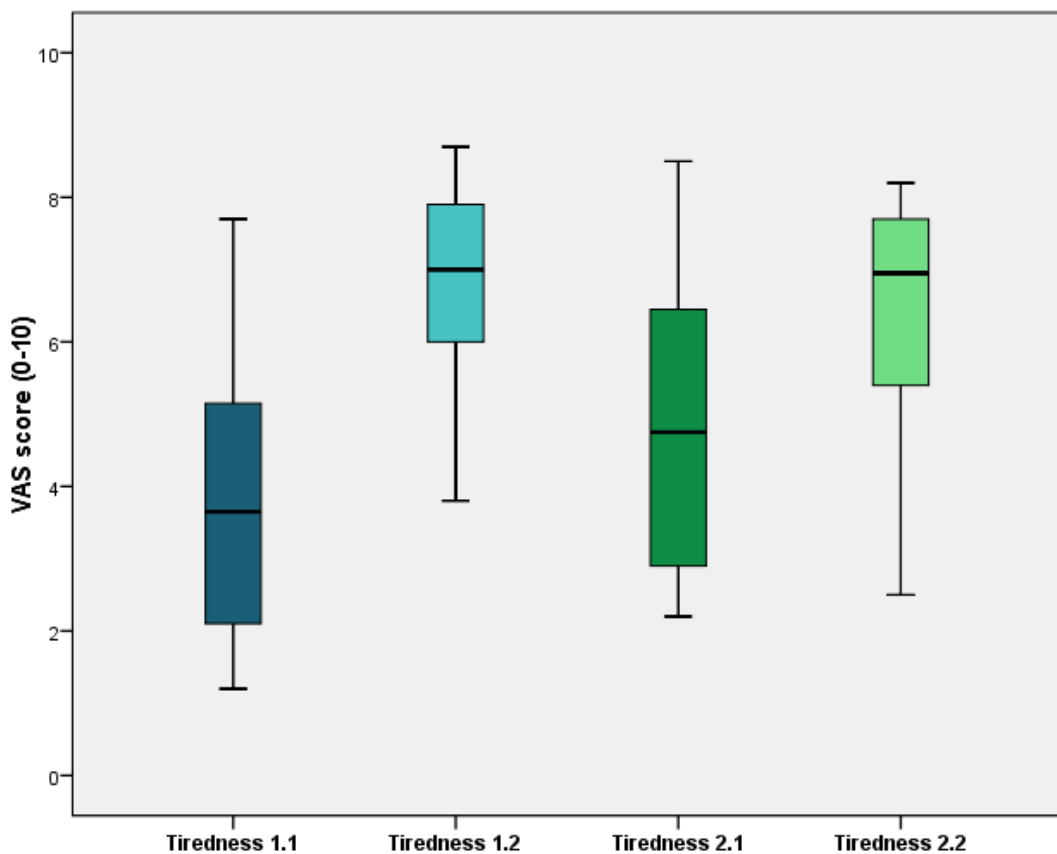


**Figure 6.3** Boxplots of the total score per subscale, for the STAI-state ('STAI-S') and the STAI-trait ('STAI-T'), for session 1 (left, N = 22) and session 2 (right, N = 23).

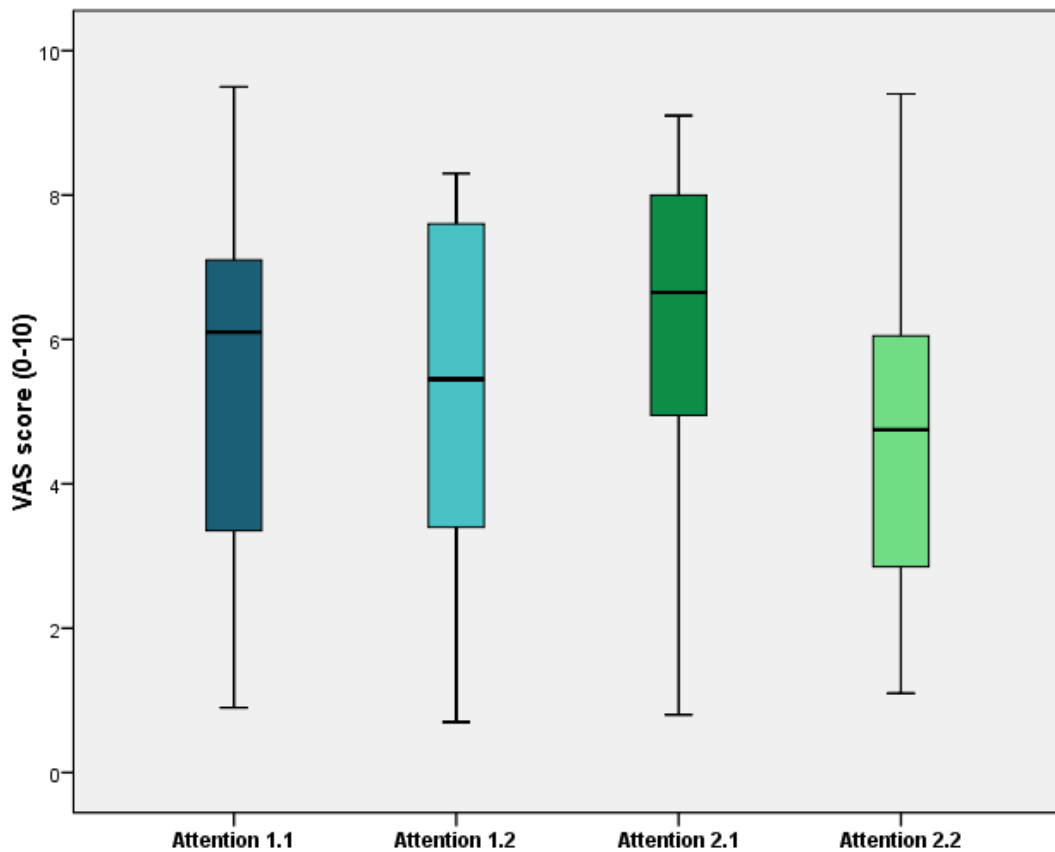
Both self-reported tiredness and attention were assessed on two VASs, at the beginning and end of the pressure pain task, in each session. For the first session a significant increase of tiredness was found over time ( $t(18)=4.34$ ;



$p < .001$ ); average reported tiredness was 3.77 (1.80) before the task and 6.81 (1.40) after the task. No significant reduction in attention was found ( $t(18) = 0.29$ ;  $p = .78$ ); average reported attention was 5.42 (2.57) before the task and 5.31 (2.56) after the task. For the second session a significant increase of tiredness was found as well ( $t(19) = 2.47$ ;  $p = .023$ ); average reported tiredness was 4.85 (2.01) before the task and 6.38 (1.63) after the task. Again, no significant reduction in attention was found ( $t(19) = 1.10$ ;  $p = .29$ ); average reported attention was 6.08 (2.36) before the task and 4.60 (2.31) after the task. Although participants became more tired over the time course of the pressure pain task, they did not report any significant reduction in attention.



**Figure 6.4** Boxplots of the VAS scores for tiredness, for the pre-task and post-task assessment during session 1 (Tiredness 1.1 and Tiredness 1.2 (N = 19)) and the pre-task and post-task assessment during session 2 (Tiredness 2.1 and Tiredness 2.2 (N = 20)). A similar significant increase in tiredness was found from pre- to post-task for session 1 and session 2.



**Figure 6.5** Boxplots of the VAS scores for attention, for the pre-task and post-task assessment during session 1 (Attention 1.1 and Attention 1.2 (N = 19)) and the pre-task and post-task assessment during session 2 (Attention 2.1 and Attention 2.2 (N = 20)). Both in session 1 and session 2 no significant change in attention was found from pre- to post-task.

## 6.3 Results

### 6.3.1 Effect of alpha tACS on intensity and unpleasantness ratings

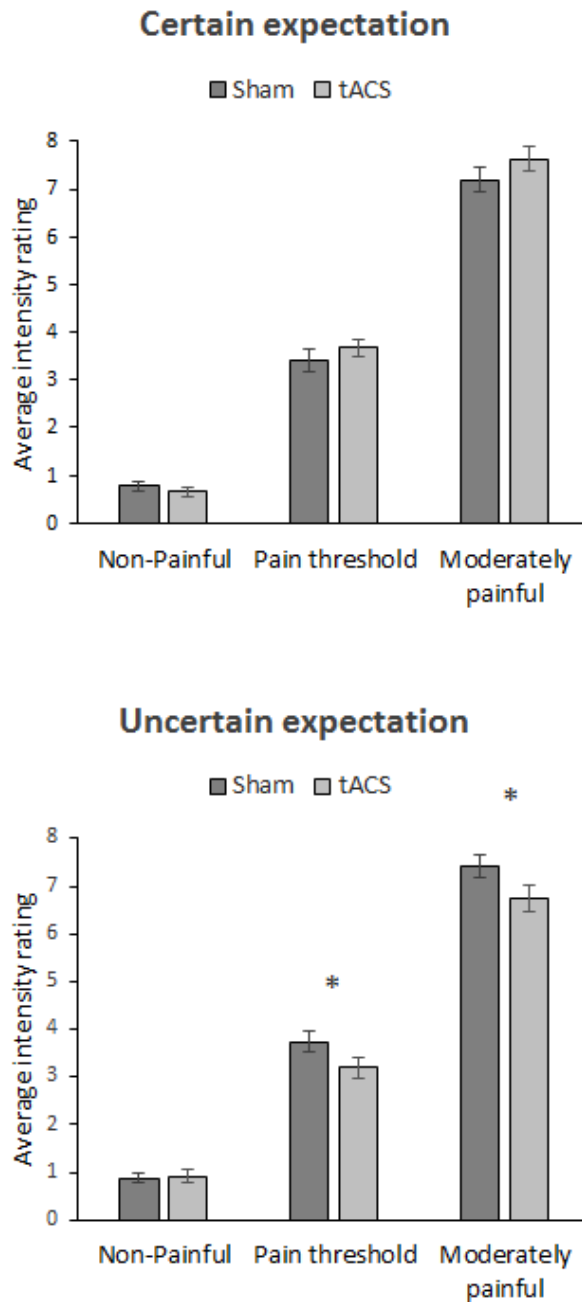
A repeated-measures ANOVA with the factors tACS (alpha tACS, sham), expectation (certain, uncertain) and pressure intensity (non-painful, pain threshold, moderately painful) was conducted for the intensity and unpleasantness ratings separately. A significant main effect of tACS was found for the unpleasantness ratings ( $F_{(1,22)} = 4.35$ ;  $p = .049$ ; Partial  $\eta^2 = .17$ ) with an overall average unpleasantness rating (mean (SD)) of 3.30 (0.73) for the alpha tACS and 3.42 (0.75) for the sham condition. No significant main effect of

tACS was found for the intensity ratings ( $F(1,22) = 2.31$ ;  $p = .14$ ; Partial  $\eta^2 = .095$ ).

However, for the intensity ratings a significant interaction between tACS, expectation, and pressure intensity was found ( $F(2,44) = 4.50$ ;  $p = .017$ ; Partial  $\eta^2 = .17$ ). In addition, a trend towards significance was found for the interaction between tACS and expectation ( $F(1,22) = 3.56$ ;  $p = .073$ ; Partial  $\eta^2 = .14$ ). In the certain condition, intensity ratings for alpha tACS and sham respectively were: 0.66 (0.44) and 0.77 (0.49) for non-painful pressure stimuli; 3.67 (0.82) and 3.40 (1.08) for pain threshold pressure stimuli; and 7.63 (1.14) and 7.19 (1.08) for moderately painful pressure stimuli. In the uncertain condition, intensity ratings, for alpha tACS and sham respectively, were: 0.92 (0.62) and 0.88 (0.50) for non-painful pressure stimuli; 3.19 (1.14) and 3.75 (1.08) for pain threshold pressure stimuli; and 6.74 (1.39) and 7.41 (1.09) for moderately painful pressure stimuli.

Post hoc paired-samples t-tests, to compare the intensity ratings for alpha tACS and sham, at each pressure intensity and each expectation condition separately, demonstrated that a significant difference in intensity ratings between alpha tACS and sham was only present when pain intensity was uncertain, and only for the pain threshold and moderately painful pressure stimuli. In the certain condition, no significant improvement of perceived pain intensity was found for any of the three pressure stimulus intensities:  $t(22) = -1.05$ ,  $p = .31$ , for the non-painful stimuli;  $t(22) = 1.08$ ,  $p = .29$ , for the pain threshold pressure stimuli; and  $t(22) = 1.60$ ,  $p = .12$ , for the moderately painful pressure stimuli. When pain intensity was uncertain, a significant improvement of perceived pain intensity was found for the pain threshold and moderately painful stimuli only. For the non-painful pressure stimuli only a non-significant difference of 0.04 was found for alpha tACS compared to sham ( $t(22) = 0.40$ ,  $p = .69$ ); for the pain threshold pressure stimuli the intensity ratings were 0.56 lower in for alpha tACS compared to sham ( $t(22) = -2.18$ ,  $p = .040$ ); and for the moderately painful pressure stimuli the intensity ratings were 0.67 lower for alpha tACS compared to sham ( $t(22) = -2.73$ ,  $p = .012$ ) (Figure 6.6).

## Intensity ratings

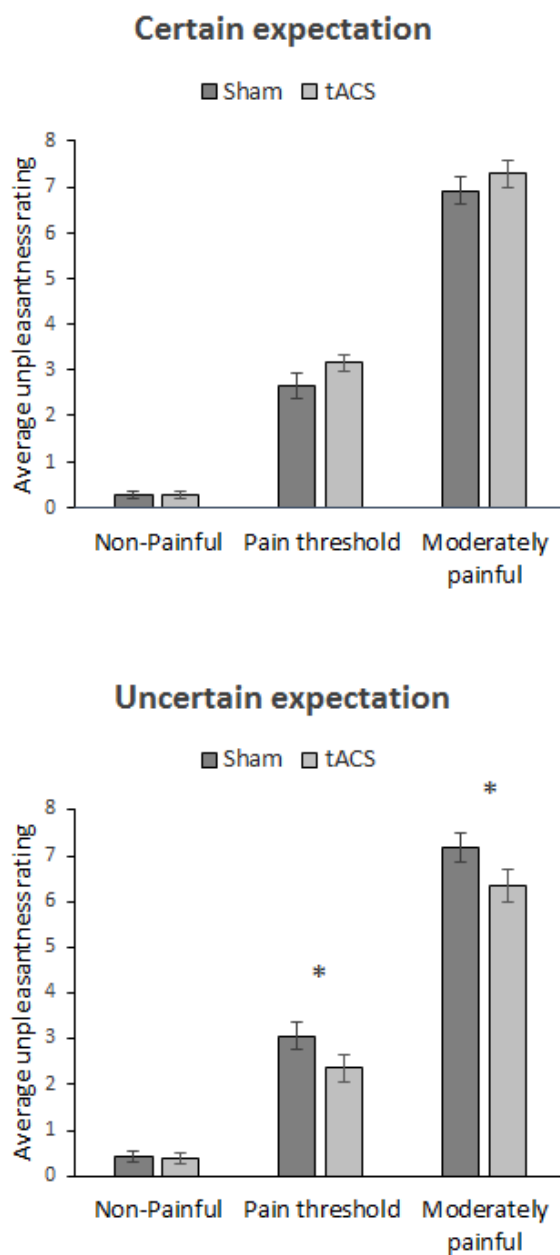


**Figure 6.6** Average intensity rating scores and standard error of means (SEM) for the three pressure intensities, comparing alpha tACS and sham, for the certain (top) and uncertain (bottom) expectation conditions separately (N = 23). Significant outcomes for the post hoc t-tests comparing rating scores for tACS and sham, for each pressure intensity and each expectation condition (certain, uncertain), are marked (\*) for significant outcomes ( $p < .05$ ). Pain intensity ratings were significantly lower during alpha tACS compared to sham stimulation for pain threshold and moderately painful stimuli, but only when pain intensity was uncertain.

For the unpleasantness ratings a similar pattern of interactions was found. A significant interaction between tACS, expectation, and pressure intensity was present ( $F_{(1,22)} = 4.78$ ;  $p = .040$ ; Partial  $\eta^2 = .18$ ). Here, a significant interaction between tACS and expectation was found as well ( $F_{(2,44)} = 3.42$ ;  $p = .042$ ; Partial  $\eta^2 = .14$ ). In the certain condition, unpleasantness ratings (mean (SD)) for alpha tACS and sham, respectively, were: 0.28 (0.38) and 0.28 (0.37) for non-painful pressure stimuli; 3.15 (0.88) and 2.66 (1.25) for pain threshold pressure stimuli; and 7.29 (1.44) and 6.92 (1.30) for moderately painful pressure stimuli. In the uncertain condition, unpleasantness ratings (mean (SD)) for alpha tACS and sham respectively, were: 0.39 (0.58) and 0.44 (0.56) for non-painful pressure stimuli; 2.36 (1.33) and 3.07 (1.28) for pain threshold pressure stimuli; and 6.33 (1.72) and 7.17 (1.36) for moderately painful pressure stimuli. Post hoc paired-samples t-tests, to compare the unpleasantness ratings for alpha tACS and sham, at each pressure intensity and each expectation condition separately, demonstrated that a significant difference between alpha tACS and sham was only present when pain intensity was uncertain, and only for the pain threshold and moderately painful pressure stimuli. In the certain condition, no significant improvement of perceived pain unpleasantness was found for any of the three pressure intensities:  $t(22) = 0.135$ ,  $p = .89$  for non-painful;  $t(22) = 1.86$ ,  $p = .073$  for pain threshold; and  $t(22) = 1.20$ ,  $p = .24$  for moderately painful stimuli. When pain intensity was uncertain, a significant improvement of perceived pain unpleasantness was found for the pain threshold and moderately painful stimuli only. For the non-painful pressure stimuli only a non-significant difference of 0.05 was present for alpha tACS compared to sham ( $t(22) = -0.43$ ,  $p = .67$ ); for the pain threshold pressure stimuli the unpleasantness ratings were 0.71 lower for alpha tACS compared to sham ( $t(22) = -2.34$ ,  $p = .029$ ); and for the moderately painful pressure stimuli the unpleasantness ratings were 0.84 lower for alpha tACS compared to sham ( $t(22) = -2.65$ ,  $p = .015$ ) (Figure 6.7).

These results show that during alpha tACS over the somatosensory region a reduction in pain experience was present, both for perceived pain intensity and pain unpleasantness, but only when participants were uncertain about the intensity of an upcoming pain stimulus.

## Unpleasantness ratings

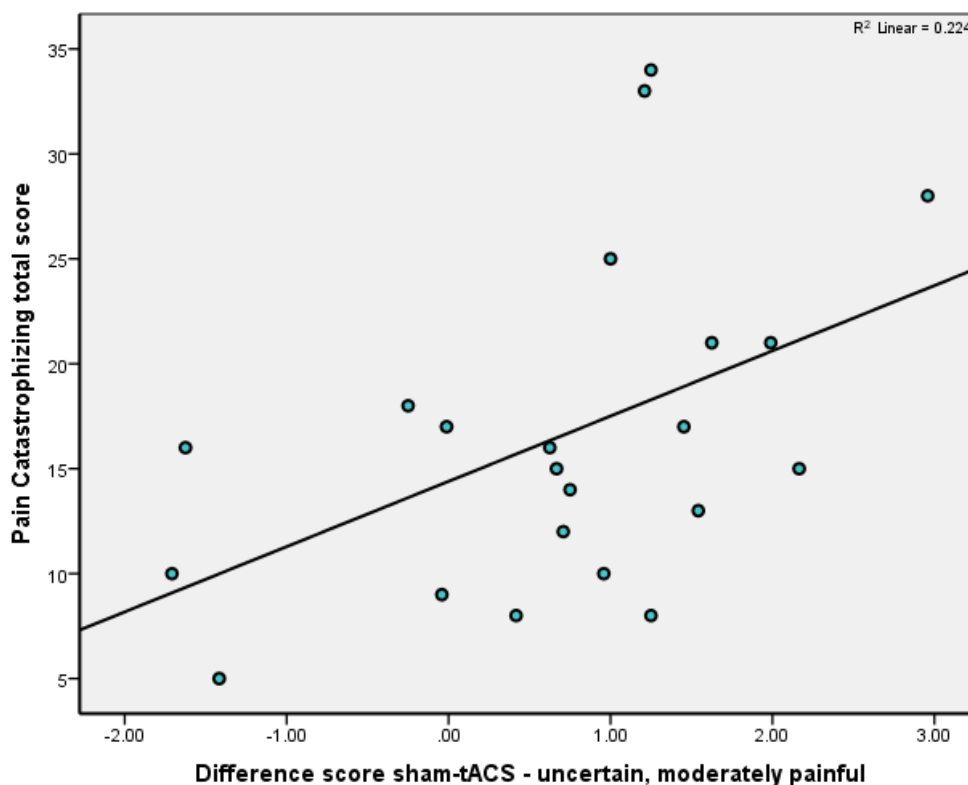


**Figure 6.7** Average unpleasantness rating scores and standard error of means (SEM) for the three pressure intensities, comparing alpha tACS and sham, for the certain (top) and uncertain (bottom) expectation condition separately. Significant outcomes for the post hoc t-tests comparing rating scores for tACS and sham, for each pressure intensity and each expectation condition (certain, uncertain), are marked (\*) for significant outcomes ( $p < .05$ ). Pain unpleasantness ratings were significantly lower during alpha tACS compared to sham stimulation for pain threshold and moderately painful stimuli, but only when pain intensity was uncertain.

### 6.3.2 The influence of fear of pain and pain catastrophising on the reduction of pain experience by alpha tACS

To investigate the relationship between fear of pain, pain catastrophising and the change in pain experience for alpha tACS, Pearson correlations were calculated between the FOP-SF and PCS total scores and the difference in intensity/unpleasantness rating for alpha tACS versus sham (rating sham – rating alpha tACS), for the moderately painful stimuli. A significant positive correlation was found between the difference in pain intensity rating and pain catastrophising when pain intensity was uncertain ( $r = .47$ ,  $p = .026$ ;  $N = 22$ ). However, this did not survive correction for multiple comparisons at a significance level of .0125 (Figure 6.8). No significant correlation was found between the difference in intensity rating and fear of pain when pain intensity was uncertain ( $r = -.19$ ,  $p = .45$ ;  $N = 19$ ). When pain intensity was certain, no significant correlation between the difference in intensity rating and pain catastrophising ( $r = -.42$ ,  $p = .055$ ;  $N = 22$ ) or fear of pain ( $r = .41$ ,  $p = .079$ ;  $N = 19$ ) was found.

For the change in unpleasantness rating, no significant correlations between the difference in unpleasantness rating and fear of pain/pain catastrophising were found. When pain intensity was uncertain, no significant correlation between the difference in unpleasantness rating and pain catastrophising ( $r = .34$ ,  $p = .13$ ;  $N = 22$ ) or fear of pain ( $r = -.25$ ,  $p = .30$ ;  $N = 19$ ) was found. When pain intensity was certain, no significant correlation between the difference in unpleasantness rating and pain catastrophising ( $r = -.31$ ,  $p = .16$ ;  $N = 22$ ) or fear of pain ( $r = .42$ ,  $p = .076$ ;  $N = 19$ ) was found either.



**Figure 6.8** Scatterplot illustration of the relationship between pain catastrophising and the difference in reported pain intensity for moderately painful pressure stimuli, comparing sham and alpha tACS (N =23). A significant positive correlation between pain catastrophising and the difference in perceived pain intensity (rating sham – rating alpha tACS) was found when pain intensity was uncertain. However, this did not survive correction for multiple comparisons.

## 6.4 Discussion

This study investigated the effects of alpha tACS, applied over somatosensory scalp regions, on the experience of pain. As hypothesised, a significant reduction of pain experience, as reflected by a reduction of both reported intensity and unpleasantness, was found for alpha tACS compared to sham stimulation. This reduction was present for painful pressure stimuli (pain threshold and moderately painful) but not non-painful pressure stimuli. However, a reduction in pain experience as a result of somatosensory alpha tACS took place only when participants were uncertain (and not when they were certain) about the intensity of an upcoming pressure stimulus. This study



is the first to demonstrate an effect of somatosensory alpha tACS on pain experience, particularly in a state of uncertain expectations about pain intensity. This finding suggests that interventions targeting somatosensory alpha activity may have potential to alter pain experience, but that cognitive-emotional states, such as uncertainty about pain, must also be taken into account.

#### **6.4.1 The influence of uncertainty on the effects of somatosensory alpha tACS**

In this study the modulation of ongoing somatosensory alpha activity using somatosensory alpha tACS led to a significant reduction in perceived pain experience. This in line with what was expected based on studies demonstrating a negative correlation between pre-stimulus somatosensory alpha activity and pain experience (Babiloni et al., 2006; Tu et al., 2016). As the present study found a relationship between alpha activity and pain experience by means of direct manipulation of somatosensory alpha activity (to increase alpha power), the findings provide some first indication of a causal relationship between alpha activity and pain experience. However, the effect of somatosensory alpha tACS on perceived pain was only detected when participants were uncertain about stimulus intensity, and not when upcoming stimulus intensity was known to participants. Furthermore, pain catastrophising was positively correlated with the reduction of perceived pain intensity as a result of alpha tACS. A larger reduction of pain by alpha tACS was related to higher levels of pain catastrophising. This suggests that alpha tACS applied over the somatosensory region might be particularly effective in reducing pain in individuals with a high pain catastrophising score.

The shortage of other studies on alpha tACS in the somatosensory domain makes it hard to come to any conclusive answer on why somatosensory alpha tACS was particularly effective in a state of uncertainty, or how the effects of alpha tACS are influenced by cognitive or emotional state in general. There are some studies that investigated the effects of alpha tACS in the visual domain, suggesting an influence of the endogenous neural state of

the stimulated neural network on the effectiveness of alpha tACS in increasing alpha power. To investigate the influence of levels of endogenous alpha power on the effect of alpha tACS applied over occipital (visual) cortex, tACS was applied when participants had their eyes open and when participants had their eyes closed, resulting in a condition of low and high endogenous alpha power in the occipital cortex, respectively. Neuling, Rach, and Herrmann (2013) found 20 minutes of alpha tACS applied over the occipital scalp region resulted in a significant offline increase of alpha power, but this was only the case when participants had their eyes open. So, the application of occipital alpha tACS only led to an offline increase of alpha power when endogenous alpha power in the occipital cortex was low. Ruhnau et al. (2016) demonstrated a similar interaction between occipital alpha tACS and the levels of endogenous alpha power in the occipital cortex, this time online (during tACS). They measured phase coherence between the alpha tACS signal and neural activity at alpha frequency, reflecting the extent of phase synchronisation between oscillatory neural activity and the tACS signal. They found significant phase synchronisation of occipital alpha activity with the alpha tACS, but again, only when endogenous alpha activity was low. These two studies in the visual domain (Neuling et al., 2013; Ruhnau et al., 2016) demonstrate that the effects of alpha tACS are not necessarily static, but depend on the levels of endogenous alpha activity of the targeted neural network as well.

Although the influence of a state of certain versus uncertain expectation cannot be directly compared to a state of high and low endogenous alpha power as a result of eyes open or close, it is possibility that uncertainty about pain intensity was related to a different level of somatosensory alpha activity in the somatosensory region (compared to when pain intensity was certain), as was also suggested by the findings of Study 1 (Chapter 4). Uncertainty about pain intensity is associated with a higher threat value, and enhanced capture of attention by pain (Crombez et al., 1998; Morley, 2008). Höfle, Pomper, Hauck, Engel, and Senkowski (2013) showed that the amount of threat perceived during the anticipation of pain affects pre-stimulus somatosensory alpha activity. Viewing a needle (threatening context) compared to viewing a cotton bud approaching the hand (non-threatening context) during the anticipation of

pain, resulted in a significantly stronger reduction of pre-stimulus somatosensory alpha activity. Thus, the findings of Höfle et al. (2013) suggest that uncertainty about pain intensity (also reflecting higher threat) might result in different endogenous alpha state. Further research on the different neural states related to certainty and uncertainty about pain intensity might lead to a better understanding of the how somatosensory alpha tACS affects pain experience.

#### **6.4.2 The application of alpha tACS in the somatosensory domain**

Apart from the value of this study with respect to the effects of somatosensory alpha tACS on pain experience specifically, this study also contributes to the more general field of alpha tACS. Most alpha tACS studies have focused on the effects on alpha activity and behavioural performance in the visual and motor domain. This study is a new addition, as it explored the potential of alpha tACS in the somatosensory domain. It is one of only a few studies to investigate the effects of alpha tACS applied over somatosensory scalp regions, besides being the first to assess the effects of somatosensory alpha tACS for pain experience in particular. It adds to the findings from Feurra, et al. (2011) and Gundlach et al. (2016) that suggested an effect of somatosensory alpha tACS on non-painful somatosensory perception. Feurra et al. (2011) investigated whether a tactile sensation could be induced by somatosensory tACS. They were able to induce a tactile sensation in the hand, far away from the stimulation electrodes placed over the right somatosensory cortex. Furthermore, the tactile sensation was specific to the location of the somatosensory tACS; a sensation was only reported in the left hand, contralateral to the tACS location. As somatosensory tACS was applied at a range of frequencies, this also allowed for the investigation of frequency-specificity of the effect. They demonstrated that the effects were frequency-dependent, where tactile sensations were perceived more strongly for some frequencies than others. Alpha tACS led to the strongest tactile sensations; they were significantly stronger than for delta, theta, and mid gamma tACS. However, there was no frequency-specificity for alpha frequency: although

alpha tACS led to stronger tactile sensations/was most effective, the tACS at alpha frequency was not the only frequency inducing tactile sensations. Although Feurra et al. (2011) were the first to show that somatosensory tACS at alpha frequency might be most effective in inducing a tactile sensation affecting somatosensory perception, they did not investigate whether somatosensory alpha tACS could modulate the perception of a tactile stimulus. Gundlach et al. (2016) did assess whether somatosensory alpha activity has an effect on the perception of a tactile stimulus. They measured if there was a change in tactile perception thresholds for near-threshold tactile stimulation. There was an increase in perception threshold during alpha tACS, participants were less sensitive to the near threshold tactile stimuli. However, this was only the case at a certain phase angle of the alpha tACS signal, and was not found when the perception thresholds were averaged over the 5-minute tACS period and compared to the average perception threshold over a 5-minute baseline (pre-tACS) period. There was also no difference in average perception for the 5-minute period immediately after alpha tACS. Thus, Gundlach et al. (2016) only found an online phase-dependent effect of somatosensory alpha tACS. No tonic effect of somatosensory alpha tACS was found during or after tACS; they did not demonstrate an overall increase in perception threshold. What they did demonstrate though, was that the phase-dependent effect of alpha tACS on tactile perception thresholds was specific to the somatosensory stimulation location. When the same experiment was repeated with alpha tACS applied over the occipital cortex (PO9 and PO10) no significant effects were found.

The present study is the first to demonstrate a tonic (not phase dependent) effect of somatosensory alpha tACS on the perception of somatosensory stimuli. A significant online reduction of perceived pain intensity and unpleasantness was found, averaged over the entire duration of the pressure pain task, compared to sham. However, similar to Gundlach et al. (2016), no overall change in perception was found for non-painful stimuli. A significant reduction was only found for the pain threshold and moderately painful stimuli. Thus, this indicates that the effect of somatosensory alpha tACS might be specific to the painful somatosensory domain. Furthermore, it

suggests that somatosensory alpha activity might be differently involved in the perception of painful and non-painful somatosensory stimuli.

### **6.4.3 Focality of the effects of somatosensory alpha tACS**

As the work on somatosensory alpha tACS in general is still in its infancy, and the present study is the first to focus on pain perception specifically, there are still many remaining questions to answer. There are limitations to what we can conclude based on the present findings. First, it is important to consider how far the changes in pain experience might be due only to the manipulation of alpha power in the somatosensory cortex. Although alpha tACS was applied on somatosensory scalp regions, we cannot be certain this only affected alpha power in the somatosensory cortex. It is likely that the alpha tACS affected more than one brain region (Cohen Kadosh, 2015). Thus, there is a possibility that the reduction of pain was due to an increase in alpha power in the somatosensory cortex and adjacent regions. However, for the practical application of somatosensory alpha tACS to reduce pain, a more widespread effect of somatosensory alpha tACS beyond the somatosensory cortex does not necessarily have to be a limitation. Pain experience does not emerge from activity in a single neural region, but is the result of processing in a widespread neural network (Melzack, 2001). Neural oscillatory activity, including alpha activity, is thought to support the communication within these functional neural networks (Basar et al., 1999; Fries, 2005). Battleday, Muller, Clayton, and Kadosh (2014) hypothesised that the effects of tACS on functions like pain experience, arising from distributed neural networks, might be due specifically to the more widespread effect of tACS. As tACS changes the oscillatory activity in one region, this could affect the communication of that region with its wider neural network, resulting in a change in effectiveness of information processing in the network. Thus, an effect of somatosensory alpha tACS beyond the somatosensory cortex may not have to be a limitation when we are concerned with achieving a reduction in pain, but instead might prove to be beneficial. However, especially as in the present study no EEG was recorded, a conclusion on the reduction of pain experience being the result of

an increase of alpha activity in the somatosensory region (only) remains tentative.

#### **6.4.4 Study evaluation and future directions**

A question that remains to be answered is why somatosensory alpha tACS during pain resulted in a reduction in pain experience in an uncertain setting, but not in a certain setting. Further investigation of why somatosensory alpha tACS is effective in some states/contexts but not others is warranted as this would allow for a better understanding of: 1) the relationship between somatosensory alpha activity and pain experience and possible mechanisms underpinning this relationship; and 2) what cognitive/emotional circumstances lead to the most optimal effectivity of somatosensory alpha tACS to reduce pain experience. This second point is particularly relevant when we consider the application of somatosensory alpha tACS to reduce pain experience in a clinical setting. Interventions that modify oscillatory neural activity, like somatosensory alpha tACS, are viewed by some as a promising approach in pain treatment (e.g., Jensen et al., 2008; Peng & Tang, 2016).

Another question to address, equally relevant for the clinical application of somatosensory alpha tACS, is the duration of a reduced experience of pain; in other words, is there an aftereffect for somatosensory alpha tACS and how long does this aftereffect remain? Although an effect of somatosensory alpha tACS was found during tACS, the present study did not measure pain experience after tACS offset, and therefore cannot answer this question. We do not know whether the same changes are present after tACS as during tACS, and for how long they might remain. Some indication that, in general, alpha tACS can lead to aftereffects can be found in studies that measured alpha power in the occipital regions after occipital alpha tACS. In the visual domain, an aftereffect of alpha tACS applied over occipital regions has been demonstrated when alpha tACS was applied for at least 10 minutes. A significant increase in alpha power remained present from at least 30 minutes (Neuling et al., 2013) up to 70 minutes after tACS offset (Kasten et al., 2016). Other studies have demonstrated aftereffects of alpha tACS on behaviour.

Wach et al. (2013) applied alpha tACS over the primary motor cortex and found a significant effect on motor performance in a fast finger tapping task, which developed over a period of 30 minutes after tACS offset. Müller, Vellage, Heinze, and Zaehle (2015) assessed the effect of alpha tACS in the visual domain. What is most interesting about this study is that it assessed performance on a set of visual search tasks after five days of alpha tACS stimulation on five consecutive days (20 minutes/day). They found a significant improvement on the visual conjunction search task in their group of elderly participants, two days after the last alpha tACS session. This study suggested that it might be possible to create a longer-lasting aftereffect of alpha tACS on perception by applying several sessions of alpha tACS.

Together these studies on the aftereffects of alpha tACS on alpha power and performance in the motor and visual domain suggested that it is possible to induce aftereffects, and that repeated tACS stimulation might result in aftereffects that remain present over several days. As no research is available yet investigating aftereffects of somatosensory alpha tACS, and whether a series of tACS sessions might increase the duration of aftereffects, this would be an important step towards further exploring the potential of somatosensory alpha tACS in a clinical pain setting.

Finally, this study assessed changes in behaviour as a result of somatosensory alpha tACS. We demonstrated an effect of alpha tACS on the experience of pain; a reduction in pain experience. An obvious next step would be to also assess changes in alpha power directly, by recording EEG. This would allow us to confirm whether somatosensory alpha power is increased comparing before and after alpha tACS, and whether there are differences in the effect of alpha tACS on somatosensory alpha power during a certain and uncertain setting. Ultimately this could lead to further confirmation of 1) a causal relationship between alpha activity and pain experience specifically; and 2) the tentative case for the effectiveness of alpha tACS applied over the somatosensory cortex in general.

### **6.4.5 Conclusions**

The present study demonstrated an effect of alpha tACS on pain experience for the first time. Alpha tACS, applied over the somatosensory scalp region, led to a significant reduction in pain experience compared to sham. This finding provides some indication of a causal relationship between alpha activity and pain experience. Furthermore, this study suggested an influence of cognitive-emotional state on the effectiveness of somatosensory alpha tACS, as a significant reduction of pain experience was only present when participants were uncertain about pain intensity (and not when pain intensity was certain). This suggests that interventions targeting somatosensory alpha activity may have the potential to reduce pain experience, but that a person's expectations about the intensity of pain must also be taken into account. Finally, as one of only a few studies investigating the effects of alpha tACS in the somatosensory domain, this study also contributes to the more general field of alpha tACS, expanding the application of alpha tACS from the visual and motor domain to the somatosensory domain.



## **Chapter 7** A pilot study to examine the effect of a mindfulness-based intervention on pre-stimulus somatosensory alpha activity and the experience of pain

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### **7.1 Introduction**

Evidence suggests that mindfulness meditation has beneficial effects on the experience of chronic pain (e.g. Brown & Jones, 2013; Grossman et al., 2007; Hilton et al., 2017; Kabat-Zinn, 1982) and experimental pain (Kingston, Chadwick, Meron, & Skinner, 2007; Zeidan et al., 2011; Zeidan, Gordon, Merchant, & Goolkasian, 2010). However, there is no clear understanding of the underlying mechanisms for these effects from a neurophysiological perspective, although a few studies point to possible explanations. For example, Kerr et al. (2011) found that, after an 8-week mindfulness-based intervention, pre-stimulus somatosensory alpha activity was modulated during the anticipation of non-painful somatosensory stimuli in intervention participants compared to controls. As a significant relationship between pre-stimulus somatosensory alpha activity and pain experience has been demonstrated (Babiloni et al., 2006; Tu et al., 2016), the effects of mindfulness meditation on the perception of painful somatosensory stimuli might also be explained through a modulation of pre-stimulus somatosensory alpha activity. However, to our knowledge, no study has yet investigated the effect of mindfulness meditation on somatosensory alpha activity during the anticipation of pain. This chapter outlines a study that examined whether pain experience is reduced

after an 8-week mindfulness-based intervention and whether this is accompanied by an increase of pre-stimulus somatosensory alpha activity, in an experimental pain setting. The chapter begins by explaining key principles of mindfulness before examining the extant literature on mindfulness and pain. It then sets out the aim and objectives of the study. The result section will address each of these individual objectives. Finally the chapter provides interpretation and discussion of the findings for each objective and an evaluation of the study.

### **7.1.1 Mindfulness and mindfulness meditation**

There are many definitions of mindfulness and different disciplines emphasise different aspects of mindfulness. Broadly, mindfulness is considered a state of consciousness that reflects a certain quality of awareness and attention to internal and external experiences (Bishop et al., 2004; Brown & Ryan, 2003; Kabat-zinn, 2003). Mindfulness meditation aims to build one's ability to be attentive and aware of the present moment. In mindfulness terms, awareness can pertain to thoughts, feelings, and/or sensations that are occurring for a person right now (i.e. present moment). Awareness of experience in the present moment is supported by sustained attention to the present. Mindfulness meditation not only promotes attentional capacity, but also attentional flexibility, permitting a shift of focus from one experience to the next (e.g. from a bodily sensation to an auditory stimulus), and from one moment to the next (Bishop et al., 2004; Brown et al., 2007).

Mindfulness meditation also promotes a certain *quality* of awareness and attention, namely acceptance and non-judgement: people try to be aware and attentive to the present experience without trying to interpret, evaluate, or ruminate on it (Bishop et al., 2004; Brown et al., 2007). Kabat-Zinn (1982) referred to this as “detached observation”, awareness from one moment to the next without becoming preoccupied with a certain thought or feeling. Shapiro, Carlson, Astin, and Freedman (2006) similarly stressed the importance of bringing a certain intention or attitude to the awareness of experiences. Mindfulness meditation tries to cultivate attitudes of openness, kindness, and

acceptance towards the thoughts, feelings, and sensations that arise, whether they are pleasant or unpleasant.

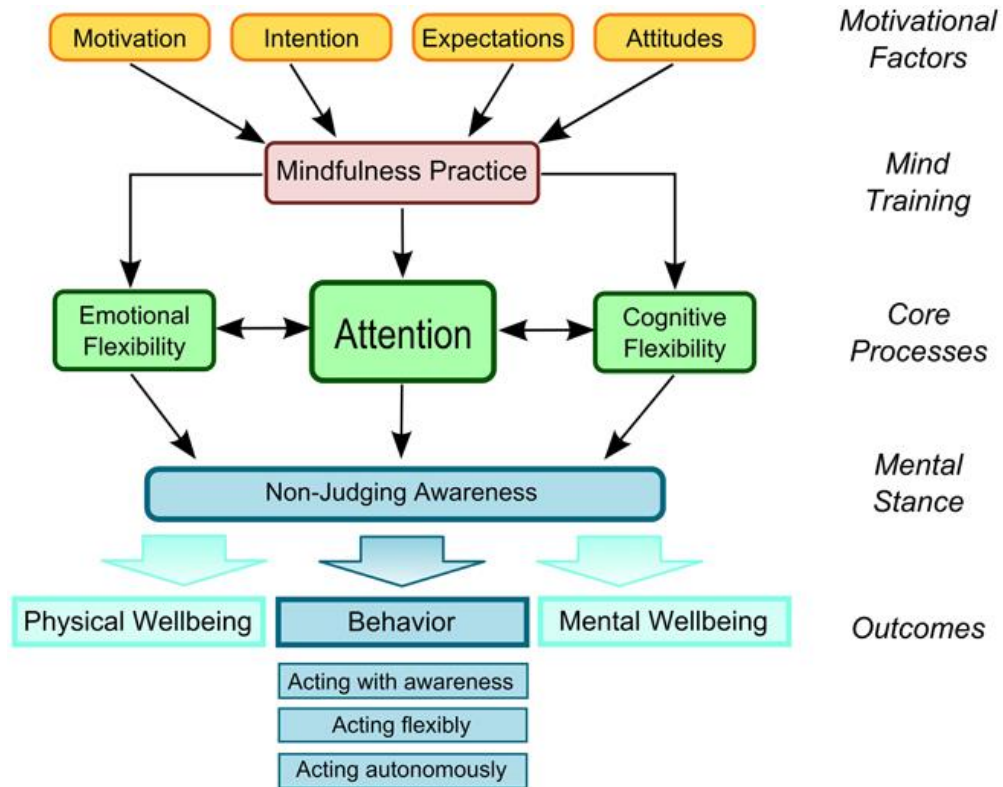
Mindfulness can be facilitated with regular and ongoing practice – often referred to as mindfulness meditation (Bishop et al., 2004; Brown & Ryan, 2003; Kabat-Zinn, 2003) – alongside everyday efforts to be mindful in day-to-day life. When people practice mindfulness meditation, they often do so by paying attention, with an attitude of curiosity and acceptance, to bodily sensations. These can include the breath, as well as other detectable sensations like temperature, comfort, tension and movements. Doing so, helps to train awareness, attention and acceptance of present moment experience – which in turn is thought to improve the regulation of responses to experience (Baer, 2003; Kabat-Zinn, 1982).

The beneficial effects of practicing mindfulness have been receiving increasing attention in medical and psychological research (Brown & Ryan, 2003) and have been linked to the improved regulation of emotions and attention associated with mindfulness meditation. Interventions have been developed that incorporate mindfulness, such as mindfulness-based stress reduction (MBSR) and mindfulness-based cognitive therapy (MBCT). Kabat-Zinn (1982) introduced the MBSR programme; an eight week programme that was originally designed to provide patients with chronic pain with a self-regulatory coping strategy. Meeting for two hours per week, the primary purpose of the MBSR programme was to help people become more mindful in relation to their chronic pain experience, and thereby relieve suffering (Kabat-Zinn, 2003). Attendees are encouraged to practice mindfulness meditation every day in their personal time as well. It offers a spectrum of meditation techniques, and it includes didactic education on the impact of stress on illness. The programme is delivered in a group format and is non-goal oriented, i.e., the emphasis is on experiencing the programme without striving to achieve a specific outcome in accordance with the mindful intention to simply be aware of present moment experience with an attitude of openness and acceptance. Finally, the programme emphasises personal responsibility, the development of coping strategies through mindfulness practice primarily relies on the

individual's sustained efforts to practice mindfulness (meditation) (Kabat-Zinn, 1982). Another popular mindfulness-based intervention is MBCT, a programme that was originally developed to prevent relapse in depression (Teasdale, Segal, & Williams, 1995; Teasdale et al., 2000). MBCT is an eight week group-based intervention that integrates aspects of cognitive-behavioural therapy (CBT) and the MBSR programme (Kabat-Zinn, 1982). The rationale for combining CBT and mindfulness meditation was that both encourage individuals to relate to their thoughts and feelings in a different manner, i.e., they both encourage a change in perspective. Mindfulness practice encourages non-judgmental awareness of depression-related thoughts and feelings and a more detached or decentred relationship with them; a depression-related thought or feeling is just another in the moment experience. Complementing this, the CBT component facilitates re-interpretation of thoughts and feelings as simply reflecting mental events and not necessarily a true reflection of reality and/or a reflection of the individual, it incorporates statements such as "thoughts are not facts" and "I am not my thoughts".

These interventions have been applied across a variety of conditions, including anxiety and depression, stress, and chronic pain (Baer, 2003) and have been found to improve a variety of mental and physical health-related outcomes (Goyal et al., 2014; Grossman, Tiefenthaler-Gilmer, Raysz, & Kesper, 2007; Khoury et al., 2013; Pascoe, Thompson, Jenkins, & Ski, 2017; Spijkerman, Pots, & Bohlmeijer, 2016). To conceptualise how mindfulness practice might result in improvements in a variety of health outcomes Malinowski (2013) provided a theoretical framework, the Liverpool Mindfulness Model (Figure 7.1). At the centre of this model is attention. Training of attention is a key component of mindfulness meditation practice; attention is often focused on a particular sensation in the body, for example the breath. Moreover, it practices attentional control functions. The ability to monitor and regulate attention is important in maintaining a focus of attention; the meditator learns to become aware when the mind has started to wander, to let go of a distracting thought as soon as it is noted, and to shift attention back to the original object of focus. Malinowski proposed that the training of attentional skills together with an enhancement of emotional and cognitive flexibility

(explained below) facilitates mindful, non-judgmental awareness of experience. This change in awareness and of the way of relating to experience is theorised to underpin the widely reported positive outcomes in both physical and mental wellbeing following sustained mindfulness meditation.



**Figure 7.1** The Liverpool Mindfulness Model (adapted from Malinowski, 2013). A theoretical framework describing the process of change related to mindfulness practice, with a central role for attention.

Non-judgmental awareness, a more objective observation of feelings and sensations, leads to a shift in perspective, a change in how people relate to their experiences (Brown et al., 2007; Shapiro et al., 2006). This change in perspective or re-interpretation is thought to promote self-regulation (Brown et al., 2007). Thoughts, feelings, and sensations are interpreted as just another observation, without attaching (negative) emotions, and evaluations, and without further elaboration or rumination. This might also lead to a reduction in

the emotional response to unpleasant sensations such as pain (Baer, 2003). Hölzel et al. (2011) also emphasised the importance of enhanced self-regulation in explaining the positive outcomes of mindfulness meditation. Mindfulness meditation is related to improved regulation of emotions, a reduction in emotional interference (Ortner, Kilner, & Zelazo, 2007), decreased emotional reactivity (Jain et al., 2007), and improved attention regulation (Jha, Krompinger, & Baime, 2007; Van Den Hurk, Gionmi, Gielen, Speckens, & Barendregt, 2010). Finally, practicing mindfulness has been suggested to change how people respond to experiences. Instead of getting caught up in the habitual cognitive and emotional response to an experience (the automatic attachment of ideas, labels, judgments), mindful awareness involves a conscious, more direct observation of experiences as they are, without assigning meaning and inevitable consequence (Brown et al., 2007). This is thought to facilitate a more conscious and flexible response to experience, involving conscious choice, instead of an automatic response (Shapiro et al., 2006).

To conclude, practicing mindfulness appears to promote a change in the way people relate to experiences, which both draws upon and improves emotion, cognitive and behavioural regulation. Attention has a key role in the manifestation of these changes (Malinowski, 2008).

### **7.1.2 Mindfulness-based interventions and pain**

With the potential of mindfulness practice to change how people relate to (bodily) sensations and to improve the regulation of emotion, cognition and attention in response to a sensation, the practice of mindfulness is of interest to the experience of pain. The experience of pain is an unpleasant sensory and emotional experience (IASP Taxonomy, 2011) that is influenced by factors such as cognitions, emotions, and our interpretation of pain (e.g., how much we catastrophise about pain) (Parr et al., 2012; Villemure et al., 2003; Wiech et al., 2008). Furthermore, attention plays an important role in the experience of pain. Pain automatically demands attention to interrupt ongoing behaviour and ensure a rapid response to the threat of injury imposed by pain (Legrain et al.,

2009; Morley, 2008). Moreover, top-down modulation of attention to pain affects pain experience. Perceived pain intensity and unpleasantness are enhanced when attention is directed towards a painful event (Miron et al., 1989). In contrast, when attention is directed away from the painful stimulus (e.g., by attending to another task) perceived pain is reduced (Tracey et al., 2002; Villemure et al., 2003).

Theoretically, there are a number of reasons why the practice of mindfulness meditation might influence the experience of pain. First, learning to perceive a pain as 'just' another observation of a sensation, without attaching negative thoughts and emotions could result in a more neutral interpretation of pain (Brown et al., 2007). Second, mindful awareness is accompanied by an attitude of curiosity, kindness, and acceptance (Bishop et al., 2004), and encourages self-compassion (Birnie, Speca, & Carlson, 2010). Relating to an unpleasant experience such as pain with kindness and acceptance might reduce the impact of such an experience; again, pain might be experienced as less threatening and less unpleasant (Birnie et al., 2010; Bishop et al., 2004). Importantly, improved sustained attention and attentional control as a result of mindfulness practice facilitates the regulation of attention, emotions, and cognitions towards pain (Hölzel et al., 2011; Malinowski, 2013).

Thus, mindfulness meditation might affect attentional processes related to pain and this in turn might modulate especially the emotional-affective dimension (emotion regulation, decreased negative affect) and cognitive dimension of pain experience (reduced pain catastrophising, increased pain acceptance) (Day, Jensen, Ehde, & Thorn, 2014; Malinowski, 2008). However, these are mostly theoretical explanations of how mindfulness meditation could affect pain experience. What is the evidence available to support these theoretical claims? Specifically, evidence to support an effect of mindfulness meditation on pain experience through a modulation of attention, and evidence for an effect of mindfulness meditation on the emotional-affective and cognitive dimension of pain experience particularly (and not necessarily the sensory-discriminative dimension). Some support is provided by studies that have assessed where in the brain neural changes take place during the anticipation

of pain and after pain onset following a mindfulness-based intervention. For instance, Brown and Jones (2013) investigated changes in neural activity and perceived pain after an 8-week mindfulness-based intervention in patients with chronic musculoskeletal pain. The intervention group demonstrated a significant improvement of perceived control over pain and mental health compared to the control group. However, there was no change in perceived pain for the experimental pain stimuli, only a reduction of the affective clinical pain scores was found in the intervention group. EEG was used to assess the anticipatory and pain-evoked response to the experimental pain stimuli. Both the anticipatory and pain-evoked potential were significantly reduced in the intervention group compared to the control group following the mindfulness-based intervention. Source analysis showed that during anticipation of pain activity in the right and left dorsolateral prefrontal cortex and the secondary somatosensory and posterior insula cortex was decreased to a lesser extent in the intervention group. In response to pain a significant difference between intervention- and control group was present in the amygdala and anterior insula. Where in the control group an increase of activity was found, the intervention group showed a nonsignificant decrease. Thus, for patients with chronic musculoskeletal pain taking part in an 8-week mindfulness-based intervention led to a change in the anticipatory and pain-evoked neural response, particularly in regions considered to reflect emotional-affective aspects of pain experience (amygdala and insula) and cognitive control (prefrontal cortex). This was accompanied by a change in affective pain ratings only. Another study by Brown and Jones (2010) compared the neural response (EEG) and pain experience for experimental pain stimuli in experienced meditators versus controls without any meditation experience. The meditators showed a reduced anticipatory response to pain compared to controls. Source analysis showed reduced activity in the midcingulate cortex and the right inferior parietal cortex. As suggested by the authors, the reduced activity in the midcingulate cortex and inferior parietal cortex might be related to cognitive control and attentional functions. Finally, Zeidan et al. (2011) assessed changes in perceived pain and neural activity (fMRI) after a four-day mindfulness meditation intervention. Along with significantly reduced perceived



pain intensity and unpleasantness, pain-related activity in the contralateral primary somatosensory cortex (S1) was reduced after the intervention. Applying regression analysis, they also found that the reduction in perceived pain intensity was associated with increased activity in the anterior cingulate cortex and anterior insula. Reductions in perceived pain unpleasantness were positively associated with activity in the orbitofrontal cortex and negatively associated with activity in the thalamus. Although a change in activity in S1 is mostly reflecting sensory-discriminative aspects of pain experience, pain-related activity in the anterior cingulate cortex, anterior insula, and frontal cortex that was associated with the reduction in perceived pain reflects affective-motivational and cognitive-attentional aspects of pain experience (Apkarian et al., 2005; Peyron et al., 2000; Treede, Kenshalo, Gracely, & Jones, 1999). Together these studies offer some evidence that a change in the processing of pain following the practice of mindfulness is mostly related to a change in activity in neural regions that are involved in cognitive-attentional and emotional-affective processing of pain.

When it comes to the effect of mindfulness meditation on chronic pain, again there is some evidence to suggest that mindfulness meditation has an effect on the emotional-affective and cognitive dimension of pain experience in particular. Evidence is less convincing for an effect on the sensory-discriminative dimension of pain, i.e., an effect on perceived pain intensity. Bawa et al. (2015) systematically reviewed the beneficial effects of mindfulness-based interventions (MBSR and MBCT) for a range of chronic pain conditions (fibromyalgia, rheumatoid arthritis, musculoskeletal pain, failed back surgery syndrome, and mixed aetiology). The majority of study participants were female, with an age range of 47 to 52 years. Chronic pain was defined as pain that persisted for at least 13 weeks. Based on the meta-analysis of 11 randomised controlled studies using MBSR or MBCT, they found a small non-significant effect of mindfulness-based interventions on perceived pain intensity, compared to controls (combined effect size based on 8 studies: 0.16). Other outcomes also failed to show a significant improvement, with a non-significant combined effect size of 0.16 for physical health-related quality of life and 0.37 for health-related quality of life (based on 4 studies), and 1.58 for pain

acceptance (based on 2 studies). The only outcome that demonstrated a significant combined effect was perceived pain control ( $p < .001$ ), with a combined effect size of 0.58 (based on 2 studies). Although these results are disappointing in relation to chronic pain outcomes, we should interpret these findings with some caution. Some outcomes were calculated on the basis of a small number of studies, in some cases only two.

Another systematic review and meta-analysis included a larger number of studies with a wider participant age range. Based on this larger number of studies an effect of mindfulness-based interventions on clinical pain intensity was found. Hilton et al. (2017) included 38 randomised controlled studies that investigated either MBSR, MBCT or another type of mindfulness meditation training (out of 38, 20 studies used MBSR and 6 used MBCT). A variety of chronic pain conditions were included; most commonly fibromyalgia or back pain (representing 8 studies each), but also osteoarthritis, rheumatoid arthritis, (migraine) headache, and irritable bowel syndrome. Participant ages ranged from 30 to 78 years, and eight of the included studies contained female participants only. Chronic pain was defined as pain that persisted for a minimum of three months. A significant but small effect on pain intensity was found compared to controls; this effect was not affected by type of mindfulness intervention. The mean percent change in perceived pain intensity for the meditation groups was -19%. The mean percent change for the control groups was -0.08%. Significant improvements were also found for depression, and both physical and mental health-related quality of life. Thus, two recent meta-analyses that assessed the effects of mindfulness-based interventions on chronic pain, only including randomised controlled studies, demonstrated some evidence for an improvement of outcomes related to emotional/cognitive aspects of pain (improved perceived control over pain and a reduction in depressive symptoms) and well-being (an improvement of physical and mental health-related quality of life), but less so for perceived pain intensity.

More consistent evidence for an effect of mindfulness meditation on perceived pain intensity (albeit based on a small number of studies) can be found in studies of experimental pain in otherwise pain-free participants, using

brief mindfulness interventions (rather than an 8-week mindfulness-based intervention). However, the duration of the intervention seems important to outcomes. Liu, Wang, Chang, Chen, and Si (2013) investigated the effect of a single 15-minute mindfulness practice using immersion of the hand in painfully cold water as a pain stimulus, in healthy pain-free volunteers. The effects were compared to a distraction control condition in which participants were instructed to direct attention away from feelings of discomfort by thinking about something relaxing or happy and a control condition in which participants rested and listened to light music. Pain tolerance was significantly increased comparing pre- and post-intervention for the mindfulness participants, but this was also the case for the distraction group. No significant reduction in pain ratings was found for any of the groups. Finally, only the mindfulness meditation group demonstrated a significant reduction in distress ratings. Thus, a single mindfulness meditation session did not result in any significantly larger reduction in pain compared to distraction from pain. Sharpe, Nicholson Perry, Rogers, Refshauge, and Nicholas (2013) also investigated the effect of a single 15-minute mindfulness meditation session on pain experience (for painfully cold water) in healthy volunteers, using a relaxation control condition. Again, no significant effect of mindfulness meditation on perceived pain was present compared to controls. Thus, a single session of mindfulness meditation does not seem to be sufficient to reduce pain. Pain was not further reduced for a single session of mindfulness meditation compared to distraction and relaxation control conditions. This suggests that mindfulness meditation might not have a unique effect on perceived pain for an experimental pain stimulus beyond a non-specific effect of distraction or relaxation.

A unique effect of mindfulness meditation on pain experience is present with higher doses of mindfulness though. Zeidan et al. (2010) investigated the effect of three group-based mindfulness meditation sessions (20 minutes each), delivered on 3 consecutive days. Participants also took part in a 13-minute mindfulness meditation practice just before receiving the electrical pain stimuli. The control conditions were relaxation or distraction (maths task). Compared to baseline, no reductions in pain ratings were found in the relaxation condition. A reduction in pain ratings was found in the distraction

condition for the high intensity pain stimuli. Only the mindfulness group showed significant reductions in pain ratings for low and high intensity pain stimuli, and a larger reduction in pain ratings than the distraction group. Thus, three mindfulness meditation sessions did result in reductions in perceived pain that could be distinguished from the non-specific effects of distraction and relaxation. The mindfulness meditation training was also related to a significant reduction in state anxiety. Zeidan et al. (2011) similarly found an effect on perceived pain after four days of group-based mindfulness meditation sessions (20 minutes each). Participants were also asked to meditate during the application of the painful stimuli. The control condition was an 'attention to breath' condition. A significant reduction in perceived pain intensity and unpleasantness was found when participants meditated during pain, compared to rest. No such reduction was found for the 'attention to breath' control condition. Finally, Kingston et al. (2007) investigated the effects of a 3-week mindfulness intervention on pain tolerance, perceived pain intensity, mood, blood pressure and heart rate. The intervention included 6 x 1 hour group sessions twice a week, and daily practice at home (using guided audio-recordings). The control group received two 1-hour group training sessions in guided visual imagery and also practiced daily at home. The mindfulness group, but not the controls, demonstrated a significant reduction in pain intensity and pain tolerance. No significant effects on mood, blood pressure, and heart rate were found. Thus, a significant effect of mindfulness meditation on perceived pain was found compared to a control condition that controlled for non-specific effects of relaxation.

To conclude, where one single session of mindfulness meditation seems insufficient to reduce pain, interventions that lasted for at least 3 or 4 days to a couple of weeks did show a reduction of pain tolerance, and pain intensity (and unpleasantness) ratings compared to a control condition. Finally, although a reduction in perceived pain for experimental pain stimuli was found in otherwise pain-free participants, the same might not be the case for participants with a chronic pain condition. One study examined the effects of an 8-week MBSR programme on the response to experimental pain stimuli in patients with chronic pain, compared to a treatment as usual control group (Brown & Jones,

2013). Participants rated pain unpleasantness on a 0-10 NRS. Although a significant improvement in mental health was found for the MBSR participants, which related to a greater perceived control of pain, no change in perceived unpleasantness was found for the experimental pain stimuli. Thus, the effects of mindfulness meditation might be different for participants that are otherwise pain-free than for participants with a chronic pain condition.

Considering the potential impact of mindfulness training duration, and the indication that a change in pain experience for experimental pain stimuli might be different for pain-free participants and participants with a chronic pain condition, in the present study, the effects of mindfulness meditation in an experimental pain setting were assessed for an 8-week MBSR training course. Moreover, pain experience was investigated in both pain-free participants and participants with a chronic pain condition.

### **7.1.3 Neural mechanisms underpinning the effects of mindfulness meditation**

There is still uncertainty about the effectiveness of mindfulness meditation to reduce pain. Moreover, the neurophysiological mechanisms that underpin the effects of mindfulness meditation on pain experience remain little understood. The present study aimed to further investigate whether a mindfulness-based intervention can reduce perceived pain and to gain a better understanding of the neurophysiological mechanism behind the potential effect of mindfulness meditation on pain. To achieve this, the present study focussed on pre-stimulus somatosensory alpha activity. Kerr et al. (2013) have proposed that somatosensory alpha activity could be an excellent mechanistic candidate for the effect of mindfulness-based interventions on somatosensory attention and perception. Alpha activity is involved in the guiding of processing of sensory information and is thought to reflect an attentional mechanism (Foxe & Snyder, 2011; Jensen & Mazaheri, 2010; Klimesch, 2012). The enhanced regulation of attention to bodily sensations by mindfulness-based interventions might therefore be linked to a modulation of somatosensory alpha activity. This

hypothesis was supported by a study investigating the effects of an 8-week MBSR programme on the modulation of pre-stimulus somatosensory alpha activity during the anticipation of a tactile stimulus (Kerr et al., 2011). Pre-stimulus somatosensory alpha activity in the primary somatosensory (S1) hand area (corresponding with the stimulated hand) was modulated by attention during the anticipation of a tactile stimulus: there was a difference in alpha power when participants directed their attention to the hand versus the foot. This modulation of alpha power in the S1 hand area by attention was significantly enhanced after the MBSR training; there was a larger differentiation in pre-stimulus somatosensory alpha power for attending to the hand or the foot. Thus, this study provided a first indication that pre-stimulus somatosensory alpha activity in preparation for a non-painful somatosensory stimulus might be altered after a MBSR intervention, likely reflecting a modulation of attention to somatosensory perception.

Pre-stimulus somatosensory alpha activity also guides the processing of painful stimuli involving an attentional mechanism; pre-stimulus somatosensory alpha has been found to be significantly reduced during the anticipation of pain (Babiloni et al., 2003) and modulated by top-down attention (Del Percio et al., 2006; May et al., 2012). Importantly, fluctuations in pre-stimulus somatosensory alpha activity have been associated with pain experience; higher pre-stimulus somatosensory alpha activity is associated with lower perceived pain intensity (Babiloni et al., 2006; Tu et al., 2016). Therefore, mindfulness meditation might affect pain experience through a modulation of pre-stimulus somatosensory alpha activity, reflecting a change in attention to pain. Specifically, a reduction in pain experience after completion of a MBSR intervention might be related to an increase of pre-stimulus somatosensory alpha activity.

There is only limited additional evidence on the effects of mindfulness meditation on alpha activity besides the study of Kerr et al. (2011). Moreover, none have examined pain perception or somatosensory alpha activity specifically. Bing-Canar et al. (2016) investigated the effect of mindfulness meditation on error-related alpha suppression using a Stroop task. They compared the effects of a single meditation practice (audio-recording) to a

control condition in which participants listened to an audio-recording with educational information about key concepts of mindfulness. EEG data was collected from 9 electrodes (F3, Fz, F4, C3, Cz, C4, P3, Pz, P4) and alpha power was assessed during the meditation practice and during the Stroop task. Alpha power during the mindfulness meditation practice was significantly increased compared to the control condition. This differentiation was most prominent at posterior electrodes. Furthermore, during the Stroop task, mindfulness participants demonstrated a more pronounced reduction of alpha power after an incorrect response (stronger error-related alpha suppression) than the control participants. These findings suggest an increase of alpha activity during mindfulness meditation and an enhanced response to errors after mindfulness meditation. Wong et al. (2015) compared oscillatory activity for experienced meditators (meditators that used any mindfulness meditation technique for at least 5 days a week for at least 5 years) to meditation-free controls. Magneto-encephalography (MEG) was recorded for 5 minutes when participants were resting with their eyes open and next while participants were meditating for 20 minutes. Experienced meditators used their usual technique and controls meditated used audio instructions. Average alpha power over the whole head was significantly higher in the experienced meditators compared to the controls, both during rest and during mindfulness meditation. Together, these two studies suggest that global alpha power (alpha power averaged over the whole head/scalp) might be increased as a result of mindfulness meditation (Bing-Canar et al., 2016; Wong et al., 2015).

To conclude, research indicates that mindfulness meditation may have a positive effect on pain experience via a modulation of attention, and it has been hypothesised that this effect could take place through a modulation of pre-stimulus somatosensory alpha activity (Kerr et al., 2013). Higher pre-stimulus somatosensory alpha activity has been related to lower perceived pain intensity (Babiloni et al., 2006; Tu et al., 2016); therefore mindfulness meditation might reduce perceived pain via an increase of pre-stimulus somatosensory alpha power. There is some initial but limited evidence that mindfulness meditation is

indeed related to an increase in alpha power (Bing-Canar et al., 2016; Wong et al., 2015). However, these studies did not address the influence of mindfulness meditation on somatosensory alpha activity and pain perception specifically. To our knowledge, there has been no direct investigation of somatosensory alpha activity in pain perception. Therefore, the present study examined the effects of mindfulness meditation on pre-stimulus somatosensory alpha activity and pain experience.

#### **7.1.4 Study objectives**

The aim of the present study was to investigate whether mindfulness meditation modulated both pre-stimulus somatosensory alpha activity and the experience of pain, for acute experimental pain. To investigate the effects of mindfulness meditation, participants took part in an 8-week MBSR programme and were compared to a group of control participants that did not take part in any training but simply attended two experimental sessions, before and after an 8-week period. Both pain-free participants and participants with chronic pain were included in the study. It was expected that the MBSR training might result in an increase of pre-stimulus somatosensory alpha activity during the anticipation of pain, followed by a reduction in pain experience.

To investigate changes in pain experience, both perceived pain intensity and unpleasantness were assessed, with the intensity scale reflective of sensory-discriminative aspects and the unpleasantness scale of affective aspects of pain experience. Although perceived pain intensity and unpleasantness are highly correlated (Turk et al., 1985) they can be differentially affected by experimental manipulations. For instance, Perlman et al. (2010) assessed the effects of two meditation practices (focussed attention and open monitoring) on pain experience in novice and long-term meditators. They found that for open monitoring meditation a significant reduction of perceived pain unpleasantness was present for long-term meditators compared to novices. However, no significant reduction in perceived pain intensity was found.



Mindfulness meditation might in particular affect the emotional-affective dimension of pain experience (Day et al., 2014) by improving the regulation of emotions and reducing the emotional response to pain (Brown et al., 2007; Hölzel et al., 2011; Malinowski, 2013). This suggests that mindfulness meditation might in particular reduce pain unpleasantness ratings. However, to date, there is little evidence to support this. Zeidan et al. (2011) who applied a brief, 4-day mindfulness meditation intervention found a significant reduction in both perceived pain intensity and unpleasantness when participants meditated during the application of experimental pain stimuli compared to rest. On average, perceived pain intensity as rated on a 15-cm visual analogue scale (VAS) was reduced by 40% (reductions ranged from 11-70%), perceived pain unpleasantness was reduced by 57% (reductions ranged from 20-93%). This suggests that perceived unpleasantness might be reduced to a larger extent than perceived pain intensity after a brief mindfulness meditation training. Unfortunately, the two other studies that found a reduction in pain experience for experimental pain stimuli (Kingston et al., 2007; Zeidan et al., 2010) only assessed perceived pain intensity, and thus did not provide any further insight. In the present study we assessed both perceived pain intensity and unpleasantness to explore if they were both reduced (to the same extent) after an 8-week MBSR training.

*Objective 1: To investigate whether an 8-week MBSR training course would increase pre-stimulus somatosensory alpha activity and reduce the experience of pain, for acute experimental pain in both healthy volunteers and those with a chronic pain condition.*

Next, as in the other studies of this thesis, it was investigated whether the effect of mindfulness meditation on pre-stimulus somatosensory alpha activity and pain experience was influenced by uncertainty about stimulus intensity. Acute pain serves as a warning signal that captures attention to promote an efficient response to the threat (Legrain et al., 2011). Uncertainty has an important influence on the capture of attention by pain. It is not just (anticipated) pain that captures attention, but particularly pain that is uncertain

or unpredictable, and more threatening (Morley, 2008). Moreover, uncertainty about pain intensity leads to higher perceived pain intensity (Lin et al., 2014; Ploghaus et al., 2001), and is related to higher reported anxiety (Ploghaus et al., 2001). Finally, there is also some evidence to suggest that uncertainty about pain intensity has an effect on pre-stimulus alpha activity (Franciotti et al., 2009).

Mindfulness meditation might reduce the emotional response to a painful sensation and improve the regulation of emotions and attention (Baer, 2003; Brown et al., 2007; Hölzel et al., 2011). With uncertainty about pain intensity associated with a stronger capture of attention and increased anxiety the effect of MBSR training on pain experience might be influenced by uncertainty, i.e., the modulation of pain experience after the MBSR training might be different in an uncertain setting related to higher threat, increased anxiety, and stronger capture of attention compared to a more predictable and less threatening setting when pain intensity is known. This will be explored in the present study.

*Objective 2: To explore the influence of uncertainty about pain intensity on somatosensory alpha activity and pain experience after MBSR training.*

The present study also explored whether after the MBSR intervention pre-stimulus somatosensory alpha activity was modulated differentially in the ipsilateral and contralateral somatosensory region with respect to the stimulated hand. Pre-stimulus somatosensory alpha power during the anticipation of pain tends to be lateralised: higher alpha power ipsilateral, lower alpha contralateral (Del Percio et al., 2006; May et al., 2012). Importantly, a relationship between pre-stimulus somatosensory alpha activity and perceived pain intensity seems present particularly in the contralateral somatosensory region. Babiloni et al. (2006) found a significant negative correlation between pre-stimulus somatosensory alpha activity and pain intensity ratings in the contralateral somatosensory region only. Thus, higher pre-stimulus alpha in the contralateral somatosensory region was associated with lower perceived pain intensity. More recently, Tu et al. (2016) also found evidence that higher pre-stimulus alpha activity in the somatosensory region was associated with lower

perceived pain intensity, this significant negative correlation was most prominent in the contralateral region (electrode location C4). There is no direct evidence for a lateralisation of the modulation of somatosensory alpha activity by mindfulness meditation, i.e., a different extent of change of somatosensory alpha power in the ipsi- and contralateral somatosensory region. It was decided that an exploration of a differential effect of mindfulness meditation on pre-stimulus somatosensory alpha activity ipsi- and contralateral was justified. Therefore, in this study, alpha power was calculated for two somatosensory regions; an ipsilateral and a contralateral somatosensory region.

*Objective 3: To explore whether an increase in pre-stimulus somatosensory alpha activity after the 8-week MBSR training was influenced by somatosensory region, i.e., if there was a difference comparing the ipsilateral and contralateral somatosensory region (with respect to the stimulated hand).*

There is also some limited evidence to suggest a relationship between alpha activity at rest and pain experience. Nir et al. (2012) found a significant negative correlation between resting-state alpha power and perceived pain intensity, with resting-state alpha activity measured 30 minutes before a 5-minute tonic painful heat stimulation; higher alpha during rest was associated with lower perceived pain intensity and vice versa. However, this relationship was not found for the somatosensory region specifically, but for electrode location T7 and T8 (bilateral temporal regions). Furthermore, placebo conditioning, inducing an expectation of pain relief, was shown to not only result in a reduction in pain ratings but also a significant increase of resting-state alpha activity (Huneke et al., 2013). However, again, this finding was not for somatosensory alpha activity specifically, but rather an increase of alpha power was indicated across the scalp. Alpha activity during the anticipation of non-painful somatosensory stimuli was modulated in the somatosensory region specifically after a MBSR intervention (Kerr et al., 2011). Therefore, the present study explored whether a change in resting-state alpha power over the somatosensory scalp region was present after the MBSR course as well.

*Objective 4: To assess whether there is an increase in resting-state somatosensory alpha activity after the 8-week MBSR training.*

Finally, as in the other studies of this thesis, the influence of two pain-related individual characteristics, fear of pain and pain catastrophising, on a change in pain experience (and pre-stimulus somatosensory alpha activity) after the MBSR training was assessed. Both fear of pain and pain catastrophising have been implicated as important factors in the development and maintenance of chronic pain, as part of the fear-avoidance model of chronic pain (Leeuw et al., 2007; Vlaeyen et al., 1995). Mindfulness meditation seems to be associated with various components of the fear-avoidance model of chronic pain, including pain-related fear and pain catastrophising. Schütze, Rees, Preece, and Schütze (2010) investigated the relationship of mindfulness meditation with the components of the fear-avoidance model (pain intensity, negative affect, pain catastrophising, pain-related fear, pain hypervigilance, and functional disability) in a group of 104 patients with a chronic pain condition. Mindfulness was assessed via the Mindful Attention Awareness Scale (MAAS) and the Five-Factor Mindfulness Questionnaire (FFMQ). Both pain catastrophising and pain-related fear were significantly negatively correlated with trait mindfulness (as measured with the MAAS) (pain-related fear and mindfulness:  $r = -.46$ ,  $p < .001$ ; pain catastrophising and mindfulness:  $r = -.49$ ,  $p < .001$ ). Regression analysis showed that all facets of mindfulness combined (as measured with the FFMQ) most strongly predicted pain catastrophising, with mindfulness accounting for 41% of variance in pain catastrophising ( $R^2 = .41$ ). In the present study it was assessed whether after the completion of an 8-week MBSR training course fear of pain and pain catastrophising might be decreased.

Finally, some studies have demonstrated that the effects of mindfulness meditation on pain might be influenced by pain catastrophising. Prins, Decuyper, and Van Damme (2014) measured pain ratings for experimental pain stimuli, before and after a 10-minute mindfulness meditation practice compared to a distraction control group. No significant main effect of group was

found for perceived pain intensity nor pain unpleasantness. However, when pain catastrophising was taken into account a change in pain unpleasantness was found in the mindfulness meditation group. Mindfulness meditation was associated with lower pain unpleasantness ratings than the control group, but only when dispositional pain catastrophising was high. Cho, Heiby, McCracken, Lee, and Moon (2010) found evidence that pain-related anxiety (as measured by the Pain Anxiety Symptoms Scale) mediated the effect of mindfulness on physical and psychosocial functioning in patients with chronic pain. Mindfulness was thought to reduce anxiety and fearful thoughts towards pain, and this in turn to result in the improvement of functioning. In the present study, it was also assessed if there was a relationship between fear of pain/pain catastrophising at baseline and the effect of the MBSR training on pain experience (and somatosensory alpha activity).

*Objective 5a: To assess if fear of pain and/or pain catastrophising were reduced after the MBSR training course.*

*Objective 5b: To assess if there was a relationship between fear of pain/pain catastrophising levels at baseline and the reduction in pain experience after the 8-week MBSR training course.*

## **7.2 Methods**

### **7.2.1 Participants**

This study was approved by the School of Psychology Research Ethics Committee, University of Leeds (reference number: 16-0180). All participants provided signed informed consent and completed a screening questionnaire to ensure safe application of EEG recordings and pressure pain.

Potential participants for the intervention group were identified in collaboration with the Staff Counselling and Psychological Service of the University of Leeds, who offer a free and voluntary 8-week MBSR course for staff. All those registered for the course, and those who attended a taster session, were invited to take part in the study (via email or flyer). Control

participants were also recruited, via the School of Psychology Subject Database, Leeds Psychology Research Email List and across the university campus using posters. Interested participants were asked to contact the researcher for study details. After reading the additional information and given the chance to ask questions, they were contacted via email to schedule an appointment for the first session.

The intervention group included four female right-handed participants with a mean age of  $46.75 \pm 6.70$  years (range 38-52 years). The control group also included four female right-handed participants; they had a mean age of  $37.25 \pm 8.50$  years (range 29-49 years). All participants completed a screening questionnaire before taking part, to ensure safe and ethical application of EEG recordings and pressure pain. All participants (of the intervention and the control group) met the inclusion criteria of being/having: aged 18 or older, no brain injury that required hospital treatment or brain surgery, no neurological conditions, not using any neurological/psychotropic medication, and no skin conditions and/or wounds on the scalp and the skin of the stimulated finger. Both participants that were pain-free at the time of measurement and participants with a chronic pain condition were included in the study. Participants with a chronic pain condition were asked to provide further information on their condition (which chronic pain condition they have and for how long) and to rate on an 11-point numeric rating scale (NRS) from 0-10: 1) pain at the present time; 2) intensity of worse pain in the last 6 months ('pain as bad as it could be'); and 3) average intensity of pain in the last 6 months ('usual pain') (Table 7.1).

**Table 7.1** Demographic details of the intervention participants (M01-M04) and control participants (C05-C08).

ID	Gender	Age	Chronic pain	Present pain (0-10 NRS <sup>a</sup> )	Worst pain (0-10 NRS)	Average pain (0-10 NRS)	
M01	Female	52	No				
M02	Female	45	No				
M03	Female	38	Yes	1	8	5	Neck and upper back pain (> 10 years)
M04	Female	52	Yes	7	8	6	Fibromyalgia (>20 years)
C05	Female	37	No				
C06	Female	34	No				
C07	Female	49	Yes	2	8	8	Lower back pain (> 18 years)
C08	Female	29	No				

<sup>a</sup> Participants with a chronic pain condition were asked to rate their pain on an 11-point numeric rating scale (NRS) from 0-10

### 7.2.2 Data collection

To assess changes in pain experience and somatosensory alpha activity in relation to an 8-week MBSR programme, participants in the intervention group took part in two sessions: at Time 1, scheduled within a 10-day period before the start of the programme; and Time 2, scheduled within a 10-day period after completion of the programme. The same procedure was followed at Time 1 and Time 2:

- At the start of the session resting-state EEG was recorded.
- The experimental task at Time 1 and Time 2 was carried out to assess pre-stimulus somatosensory alpha activity and pain experience in response to pressure pain stimuli.
- At the end of the session the following set of questionnaires was completed: the fear of pain questionnaire – short form (FoP-SF; McNeil

& Rainwater, 1998), the pain catastrophising scale (PCS; Sullivan, Bishop, & Pivik, 1995), and the Comprehensive Inventory of Mindfulness Experiences (CHIME; Bergomi, Tschacher, & Kupper, 2013).

In addition, only at Time 2 the intervention participants also took part in a 10-minute mindfulness-meditation practice during the post-MBSR session to induce a mindful state before the onset of the experimental task. For this purpose participants meditated whilst being guided by an audio-recorded mindfulness meditation practice that was also used during the MBSR training course, the 'Body and Breath' practice. Also, at Time 2 resting-state EEG was recorded not only at the start of the session before the meditation practice, but also a second time directly after the meditation practice. Finally at Time 2, one additional questionnaire was added to the set of questionnaires: the Toronto Mindfulness Scale (TMS; Lau et al., 2006).

To rule out that any changes in somatosensory alpha activity and pain experience found after the completion of the MBSR programme were a reflection of non-specific effects related to the passage of time and repetition of the task, a group of control participants was added that did not take part in the MBSR programme. The control participants also took part in two experimental sessions with 8 weeks in between sessions: at Time 1, within a 10-day period before the 8-week period; and at Time 2, within a 10-day period after the 8-week period. The control participants largely underwent the same procedure at Time 1 and Time 2 as the intervention participants, with a few exceptions: the control participants did not take part in a mindfulness meditation practice at Time 2, and they did not complete the TMS at Time 2.

### **7.2.3 The mindfulness-based intervention**

The intervention group took part in an MBSR programme originally developed by Kabat-Zinn (1982) and adapted for the workplace by the Staff Counselling and Psychological Service of the University of Leeds. The aim of the programme is to support management of work stress and to increase mental balance and effectiveness at work. The programme was delivered in a



group format, offering a spectrum of meditation techniques, and didactic material on the impact of stress on illness. It was adapted and led by an experienced psychotherapist and mindfulness practitioner. The programme ran for 8-weeks (1 x 2 hr session per week). Home mindfulness meditation was encouraged and audio-recorded practices were provided to support this. The formal mindfulness meditation practices included in this training course included body scan meditation, various sitting meditations, gentle movement and body awareness exercises. Two other components were shared enquiry (group discussion into the experiences with the practices) and theoretical input (on mindfulness, and a mindful approach to living and working and the pressures of life and work).

#### **7.2.4 Pressure stimuli**

Pressure stimuli were used following the same procedure as in the other three studies of this PhD thesis (Chapter 4-6), as explained in detail in Chapter 4 (p. 75). Pressure stimuli were applied at three different intensities: non-painful, pain threshold, and moderately painful. The average pressure (Mean (SD)) applied at Time 1 (N = 8) was 0.26 (0.05)V for the non-painful stimuli, 0.39 (0.09)V for the pain threshold stimuli; and 0.53 (0.09)V for the moderately painful stimuli. The average pressure applied at Time 2 was 0.23 (0.06)V for the non-painful stimuli, 0.35 (0.09)V for the pain threshold stimuli; and 0.47 (0.09)V for the moderately painful stimuli.

#### **7.2.5 Visual cues**

To manipulate uncertainty, i.e. to create a condition where pain intensity was uncertain and a condition where pain intensity was known/certain, each pressure stimulus was preceded by a visual cue, following the same procedure as in the other three studies of this PhD thesis, as explained in detail in Chapter 4 (p. 76).

### 7.2.6 Numeric rating scales (NRSs)

To quantify subjective pain experience, participants received two 11-point numerical rating scales (NRSs) on the computer screen after each stimulation (ranging from 0-10) to measure perceived intensity and unpleasantness (0 = not at all intense/unpleasant, 10 = extremely intense/unpleasant). They were asked to rate these scales by typing a number using the keyboard.

### 7.2.7 EEG recordings

EEG was recorded at rest and during the experimental task using a 64-channel BioSemi ActiveTwo System (BioSemi B.V., Amsterdam, the Netherlands) according to the standard 10-20 system. Four additional electrodes were placed to record eye movement and blinks (horizontal electrooculogram (EOG): 2 electrodes placed at the outside of the left and right eye; vertical EOG: 2 electrodes placed above and below the left eye). A sampling rate of 1000Hz and a low-pass filter (200Hz) was used.

### 7.2.8 Questionnaires

Both at time 1 and time 2 all participants were asked to complete: the FPQ-SF (McNeil & Rainwater, 1998); the PCS (Sullivan et al., 1995); and the CHIME (Bergomi et al., 2013 see below for details). In addition, the TMS (Lau et al., 2006) was also completed by the intervention participants only, at Time 2 (see below for details). A detailed description of the FPQ-SF and PCS can be found in the methodology chapter (Chapter 3, p. 64).

The CHIME was developed by Bergomi et al. (2013) for the assessment of mindfulness as a quasi-trait in the general population. Based on factor analysis for a sample of participants mostly untrained in mindfulness, they found that the scale reflects the four factors of mindfulness: 1) present awareness; 2) accepting, non-reactive, and insightful orientation; 3) open, non-avoidant orientation; and 4) describing of experiences. The scale contains 37

items, for example “when my mood changes, I notice it right away” and “when I am sitting or lying, I perceive the sensations in my body“, with answer options ranging from 1 (almost never) and 6 (almost always). The total score on the scale ranges from 37-222, with a higher total score reflecting higher mindfulness.

The Toronto Mindfulness Scale (TMS) (Lau et al., 2006) was also completed by intervention participants only to assess the extent to which participants achieved a mindful state as a result of doing the 10-minute mindfulness meditation practice. The TMS was developed by Lau et al. (2006) to measure the capacity to evoke a mindfulness state. They found a two-factor structure for the scale, with the factors curiosity and decentring. Participants are asked to report on what they have just experienced by indicating to what extent they have experienced the statement in each item: “Please indicate the extent to which you agree with each statement. In other words, how well does the statement describe what you just experienced, just now?” Examples of items are: “I experienced myself as separate from my changing thoughts” and “I was receptive to observing unpleasant thoughts and feelings without interfering with them”. The scale contains 13 items, with answer options ranging from 0 (not at all) to 4 (very much). The total score on the scale ranges from 0-52, with a higher total score reflecting a stronger evoked mindful state.

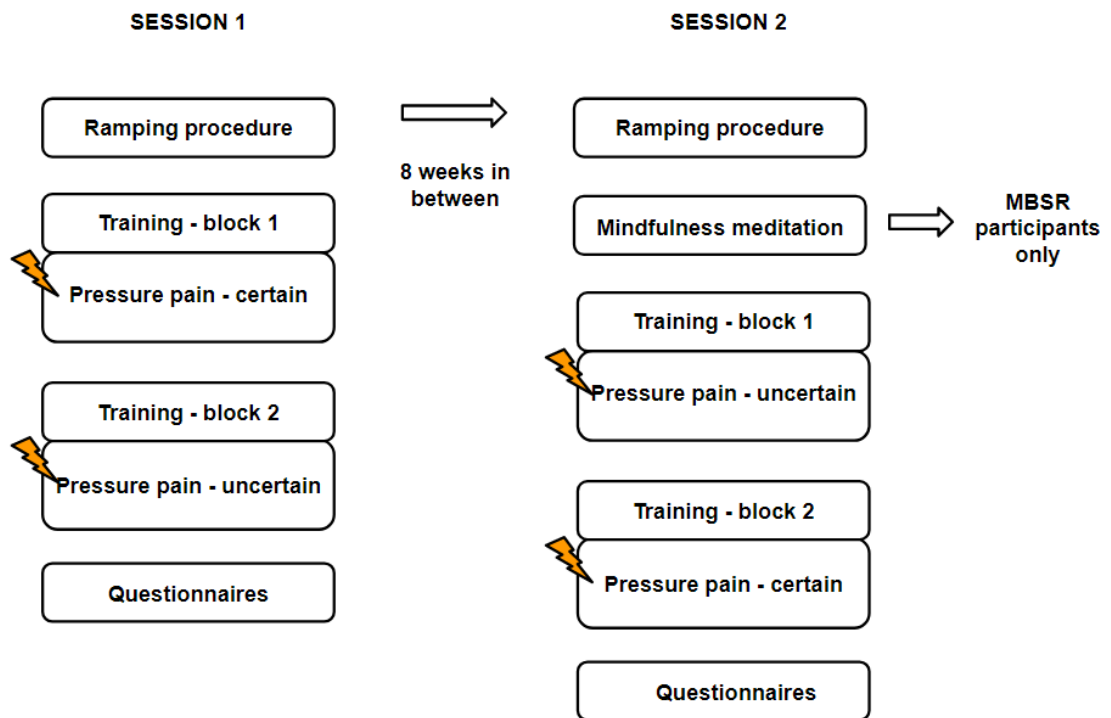
### **7.2.9 Study design**

The present study used a 2x2x2x3 mixed design with the between-subject factor group (MBSR, control) and the within-subject factors: time (Time 1, Time 2), expectation (certain, uncertain) and pressure stimulus intensity (non-painful, pain threshold, moderately painful). To assess pain experience, intensity ratings and unpleasantness ratings were used.

### **7.2.10 Experimental procedure**

Both intervention and control participants attended two experimental sessions. Total duration of the session at Time 1 was about 2 hours and about

2 hours and 15 minutes at Time 2. The general procedure was largely the same at Time 1 and Time 2 and for intervention and control participants (Figure 7.2). First the ramping procedure was carried out to identify the three individual pressure stimulus intensities. Next, after the EEG preparation, resting-state EEG was recorded. Only at Time 2, and only in the intervention group, participants then completed the 10-minute mindfulness meditation practice, followed by a second resting-state EEG recording. Next, the experimental task was carried out. The experimental task included two separate blocks, one block where stimulus intensity was known/certain and one block where stimulus intensity was uncertain. Each block contained 72 trials (24 trials for each of the three pressure stimulus intensities). Every trial started with the presentation of a fixation cross (with a jittered duration of 750-1000ms) followed by a visual cue (with a jittered duration of 2000-2750ms) and finally a pressure stimulation at one of the three intensities (non-painful, pain threshold, and moderately painful). After each pressure stimulus, participants rated perceived pain intensity and pain unpleasantness using two 11-point NRSs. Participants received regular short breaks throughout the experiment. All participants started with the certain condition in one session and the uncertain condition in the other session. The order of the two conditions was counterbalanced between participants: half of the participants started with the block with the certain condition at Time 1 and with the uncertain condition at Time 2. The other half of the participants started with the block of the uncertain condition at Time 1 and with the certain condition at Time 2. Each block was preceded by a short practice to familiarise the participant with the task and the function of the visual cues. Total duration of the experimental task was variable, depending on the time individual participants took to rate intensity and unpleasantness and duration of breaks, but was between 15 to 20 minutes for each block, adding up to 30-40 minutes in total.



**Figure 7.2** Overview of experimental procedure. The study contained two sessions at Time 1 (before an 8-week period) and Time 2 (after the 8-week period). Intervention participants took part in a MBSR training during the 8-week period, control participants did not take part in any training during the 8-week period. At Time 1 and Time 2 participants carried out the same experimental task containing two blocks. One block for the certain condition and one block for the uncertain condition. All participants started with the certain condition in one session and the uncertain condition in the other session. Furthermore, half of the participants started with the certain condition at Time 1 and the uncertain condition in Time 2, the other half started with the uncertain condition in session 1.

### 7.2.11 EEG analysis

For the pre-processing, artifact rejection, and frequency analysis of the EEG data largely the same procedure was applied as in the first study of this thesis (Chapter 4). The EEG data was analysed using Matlab version R2014a (Mathworks, Natick, MA, USA).

Nir et al. (2012) who identified a significant negative relationship between resting-state alpha activity and perceived pain, found this for resting-state EEG that was recorded during rest when participants had their eyes

closed. In the present study it was similarly decided to use the 1-minute resting-state recordings when participants had their eyes closed for further analysis. All pre-processing and artifact detection steps were carried out using the Matlab toolbox EEGLAB (Delorme & Makeig, 2004). For both the experimental EEG data and the resting-state EEG data, the continuous data was down-sampled (500 Hz), re-referenced to an average-reference (all electrodes minus the two mastoid electrodes and the vertical and horizontal EOG), and high-pass filtered (cut-off frequency 0.1Hz, Hamming window FIR filter). Next, epochs were extracted from the continuous recordings. For the experimental EEG data epochs of -2.75 to 2s were extracted with respect to pressure stimulus onset. For the resting-state EEG data the 1-minute recordings were segmented into 1-second epochs. Finally, a low-pass filter was applied (cut-off frequency 40Hz, Hamming window FIR filter).

For the artifact correction of the experimental EEG data Independent Component Analysis (ICA) was carried out. First epochs were visually checked to remove trials with large steps or spikes, and other abnormalities not related to blinks, eye-movements and muscle activity. Epochs containing blinks, eye-movements and muscle activity were kept at this point. Next the ICA procedure was started using the Runica function in EEGLAB. Principle components analysis (PCA) was applied before carrying out the ICA, as a data reduction technique to reduce dimensionality of the high-dimensional EEG data. Components reflecting artifactual sources were removed and the EEG data was reconstructed from the remaining components. Each experimental EEG dataset originally contained 72 trials. On average 69.31 trials remained after artifact correction. On average 2.03 components were removed.

For the resting-state EEG data visual artifact rejection was applied only to reject trials with artifacts, as for the 1-minute recording with participants having their eyes closed relatively few (eye) artifacts were present. On average 1.76 1-second trials were rejected per recording.

To calculate the power of alpha activity the Matlab toolbox Fieldtrip (Oostenveld et al., 2011) was used. Power estimates were calculated for frequencies between 2 and 30Hz. The convolution method was applied, using a

single Hanning taper. An adaptive sliding time window, with 4 cycles for each frequency length with 25ms time steps was used. For the pre-stimulus EEG data the following data was extracted: average alpha-band power (8-12Hz) for two regions of interest; an ipsilateral and contralateral S1 region with respect to the stimulated hand that was based on the average of electrode C3, C5, CP3, and CP5 (ipsilateral) and electrode C4, C6, CP4, CP6 (contralateral). Alpha power for these two somatosensory regions was averaged over the time window of -1 to 0s before pain onset. This particular time window was selected as it corresponds with the pre-stimulus time window of the studies that have so far identified a significant relationship between pre-stimulus somatosensory alpha activity and pain experience. Tu et al. (2016) found a significant negative relationship in a brief period directly before pain onset (-0.221 to -0.031s). Babiloni et al. (2006) found a significant negative relationship not directly before pain onset but from -1.0 to -0.5s before pain onset. Finally, in the first study of the thesis (Chapter 4) a marginally significant positive correlation between somatosensory alpha activity and perceived pain intensity was only shown during the time window of -1 to 0s before pain onset, not the -2 to -1s time window.

For the resting-state EEG data average alpha-band power (8-12Hz) was extracted for the same two somatosensory regions. Average somatosensory alpha power was calculated for each region and overall 1-second epochs per recording, resulting in one average somatosensory alpha power outcome ipsi- and one contralateral per resting-state recording.

### **7.2.12 Data analysis and interpretation**

Due to a small sample size, analyses were conducted at an individual level to assess changes in perceived pain and somatosensory alpha activity after the MBSR training course. For each individual, the difference in intensity/unpleasantness rating and alpha power was calculated for Time 1 versus Time 2 (score Time 2 – score Time 1). Furthermore, a percentage change score was calculated, using the following calculation: (score Time 2 – score Time 1) / score Time 1.

To interpret the percentage change outcomes, some guidelines with respect to pain ratings have been proposed. Farrar, Young, Lamoreaux, Werth, and Poole (2001) compared the change in pain intensity rating on a 11-point NRS to what patients reported verbally as their global impression of change (choosing one of 7 labels: very much improved, much improved, minimally improved, no change, minimally worse, much worse, or very much worse). A large group of patients with a variety of chronic pain conditions that took part in a series of clinical trials to assess pregabalin treatment for chronic pain was included in the study. Changes in pain intensity ratings from baseline to the end of treatment were compared to the 'global impression of change' label for each participant. The labels 'much improved' and 'very much improved', together representing a clinically important reduction in pain, were reflected by at least a -30% change in pain intensity ratings compared to baseline. This relationship between labels and rating scores was consistent across the different clinical trials included and regardless of the baseline level of pain.

Further recommendations on the importance of a change in perceived pain come from the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) consensus statement (Dworkin et al., 2008). The IMMPACT suggested that a percentage change of around 15-20% represents a 'minimally important' change, corresponding with the verbal label 'slightly better'. A change of around 30-36% was recommended as representing a clinically meaningful improvement, corresponding with the verbal labels 'much better' and 'much improved'. Finally, a percentage change of 50% was recommended as representing a substantial improvement, corresponding with the verbal label 'very much improved' and 'treatment success'.

In the present study, the recommendations in the IMMPACT statement with respect to clinical importance (Dworkin et al., 2008) were applied. First, with regards to the recommendation of a 15 to 20% change to identify a minimally important change (corresponding with a label of 'slightly better'); in the present study we decided to use > 17.5% change as a cut-off to identify a minimal important change in perceived pain. Furthermore, to identify a clinically meaningful improvement a cut-off of > 30% change was used.



### 7.3 Results

Due to a small sample size the results will describe changes in perceived pain and somatosensory alpha activity after the MBSR training at an individual level. Five sections will address the five objectives as stated in the introduction. The first objective “*To investigate whether an 8-week MBSR training course would increase pre-stimulus somatosensory alpha activity and reduce the experience of pain, for acute experimental pain in both healthy volunteers and those with a chronic pain condition*” will be answered first by focussing on the outcomes when pain intensity was known. These outcomes will then be compared to the outcomes when pain intensity was uncertain in the next section, relating to the objective “*To explore the influence of uncertainty about pain intensity on somatosensory alpha activity and pain experience after MBSR training*”. This will be followed by three sections addressing objective 3-5. Finally, a section describing the findings of two mindfulness measures (TMS and CHIME) will be provided.

*Objective 1: To investigate whether an 8-week MBSR training course would increase pre-stimulus somatosensory alpha activity and reduce the experience of pain, for acute experimental pain in both healthy volunteers and those with a chronic pain condition.*

When pain intensity was certain, three out of four intervention participants demonstrated a reduction in both reported pain intensity and unpleasantness at Time 2 (Table 7.2). Participant M01, M03, and M04 all demonstrated a reduction in perceived pain intensity and unpleasantness for both the pain threshold and moderately painful stimuli. The reduction in pain intensity ratings (both pain threshold and moderately painful) ranged from 6-53% change, the reduction in unpleasantness ratings (both pain threshold and moderately painful) ranged from 28-100% change.

Pain experience was assessed in both pain-free participants and participants with a chronic pain condition. Of the three intervention participants that demonstrated a reduction in perceived pain intensity and unpleasantness, two participants (M03 and M04) had a chronic pain condition. Thus, perceived pain was reduced at Time 2 for both participants with a chronic pain condition and pain-free participants.

**Table 7.2** Intensity and unpleasantness ratings for the four intervention participants (M01-M04) when stimulus intensity was certain. The table displays the average intensity rating and unpleasantness rating for each of the three pressure stimulus intensities at Time 1 and Time 2, the change in rating score at Time 2 (score Time 2 – Time 1) and the percentage change at Time 2 ((score Time 2 – score Time 1) / score Time 1). Three out of four intervention participants (M01, M03, and M04) demonstrated a reduction in both reported pain intensity (ranging from 6-53% change) and pain unpleasantness (ranging from 28-100% change) at Time 2, for the pain threshold and moderately painful stimuli.

ID	Intensity ratings (score time 1; score time 2; difference time 2 - time 1; % change)			Unpleasantness ratings (score time 1; score time 2; difference time 2 - time 1; % change)		
	Non-painful	Pain threshold	Moderately painful	Non-painful	Pain threshold	Moderately painful
M01	0.25; 0.08; -0.17; -67%	2.42; 1.46; -0.96; -40%	7.50; 5.63; -1.88; -25%	0.04; 0.00; -0.04; -100%	0.33; 0.00; -0.33; -100%	6.04; 3.92; -2.13; -35%
M02	0.00; 0.00; 0.00; 0%	2.09; 2.83; 0.75; 36%	7.00; 8.25; 1.25; 18%	0.00; 0.00; 0.00; 0%	0.00; 0.21; 0.21; -	3.17; 6.21; 3.04; 96%
M03	0.87; 0.17; -0.70; -80%	3.74; 1.75; -1.99; -53%	5.75; 4.46; -1.29; -22%	0.83; 0.08; -0.75; -90%	3.71; 1.75; -1.96; -53%	5.75; 4.13; -1.63; -28%
M04	0.67; 0.88; 0.21; 31%	2.88; 2.71; -0.17; -6%	6.92; 5.92; -1.00; -14%	1.04; 0.25; -0.79; -76%	3.04; 2.17; -0.88; -29%	7.08; 5.13; -1.96; -28%

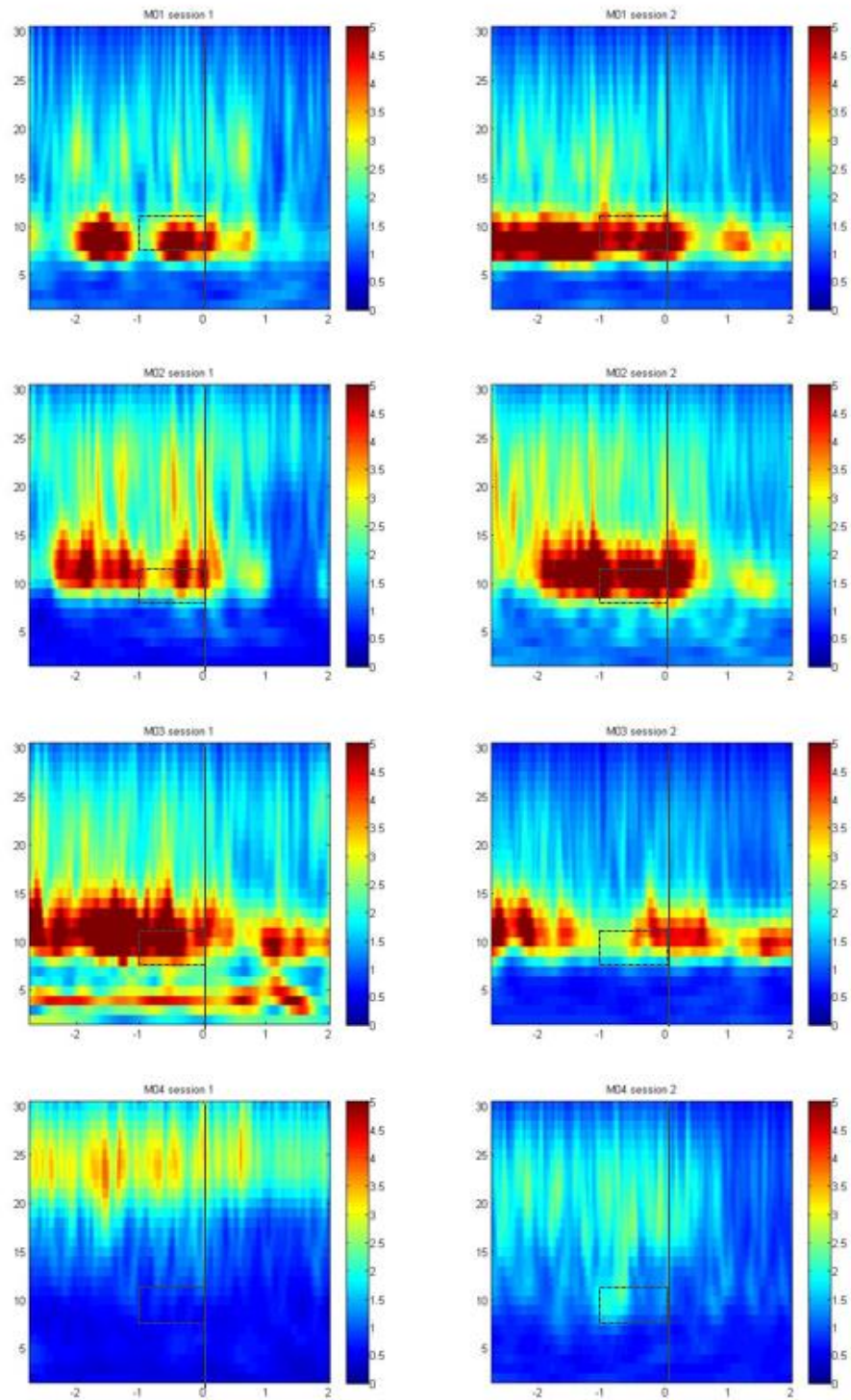
When pain intensity was certain, three intervention participants (M01, M02, M04) demonstrated a consistent increase of pre-stimulus somatosensory alpha power in the period of -1 to 0s before pain onset (Table 7.3; Figure 7.3). At Time 2 pre-stimulus alpha was increased in both in the ipsilateral and contralateral somatosensory region and for pain threshold and moderately painful stimuli. The increase in alpha power ranged from 5-168% change in the ipsilateral region, and from 30-99% change in the contralateral region.

Intervention participant M01 and M04 showed a reduction of perceived pain that was accompanied by an increase of pre-stimulus somatosensory alpha activity at Time 2. Participant M02, who also showed a consistent increase of pre-stimulus somatosensory alpha power, did not show a post-intervention reduction in reported pain intensity and unpleasantness. In contrast, intervention participant M03, did show a consistent reduction of perceived pain, but no consistent increase of pre-stimulus somatosensory alpha activity. Pre-stimulus alpha activity was only increased in the ipsilateral region for the pain threshold stimuli.

**Table 7.3** Pre-stimulus somatosensory alpha power ( -1 to 0s before pain onset) for the four intervention participants (M01-M04) when stimulus intensity was certain. The table displays average alpha power for each of the three pressure stimulus intensities at Time 1 and Time 2, the change in alpha at Time 2 (score Time 2 – Time 1) and the percentage change at Time 2 ((score Time 2 – score Time 1) / score Time 1). Three intervention participants (M01, M02, M04) demonstrated a consistent increase of pre-stimulus somatosensory alpha power that ranged from 5-168% change ipsilateral and from 30-99% change contralateral.

ID	Non-painful		Pain threshold		Moderately painful	
	(score time 1; score time 2; difference time 2 - time 1; % change)		(score time 1; score time 2; difference time 2 - time 1; % change)		(score time 1; score time 2; difference time 2 - time 1; % change)	
	Ipsilateral	Contralateral	Ipsilateral	Contralateral	Ipsilateral	Contralateral
M01	2.41; 2.48; 0.07; 3%	2.75; 3.59; 0.85; 31%	3.04; 3.18; 0.14; 5%	2.49; 3.70; 1.21; 48%	3.76; 3.94; 0.18; 5%	2.98; 3.86; 0.88; 30%
M02	2.50; 3.13; 0.63; 25%	2.63; 2.91; 0.28; 11%	2.23; 3.38; 1.14; 51%	1.75; 3.48; 1.73; 99%	3.63; 5.57; 1.94; 53%	2.93; 4.12; 1.19; 41%
M03	3.83; 3.99; 0.15; 4%	3.71; 2.21; -1.49; -40%	4.16; 5.82; 1.66; 40%	3.49; 2.33; -1.15; -33%	5.46; 3.97; -1.49; -27%	4.67; 2.52; -2.15; -46%
M04	0.71; 1.38; 0.67; 94%	0.72; 1.01; 0.28; 39%	0.85; 1.90; 1.05; 123%	0.92; 1.42; 0.50; 54%	0.83; 2.22; 1.39; 168%	0.72; 1.32; 0.59; 82%

## Certain pain intensity



**Figure 7.3** TFRs for each intervention participant (M01-M04, from top to bottom) and Time 1 (left) and Time 2 (right), with time (s) on the x-axis and frequency (Hz) on the y-axis. The representation was based on the average over the two somatosensory regions, for the moderately painful stimuli.

Compared to the three out of four intervention participants who demonstrated a Time 2 reduction in pain intensity and unpleasantness ratings for both the pain threshold and moderately painful stimuli, only one out of four control participants did so (C06). The other three control participants only demonstrated a (usually small) reduction for one out of four pain rating outcomes (intensity and unpleasantness rating x pain threshold and moderately painful stimulus). A (usually small) increase of pain intensity and unpleasantness ratings was present for the other three outcomes (Table 7.4).

An increase of pre-stimulus somatosensory alpha power was only present for all alpha power outcomes in one control participant (C08) the other three control participants demonstrated a mix of increased and decreased alpha power (Table 7.5). Furthermore, the increase in alpha power was not linked with a reduction in perceived pain as for two of the intervention participants, where participant C06 was the only control participant that demonstrated a consistent reduction of reported pain intensity and unpleasantness, participant C08 was the only participant demonstrating a consistent increase of alpha power.

**Table 7.4** Intensity and unpleasantness ratings for the four control participants (C05-C08) when stimulus intensity was certain. The table displays the average intensity rating and unpleasantness rating for each of the three pressure stimulus intensities at Time 1 and Time 2, the change in rating score at Time 2 (score Time 2 – Time 1) and the percentage change at Time 2 ((score Time 2 – score Time 1) / score Time 1). Only one out of four control participants (C06) showed a consistent reduction at Time 2 of both intensity and unpleasantness ratings for both pain threshold and moderately painful stimuli.

ID	Intensity ratings (score time 1; score time 2; difference time 2 - time 1; % change)			Unpleasantness ratings (score time 1; score time 2; difference time 2 - time 1; % change)		
	Non-painful	Pain threshold	Moderately painful	Non-painful	Pain threshold	Moderately painful
C05	1.00; 1.17; 0.17; 17%	4.33; 4.38; 0.04; 0.96%	7.79; 7.48; -0.31; -4%	0.04; 1.00; 0.96; 2298%	2.08; 2.08; 0.00; 0%	7.08; 7.88; 0.79; 11%
C06	0.21; 0.25; 0.04; 20%	4.75; 3.5; -1.25; -26%	8.00; 7.54; -0.46; -6%	0.00; 0.00; 0.00; 0%	4.50; 1.50; -3.00; -67%	7.58; 5.54; -2.04; -27%
C07	0.58; 0.70; 0.11; 19%	2.70; 3.09; 0.39; 15%	6.48; 6.96; 0.48; 7%	1.00; 0.70; -0.30; -30%	3.30; 3.04; -0.26; -8%	6.79; 6.82; 0.03; 0.39%
C08	0.96; 1.13; 0.17; 17%	4.42; 3.71; -0.70; -16%	7.38; 8.46; 1.08; 15%	0.00; 0.00; 0.00; 0%	0.29; 0.42; 0.13; 43%	2.42; 4.46; 2.04; 84%



**Table 7.5** Pre-stimulus somatosensory alpha power ( -1 to 0s before pain onset) for the four control participants (C05-C08) when stimulus intensity was certain. The table displays average alpha power for each of the three pressure stimulus intensities at Time 1 and Time 2, the change in alpha at Time 2 (score Time 2 – Time 1) and the percentage change at Time 2 ((score Time 2 – score Time 1) / score Time 1). An increase of pre-stimulus somatosensory alpha power was only present for all alpha power outcomes in one control participant (C08).

ID	Non-painful		Pain threshold		Moderately painful	
	(score time 1; score time 2; difference time 2 - time 1; % change)		(score time 1; score time 2; difference time 2 - time 1; % change)		(score time 1; score time 2; difference time 2 - time 1; % change)	
	Ipsilateral	Contralateral	Ipsilateral	Contralateral	Ipsilateral	Contralateral
C05	1.47; 2.71; 1.23; 84%	1.49; 2.51; 1.03; 69%	1.39; 3.15; 1.76; 127%	1.67; 2.62; 0.95; 57%	1.40; 1.45; 0.05; 4%	1.80; 1.42; -0.38; -21%
C06	1.11; 1.09; -0.02; -2%	1.05; 1.66; 0.61; 59%	1.14; 1.05; -0.10; -8%	1.14; 1.86; 0.72; 64%	1.11; 1.10; -0.01; -0.6%	0.92; 1.83; 0.92; 100%
C07	0.32; 0.47; 0.15; 48%	2.31; 0.71; -1.60; -69%	0.32; 0.43; 0.12; 37%	2.40; 0.74; -1.66; -69%	0.32; 0.61; 0.29; 89%	1.96; 0.94; -1.02; -52%
C08	0.28; 0.35; 0.07; 27%	0.37; 0.38; 0.01; 3%	0.31; 0.41; 0.10; 34%	0.38; 0.40; 0.02; 6%	0.29; 0.37; 0.07; 25%	0.37; 0.41; 0.04; 11%

To summarise, when pain intensity was known (certain) three out of four intervention participants (M01, M03, M04) demonstrated a consistent reduction of perceived pain intensity and unpleasantness at Time 2, which was accompanied by a consistent increase of pre-stimulus somatosensory alpha power in two of these three intervention participants. A third intervention participant (M02) also showed an increase of alpha but here perceived pain was not reduced. In the control group only one participant demonstrated a consistent reduction of perceived pain intensity and unpleasantness at Time 2, but this was not accompanied by a consistent increase of pre-stimulus somatosensory alpha power.

*Objective 2: To explore the influence of uncertainty about pain intensity on somatosensory alpha activity and pain experience after MBSR training.*

The general pattern of change across the four intervention participants from Time 1 to Time 2 was the same in the uncertain and certain condition (see Table 7.6). However, the decrease in perceived pain intensity and unpleasantness was slightly less consistent in the uncertain condition. Similar to when pain intensity was known, intervention participant M01, M03, and M04 showed a reduction in pain rating outcomes when pain intensity was uncertain. But participant M03 was the only intervention participant to show a reduction of all four pain rating outcomes at Time 2, M01 and M03 showed a reduction in three out of four pain rating outcomes. For the outcomes that were reduced, the reduction in pain intensity ratings ranged from 16-63% change and reduction in pain unpleasantness ratings from 5-63% change.

When pain intensity was uncertain, all three intervention participants that demonstrated a reduction in perceived pain also demonstrated a consistent increase of pre-stimulus somatosensory alpha power (Table 7.7; Figure 7.4) (with one exception: there was no increase of alpha power in the contralateral region for the moderately painful stimuli for participant M01). For the outcomes that were increased, the increase in alpha power ranged from 28-223% change in the ipsilateral region and from 9-213% in the contralateral region. Participant

M02, who did not demonstrate a reduction in pain ratings, still demonstrated a consistent increase in pre-stimulus somatosensory alpha power too.

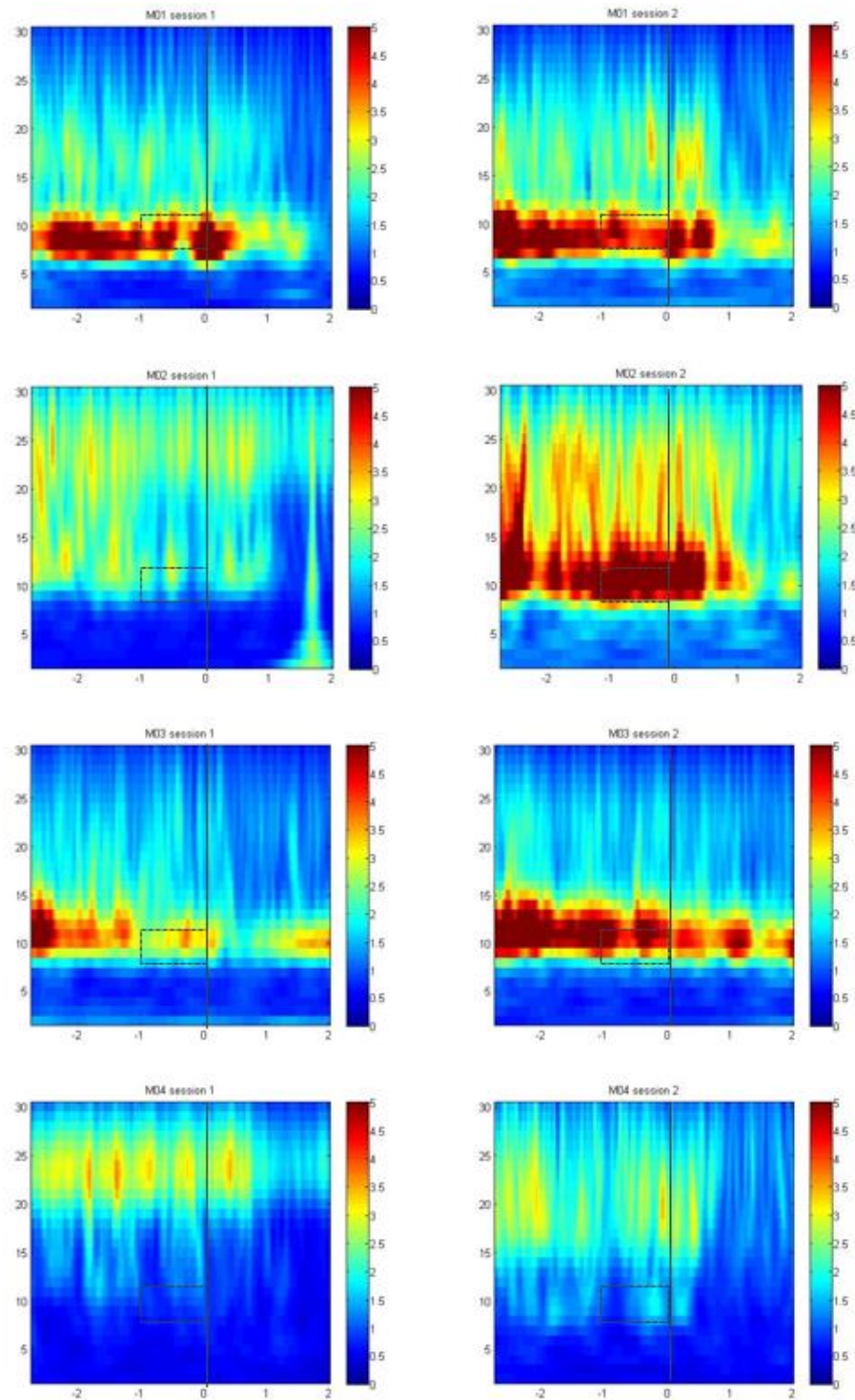
Table 7.6 Intensity and unpleasantness ratings for the four intervention participants (M01-M04) when stimulus intensity was uncertain. The table displays the average intensity rating and unpleasantness rating for each of the three pressure stimulus intensities at Time 1 and Time 2, the change in rating score at Time 2 (score Time 2 – Time 1) and the percentage change at Time 2 ((score Time 2 – score Time 1) / score Time 1). Intervention participant M01, M03, and M04 showed a reduction in pain ratings for the pain threshold and moderately painful stimuli, participant M03 for all four pain rating outcomes and participant M01 and M03 for three outcomes. The reduction in pain intensity ratings ranged from 16-63% change and the reduction in pain unpleasantness ratings from 5-63% change.

ID	Intensity ratings (score time 1; score time 2; difference time 2 - time 1; % change)			Unpleasantness ratings (score time 1; score time 2; difference time 2 - time 1; % change)		
	Non-painful	Pain threshold	Moderately painful	Non-painful	Pain threshold	Moderately painful
M01	0.96; 0.08; -0.88; -91%	3.23; 1.5; -1.72; -54%	7.17; 5.96; -1.21; -17%	0.00; 0.00; 0.00; 0%	0.08; 0.63; 0.54; 650%	5.63; 4.54; -1.08; -19%
M02	0.04; 0.09; 0.04; 109%	3.33; 4.42; 1.08; 33%	6.92; 8.13; 1.21; 17%	0.00; 0.00; 0.00; 0%	0.04; 0.58; 0.54; 1299%	3.38; 6.00; 2.63; 78%
M03	0.96; 0.17; -0.79; -83%	3.17; 1.17; -2.01; -63%	6.35; 3.52; -2.83; -45%	0.96; 0.17; -0.79; -83%	3.17; 1.17; -2.00; -63%	6.33; 3.50; -2.83; -45%
M04	0.42; 1.71; 1.29; 310%	2.88; 3.63; 0.75; 26%	7.08; 5.96; -1.13; -16%	0.67; 1.17; 0.5; 75%	3.04; 2.88; -0.17; -5%	7.63; 5.21; -2.42; -32%

**Table 7.7** Pre-stimulus somatosensory alpha power ( -1 to 0s before pain onset) for the four intervention participants (M01-M04) when stimulus intensity was uncertain. The table displays average alpha power for each of the three pressure stimulus intensities at Time 1 and Time 2, the change in alpha at Time 2 (score Time 2 – Time 1) and the percentage change at Time 2 ((score Time 2 – score Time 1) / score Time 1). All four intervention participants demonstrated a consistent increase of pre-stimulus somatosensory alpha power. The increase in alpha power ranged from 28-223% change ipsilateral region and 9-213% change contralateral.

ID	Non-painful		Pain threshold		Moderately painful	
	(score time 1; score time 2; difference time 2 - time 1; % change)		(score time 1; score time 2; difference time 2 - time 1; % change)		(score time 1; score time 2; difference time 2 - time 1; % change)	
	Ipsilateral	Contralateral	Ipsilateral	Contralateral	Ipsilateral	Contralateral
M01	2.97; 5.09; 2.12; 71%	2.62; 3.83; 1.20; 46%	2.61; 4.85; 2.25; 86%	2.36; 3.48; 1.12; 48%	3.02; 3.85; 0.84; 28%	3.96; 3.20; -0.75; -19%
M02	1.88; 5.78; 3.90; 207%	1.69; 6.09; 4.40; 261%	1.90; 4.67; 2.77; 146%	1.78; 4.71; 2.93; 165%	1.82; 5.88; 4.06; 223%	1.58; 4.95; 3.37; 213%
M03	4.07; 4.51; 0.44; 11%	2.94; 3.12; 0.18; 6%	3.64; 5.88; 2.23; 61%	3.42; 4.29; 0.87; 26%	3.43; 5.46; 2.04; 59%	2.30; 3.16; 0.85; 37%
M04	1.06; 1.31; 0.25; 23%	0.99; 1.09; 0.10; 10%	1.25; 1.76; 0.51; 41%	1.14; 1.24; 0.10; 9%	0.99; 1.41; 0.42; 42%	0.91; 1.22; 0.32; 35%

## Uncertain pain intensity



**Figure 7.4** TFRs for each intervention participant (M01-M04, from top to bottom) and Time 1 (left) and Time 2 (right), with time (s) on the x-axis and frequency (Hz) on the y-axis. The representation was based on the average over the two somatosensory regions, for the moderately painful stimuli.

*Objective 3: To explore whether an increase in pre-stimulus somatosensory alpha activity after the 8-week MBSR training was influenced by somatosensory region, i.e., if there was a difference comparing the ipsilateral and contralateral somatosensory region (with respect to the stimulated hand).*

The limited data of the three intervention participants that demonstrated an increase of pre-stimulus somatosensory alpha activity did not indicate a systematic difference in the extent of increase of alpha power comparing the ipsi- and contralateral somatosensory region. For each intervention participant alpha power was not equally changed in the ipsi- and contralateral region at Time 2. But where some participants demonstrated a larger increase of alpha power ipsilateral others demonstrated a larger increase contralateral. Moreover, within each participant the pattern of alpha power increase ipsi-versus contralateral at Time 2 also varied comparing the certain and uncertain condition or comparing the pain threshold and the moderately painful stimuli.

Thus, although there were differences in the increase of pre-stimulus somatosensory alpha power comparing the ipsilateral and contralateral somatosensory region, no consistent pattern could be discovered for the three intervention participants.

*Objective 4: To assess whether there is an increase in resting-state somatosensory alpha activity after the 8-week MBSR training.*

Resting-state somatosensory alpha activity measured at the beginning of each session increased in all four intervention participants, both ipsi- and contralateral from Time 1 to Time 2 (Table 7.8). M03, who only demonstrated a consistent increase of pre-stimulus alpha power in the uncertain condition, demonstrated the smallest increase of resting-state alpha power. Across the four intervention participants the increase of resting-state alpha power ranged from 26-192% change.

In the control group, only two of four participants demonstrated an increase of resting-state alpha power in both the ipsi- and contralateral

somatosensory region (Table 7.9). For these two participants the increase of resting-state alpha power ranged from 13-51% change.

**Table 7.8** Average resting-state somatosensory alpha power outcomes intervention participants. The table contains both the change in resting-state alpha power comparing Time 1 and Time 2, and the change in resting-state alpha power comparing before and after the 10-minute mindfulness meditation practice at Time 2. All four intervention participants showed an increase of resting-state somatosensory alpha power from Time 1 to Time 2, ranging from 26-192% change ipsilateral and 26-159% change contralateral.

Resting-state alpha power (Score time 1; score time 2; difference time 2 - time 1; % change)				
ID	Time 1 versus Time 2		Time 2: pre-MM versus post-MM	
	Ipsilateral	Contralateral	Ipsilateral	Contralateral
M01	4.92; 7.85; 2.93; 60%	4.10; 6.36; 2.26; 55%		
M02	2.54; 5.72; 3.19; 126%	2.39; 6.18; 3.79; 159%	5.72; 4.91; -0.82; -14%	6.18; 6.02; -0.15; -3%
M03	5.69; 7.17; 1.48; 26%	5.77; 7.30; 1.52; 26%	7.17; 11.19; 4.02; 56%	7.30; 8.90; 1.60; 22%
M04	2.60; 7.59; 4.99; 192%	2.33; 5.21; 2.88; 123%	7.59; 7.33; -0.26; -3%	5.21; 4.97; -0.24; -5%

Finally, at Time 2, for intervention participants M02, M03, and M04 resting-state somatosensory alpha power was assessed at the start of the session before the 10-minute mindfulness meditation practice and again directly after the meditation practice. Only M03 showed an increase of resting-state alpha power after the meditation practice. M02 and M04 did not show an increase in resting-state alpha power, but instead a slight decrease of resting-state alpha power.



**Table 7.9** Average resting-state somatosensory alpha power outcomes control participants; the change in resting-state alpha power comparing Time 1 and Time 2. Only two of four control participants (C05 and C06) showed an increase of resting-state alpha power in both the ipsi- and contralateral somatosensory region. For these two participants the increase of alpha ranged from 13-51% change.

Resting-state alpha power		
Time 1 versus Time 2		
(Score time 1; score time 2; difference time 2 - time 1; % change)		
ID	Ipsilateral	Contralateral
C05	1.36; 2.06; 0.70; 51%	1.54; 2.03; 0.49; 32%
C06	1.45; 1.64; 0.19; 13%	1.23; 1.77; 0.54; 44%
C07	0.36; 0.72; 0.36; 100%	1.34; 0.80; -0.54; -40%
C08	1.94; 0.71; -1.23; -63%	1.88; 0.61; -1.27; -68%

***Objective 5a:** To assess if fear of pain and/or pain catastrophising were reduced after the MBSR training course.*

To assess individual levels of fear of pain the FPQ-SF was used (McNeil & Rainwater, 1998). The total score on the scale ranges from 9-45, with a higher total score indicating higher levels of fear of pain. At Time 1, the total score on the FPQ-SF ranged from 23-31 in the intervention group (N = 4) and from 14-24 in the control group (N = 4). At Time 2, the total score on the FPQ-SF ranged from 28-32 in the intervention group (N = 4) and from 16-30 in the control group (N = 4). There was no indication of a reduction of fear of pain at Time 2 (Table 7.10). Two intervention participants (M02 and M04) did not show any change in fear of pain and two showed a small increase in fear of pain (7-22%) post-intervention. In comparison, three control participants (C06, C07,

C08) showed a small increase (14-25%) and one showed a decrease in fear of pain (-25%).

To assess individual levels of pain catastrophising the PCS was used (Sullivan et al., 1995). The total score on the scale ranges from 0-52, with a higher score indicating higher levels of pain catastrophising. At Time 1, the total score on the PCS ranged from 9-33 in the intervention group (N = 4) and from 3-23 in the control group (N = 4). At Time 2, the total score on the PCS ranged from 7-29 in the intervention group (N = 4) and from 2-22 in the control group (N = 4). There was also no consistent reduction in pain catastrophising at Time 2 (Table 7.10). Two intervention participants demonstrated a reduction, with a decrease of 61% for M02 and a decrease of 42% for M04. However, the two other intervention participants demonstrated an increase of pain catastrophising, with a small increase for M01 (12%) and a large increase for M03 (156%). Furthermore, in the control group three participants showed a reduction of pain catastrophising at Time 2 (C06, C07, and C08) ranging from 26-82% change. C05 demonstrated a slight increase of pain catastrophising (5%).

*Objective 5b: To assess if there was a relationship between fear of pain/pain catastrophising levels at baseline and the reduction in pain experience after the 8-week MBSR training course.*

M02 was the only intervention participant that did not show a reduction in perceived pain after the MBSR training course. However, M02 did not have a higher level of fear of pain or pain catastrophising compared to the three MBSR participants that did show a reduction in perceived pain.

**Table 7.10** The change from Time 1 to Time 2 in total score for the FoP-SF (fear of pain) and the PCS (pain catastrophising), for the intervention participants (M01-M04) and the control participants (C05-C08). There was no evidence for a consistent reduction of fear of pain and pain catastrophising following the MBSR training course. There was also no evidence for a relationship between fear of pain/pain catastrophising levels at baseline and a reduction in perceived pain following the MBSR training course.

Time 1 versus Time 2		
(Score time 1; Score time 2; difference time 2 - time 1; % change)		
ID	Fear of Pain	Pain catastrophising
M01	30; 32; 2; 7%	26; 29; 3; 12%
M02	31; 31; 0; 0%	18; 7; -11; -61%
M03	23; 28; 5; 22%	9; 23; 14; 156%
M04	31; 31; 0; 0%	33; 19; -14; -42%
C05	24; 18; -6; -25%	21; 22; 1; 5%
C06	14; 16; 2; 14%	23; 17; -6; -26%
C07	24; 30; 6; 25%	17; 3; -14; -82%
C08	22; 26; 4; 18%	3; 2; -1; -33%

#### State (TMS) and trait (CHIME) mindfulness measures

The CHIME (Bergomi et al., 2013) was designed for the assessment of mindfulness as a quasi-trait. The total score on the scale ranges from 37-222, with a higher total score reflecting higher mindfulness. At Time 1, the total score on the CHIME ranged from 120-161 in the intervention group (N =2) and from 97-188 in the control group (N = 4) (Table 7.11). At Time 2, the total score on the CHIME ranged from 111-165 in the intervention group (N =4) and from 87-199 in the control group (N = 3). Thus, based on the limited data there was no clear indication of a difference in the total score on the CHIME comparing the intervention and control participants, and no clear indication of a higher total score for the intervention participants from Time 1 to Time 2.

Intervention participants M01, M03, and M04 demonstrated a reduction in perceived pain, participant M02 did not demonstrate a reduction in perceived pain. There was no clear relationship between the total score on the CHIME at Time 2 and whether or not a reduction in perceived pain was present. Similarly, there was no clear relationship between the total score of the TMS at Time 2 and the reduction in perceived pain.

**Table 7.11** Total score on the CHIME at Time 1 and Time 2 for both the intervention participants (M01-M04) and the control participants (C05-C08) and the total score on the TMS at Time 2 for the intervention participants only. Based on the limited data available no evidence for a clear increase of the CHIME score following the MBSR training course was found.

ID	CHIME (Time 1)	CHIME (Time 2)	TMS (Time 2)
M01	Missing	151	40
M02	161	165	35
M03	Missing	111	29
M04	120	132	26
C05	153	152	n.a.
C06	97	87	n.a.
C07	139	Missing	n.a.
C08	188	199	n.a.

To summarise, analysis at an individual level to assess changes in perceived pain and somatosensory alpha activity after the MBSR training course showed a reduction in perceived pain intensity and unpleasantness accompanied by an increase of somatosensory alpha activity before pain onset (both pre-stimulus and resting-state alpha), when pain intensity was known. When pain intensity was uncertain, a similar increase of pre-stimulus somatosensory alpha activity was present, but there was some suggestion that the reduction of perceived pain was less consistent. No clear evidence for an

influence of fear of pain and pain catastrophising on the change in pain experience after the MBSR training was found.

## 7.4 Discussion

The aim of this study was to investigate whether pre-stimulus somatosensory alpha activity and pain experience were modulated after completion of an 8-week MBSR programme. Intervention participants were compared to a group of control participants that did not take part in any training but simply attended two experimental sessions, before and after an 8-week period. Below, the findings of the study will be discussed with respect to each of the objectives as stated in the introduction. This will be followed by a broader interpretation of the findings and a consideration of limitations.

*Objective 1: To investigate whether an 8-week MBSR training course would increase pre-stimulus somatosensory alpha activity and reduce the experience of pain, for acute experimental pain in both healthy volunteers and those with a chronic pain condition.*

The results of this study suggest that an 8-week MBSR training might be able to reduce pain experience and increase pre-stimulus somatosensory alpha activity. When pressure stimulus intensity was certain, three intervention participants demonstrated consistently lower perceived pain intensity and unpleasantness post-intervention. Two of these participants also demonstrated an increase in pre-stimulus somatosensory alpha power. The findings of the intervention participants were compared to a group of control participants, to address any non-specific changes related to the passage of time and repetition of the task. Only one control participant showed consistently lower perceived pain intensity and unpleasantness at Time 2. Furthermore, this was not accompanied by an increase of pre-stimulus somatosensory alpha activity.

In the intervention group, at least a minimally important improvement (greater than 17.50%) in perceived pain intensity (as per the IMMPACT

statement; Dworkin et al., 2008) was present for two participants. A stronger indication of at least a minimally important improvement was present for perceived pain unpleasantness, with three of four interventions participants showing a reduction greater than 17.50%. In contrast, in the control group there was little evidence of at least a minimally important improvement of perceived pain. One control participant showed a reduction greater than 17.50% in perceived pain intensity, for the pain threshold stimuli only. For the moderately painful stimuli none showed at least a slight improvement of perceived pain intensity. Similarly for perceived pain unpleasantness only one control participant showed a reduction greater than 17.5%, (for both the pain threshold and moderately painful stimuli).

Furthermore, a consistent relationship between change in perceived pain and pre-stimulus somatosensory alpha power at Time 2 seemed to be present for intervention participants only. Of the three intervention participants that showed a reduction in perceived pain, two participants showed an increase of somatosensory alpha power before the onset of pain too. Further evidence for a consistent relationship between change in alpha and pain in the intervention group was present in the uncertain condition, described below. In the control group, there was one participant who demonstrated an increase of alpha power at Time 2, but for this control participant the increase in alpha power was not accompanied by a reduction of perceived pain. Vice versa, there was one control participant that did show a consistent reduction of perceived pain, but here there was no consistent increase of alpha power.

It should be noted though, that despite no convincing evidence for a reduction in perceived pain in the control group and for a 'combined' reduction in pain and increase of alpha, there were some indications for an increase in pre-stimulus somatosensory alpha power still. However, the control participants demonstrated a larger variation in alpha power changes (both increases and decreases) and/or a less consistent increase of alpha power across alpha power outcomes (e.g., a control participant might show an increase of alpha power ipsilateral for the pain threshold stimuli but not for the moderately painful stimuli). In the intervention group, three participants showed an increase of

alpha power across all alpha power outcomes (i.e., both ipsilateral and contralateral, and both for the pain threshold and the moderately painful stimuli). In contrast, only one control participant showed a consistent increase of alpha power for all alpha outcomes. It still seems that there is more evidence for an increase of pre-stimulus somatosensory alpha power in the intervention group, but the difference between intervention and control group is not as convincing as for the perceived pain outcomes. To really be able to confirm that there is indeed an increase in pre-stimulus somatosensory alpha power during the anticipation of a painful stimulus that can be distinguished/differentiated from the control group, i.e., that is not just the result of the non-specific effects of the passage of time and the repetition of the experimental task, a full-scale investigation allowing for statistical testing is key.

A reduction of pain experience after brief mindfulness meditation training has previously been shown in an experimental pain setting (Kingston et al., 2007; Zeidan et al., 2011; Zeidan et al., 2010). However, an understanding of the neurophysiological mechanisms that underpin the effects of mindfulness meditation on pain experience was largely lacking. This study provides some tentative support for the hypothesis that the effects of a MBSR intervention on pain experience involves a modulation of somatosensory alpha activity, supporting the hypothesis of Kerr et al. (2013). Where Kerr et al. (2011) found a modulation of pre-stimulus somatosensory alpha activity specifically during the anticipation of a non-painful somatosensory stimulus (after an 8-week MBSR programme), this study for the first time suggests that this might also apply to painful somatosensory perception.

*Objective 2: To explore the influence of uncertainty about pain intensity on somatosensory alpha activity and pain experience after MBSR training.*

It was also assessed whether there was an influence of uncertainty about pain intensity on the change in pain experience and pre-stimulus somatosensory alpha activity after the MBSR intervention. Uncertainty about

pain intensity is related to higher reported anxiety (Ploghaus et al., 2001), a higher threat value, and enhanced capture of attention by pain (Crombez et al., 1998; Eccleston & Crombez, 1999; Morley, 2008). Moreover, uncertainty about pain intensity leads to higher perceived pain intensity (Lin et al., 2014; Ploghaus et al., 2001) and might have an effect on alpha activity (Franciotti et al., 2009; Huneke et al., 2013). Mindfulness meditation can reduce the emotional response to sensations and improves the regulation of emotions and attention (Baer, 2003; Brown et al., 2007; Hölzel et al., 2011). Therefore, it was expected that a modulation of pain experience after the MBSR training course might be different in an uncertain setting related to higher threat and stronger capture of attention compared to when pain intensity is known (a predictable and less threatening setting).

First, when pain intensity was uncertain, a consistent relationship between change in perceived pain and pre-stimulus somatosensory alpha power at Time 2 was present for the intervention participants. The three intervention participants that demonstrated lower perceived pain intensity and unpleasantness post-intervention also demonstrated a consistent increase in pre-stimulus somatosensory alpha power. However, this study did not provide clear evidence for an influence of uncertainty on the reduction of pain experience after the MBSR programme; there was only a slight suggestion of a less consistent reduction in perceived pain in the uncertain condition for the moderately painful stimuli. When pain intensity was known, two intervention participants demonstrated at least a slight improvement (greater than 17.50%) of perceived pain intensity and three intervention participants at least a slight improvement of perceived pain unpleasantness for both the pain threshold and the moderately painful stimuli. When pain intensity was uncertain, similarly two intervention participants showed at least a slight improvement of perceived pain intensity for the pain threshold stimuli. However, only one participant showed at least a slight improvement of perceived pain intensity for the moderately painful stimuli. Perceived pain unpleasantness was at least slightly improved in three intervention participants for the pain threshold stimuli, as was the case when pain intensity was known. However, for the moderately painful stimuli perceived pain unpleasantness was at least slightly improved in only one intervention



participant when pain intensity was uncertain. Nonetheless, all intervention participants demonstrated a consistent increase of pre-stimulus somatosensory alpha activity.

Thus, based on the findings of the present study, completing a MBSR course - thought to be related to an improved regulation of emotions and attention - was not more effective in reducing perceived pain in a setting of uncertainty about pain intensity, a setting associated with higher threat value and higher anxiety.

*Objective 3: To explore whether an increase in pre-stimulus somatosensory alpha activity after the 8-week MBSR training was influenced by somatosensory region, i.e., if there was a difference comparing the ipsilateral and contralateral somatosensory region (with respect to the stimulated hand).*

This study also explored whether any change in pre-stimulus somatosensory alpha activity after the MBSR training might be different for the ipsilateral and the contralateral somatosensory region. A number of studies have demonstrated that pre-stimulus somatosensory alpha activity in preparation for a painful stimulus tends to be lateralised. For instance, Del Percio et al. (2006) found an event-related decrease in pre-stimulus alpha power that was more prominent in the contralateral central region than the ipsilateral central region, with respect to the location of pain stimulation. May et al. (2012) also found that pre-stimulus somatosensory alpha activity was lateralised, with lower alpha power at the contralateral S1 region and higher alpha power at the ipsilateral S1 region. This likely reflects functional inhibition, i.e. higher alpha activity in task-irrelevant neural regions inhibiting the processing of information in these regions, which results in the gating of information processing towards task-relevant neural pathways. Furthermore, Babiloni et al. (2006) and Tu et al. (2016) found a significant negative relationship between pre-stimulus somatosensory alpha activity and perceived pain intensity particularly in the contralateral somatosensory region.

The limited data available in this study did not provide sufficient evidence for consistent pattern of lateralisation in the increase of pre-stimulus somatosensory alpha activity as a result of the MBSR training course. Although for each individual intervention participant alpha power was increased to a different extent ipsi- and contralateral, the pattern of lateralisation was not consistent from participant to participant; where some demonstrated a larger increase ipsilateral, others demonstrated a larger increase contralateral. Moreover, the pattern of lateralisation was sometimes also different within the same participant, comparing the certain versus the uncertain condition or pain threshold versus moderately painful stimuli. For example, participant M01 demonstrated only a small increase ipsilateral but a moderate increase contralateral when pain intensity was known. In contrast, when pain intensity was uncertain an increase of alpha power was more prominent ipsilateral. Thus, although there were differences in the increase of pre-stimulus somatosensory alpha power comparing the ipsilateral and contralateral somatosensory region, no consistent pattern was present.

*Objective 4: To assess whether there is an increase in resting-state somatosensory alpha activity after the 8-week MBSR training.*

With some preliminary evidence supporting an increase of pre-stimulus somatosensory alpha power as a result of the MBSR intervention, in the present study the strongest indication of an effect of MBSR on somatosensory alpha activity was found for resting-state somatosensory alpha power. The individual data suggests that the reduction in perceived pain at Time 2 was preceded by not only an increase of pre-stimulus somatosensory alpha activity (task-related activity) directly before pain onset, but also an increase of resting-state somatosensory alpha activity (spontaneous, background activity) before the onset of the experimental task. The three intervention participants that showed a reduction in perceived pain and an increase of pre-stimulus somatosensory alpha power (M01, M03, M04), all demonstrated a large increase of resting-state alpha power after the MBSR training course, both ipsi- and contralateral, ranging from 55-192%. Moreover, the intervention participant

that did not show a reduction of perceived pain and increase of pre-stimulus somatosensory alpha power, demonstrated an increase of resting-state somatosensory alpha power nonetheless, albeit of a smaller size (26% ipsi- and contralateral). In contrast, an increase of resting-state somatosensory alpha power both ipsi- and contralateral was only found in two control participants, and they demonstrated a considerably smaller increase than the intervention participants, ranging from 13-51%.

Two previous studies found an increase of alpha activity related to mindfulness. Bing-Canar et al. (2016) compared the effects of a single meditation practice (audio-recording) to a control condition in which participants listened to an audio-recording with educational information about key concepts of mindfulness. EEG data was collected from 9 electrodes (F3, Fz, F4, C3, Cz, C4, P3, Pz, P4). Alpha power during the mindfulness meditation practice was significantly increased compared to the control condition. Wong et al. (2015) compared alpha activity for experienced meditators (meditators that used any mindfulness meditation technique for at least five days a week for at least five years) to meditation-free controls. Average alpha power over the whole head was significantly higher in the experienced meditators compared to the controls, both during rest and during mindfulness meditation. Thus, these two studies suggest an increase of global alpha activity during mindfulness meditation practice and at rest for experienced meditators compared to novices. The present study uniquely shows tentative evidence for an increase of resting-state alpha activity in the somatosensory region specifically after an 8-week MBSR programme, in the context of pain experience.

Huneke et al. (2013) also demonstrated a change in resting-state alpha related to pain experience, not for a mindfulness-based intervention but for a placebo procedure that induced an expectation of pain relief. They showed that the application of placebo cream to induce an expectation of pain relief led to a significant reduction of pain ratings. Importantly, this reduction in pain ratings was accompanied by an increase in resting-state alpha activity after the placebo procedure. No significant reduction in pain ratings or increase of resting-state alpha activity was found for the control group. It should be noted

though that the findings of Huneke et al. (2013) did not apply to somatosensory alpha activity specifically, but were based on an increase of global alpha activity. Source localisation estimated that the this increase of alpha originated in the insula and medial prefrontal cortex, two neural regions considered part of the pain network that have previously been found activated during the anticipation of pain (Ploghaus et al., 1999). Furthermore, the significant increase in resting-state alpha activity was measured after the application of the painful stimuli, therefore we cannot conclude with certainty that an increase in alpha led to the reduction in pain experience in the study of Huneke et al. (2013). The present study offers some improvement on this, as increased resting-state alpha activity at Time 2 was measured before the experimental task. Thus we can exclude the possibility that the increase of resting-state alpha was the result of the pain experienced during the task.

Finally, one study has demonstrated a relationship between resting-state alpha and pain experience. Nir et al. (2012) found a significant negative correlation between resting-state alpha power and reported pain intensity, with resting-state alpha activity measured 30 minutes before a 5-minute tonic painful heat stimulation. However, this relationship was not found for the somatosensory region specifically, but for electrode locations T7 and T8 (bilateral temporal regions). In the present study, an increase of resting-state somatosensory alpha power was predominantly identified in the intervention group, where a reduction in perceived pain was present, and not so much for the control group that did not show a reduction in perceived pain. Furthermore, in the intervention group the increase of resting-state somatosensory alpha power was largest for the three participants that demonstrated a consistent reduction in perceived pain, and only small for the participant that did not demonstrate a reduction in perceived pain. Thus, in the present study there is also some suggestion of a negative relationship between resting-state somatosensory alpha activity and perceived pain.

*Objective 5a: To assess if fear of pain and/or pain catastrophising was reduced after the MBSR training course.*

Both fear of pain and pain catastrophising have been implicated as important factors in the development and maintenance of chronic pain, as part of the fear-avoidance model of chronic pain (Leeuw et al., 2007; Vlaeyen et al., 1995). Mindfulness meditation seems to be associated with various components of the fear-avoidance model of chronic pain, including pain-related fear and pain catastrophising. Schütze et al. (2010) found that pain catastrophising and pain-related fear were significantly negatively correlated with trait mindfulness (as measured with the MAAS). Furthermore, regression analysis showed that all facets of mindfulness (as measured with the FFMQ) predicted pain catastrophising, with mindfulness accounting for 41% of variance in pain catastrophising. Therefore, in the present study it was assessed whether after the completion of the 8-week MBSR training fear of pain and pain catastrophising might be decreased.

The limited data of this study did not provide any evidence for a decrease of fear of pain and/or pain catastrophising after the MBSR training. There was no indication of a reduction of fear of pain at Time 2; two intervention participants did not show any change in fear of pain and two showed a small increase in fear of pain post-intervention. There was also no consistent reduction in pain catastrophising at Time 2. The total score on the PCS ranges from 0-52, with a higher score indicating higher levels of pain catastrophising. Two intervention participants demonstrated a reduction post-intervention. Participant M02 had a total score of 18 at Time 1 and a total score of 7 at Time 2, participant M04 had a total score of 33 at Time1 and a total score of 19 at Time 2. However, the two other intervention participants demonstrated an increase of pain catastrophising. Participant M01 had a total score of 26 at Time 1 and a total score of 29 at Time 2, participant M03 had a total score of 9 at Time1 and a total score of 23 at Time 2.

*Objective 5b: To assess if there was a relationship between fear of pain/pain catastrophising levels at baseline and the reduction in pain experience after the 8-week MBSR training course.*

Some studies have also demonstrated that the effects of mindfulness meditation on pain might be influenced by pain catastrophising. Prins et al. (2014) measured perceived pain before and after a 10-minute mindfulness meditation practice. Only when pain catastrophising was taken into account a change in pain unpleasantness was found in the mindfulness meditation group compared to the distraction control group. Mindfulness meditation was associated with lower pain unpleasantness ratings, but only when dispositional pain catastrophising was high. Cho et al. (2010) found evidence that pain-related anxiety (as measured by the Pain Anxiety Symptoms Scale 20) mediated the effect of mindfulness on physical and psychosocial functioning in patients with chronic pain. Mindfulness was thought to reduce anxiety and fearful thoughts towards pain, and this in turn to result in the improvement of functioning. Therefore, the present study assessed whether there was a relationship between fear of pain/pain catastrophising at baseline and the change in pain experience (and somatosensory alpha) after the MBSR training.

The limited data of this study did not provide any evidence for this. Intervention participants M01, M03, and M04 demonstrated a reduction in perceived pain, participant M02 did not demonstrate a reduction in perceived pain. However, there was no clear relationship between fear of pain/pain catastrophising at baseline (Time 1) and whether or not a reduction in perceived pain was present.

To conclude, the present study provides some tentative evidence that an eight week MBSR programme is followed by a reduction of pain experience and an increase of somatosensory alpha activity before the onset of pain (both pre-stimulus and resting-state alpha). However, the limited data available did not allow for a clear interpretation of a potential influence of uncertainty about pain intensity and did not indicate an influence of fear of pain and pain catastrophising on the reduction in pain experience after the MBSR training.

So far, in the extant literature, a relationship between pre-stimulus somatosensory alpha activity and pain experience has been largely based on correlation findings, i.e., a negative correlation between pre-stimulus somatosensory alpha activity and pain experience (Babiloni et al., 2006; Tu et al., 2016). This study is the first to present preliminary evidence in an experimental pain setting that, after MBSR training, somatosensory alpha activity before the onset of pain (both pre-stimulus and resting-state) is increased and that this is followed by a reduction in pain experience. The present findings support the initial indications from Huneke et al. (2013) and Kerr et al. (2011) that a manipulation of somatosensory alpha activity might reduce pain, which further suggests that pre-stimulus somatosensory alpha activity and pain experience might have a causal relationship. Furthermore, this study offers an initial indication that the effects of mindfulness meditation on pain experience might reflect a change in attention. The general function of alpha activity is to guide information processing via an attentional mechanism, as has also been found for both non-painful and painful somatosensory alpha activity (Del Percio et al., 2006; Haegens et al., 2012; Jones et al., 2010; May et al., 2012). Thus, a positive effect of a mindfulness-based intervention on pain experience accompanied by an increase of somatosensory alpha activity before pain onset, might reflect a modulation of attention to pain by mindfulness meditation.

Although the present findings show that a mindfulness-based intervention might be associated with an increase of pre-stimulus and resting-state somatosensory alpha power and a reduction of pain experience, the small number of participants and therefore poorly powered study limits the extent to which we can draw conclusions. What we can take away from the present study is that, on an individual level, participants that took part in a MBSR course, both pain-free and with a chronic pain condition, demonstrated: 1) the potential of mindfulness-based interventions to reduce pain for an acute experimental stimulus; and 2) a valuable first indication of what the neurophysiological mechanism involved in the reduction of pain as a result of mindfulness meditation might be, that the effects of mindfulness meditation on pain experience might be the result of a modulation of somatosensory alpha

activity. The study findings therefore provide justification for further study of this mechanism in well powered studies.

Not only is the indication of a reduction of pain experience and an increase of somatosensory alpha activity after the MBSR intervention valuable for our understanding of the nature of the relationship between pre-stimulus somatosensory alpha activity and pain experience, it also has clinical relevance. Jensen et al. (2008) emphasised the potential of neuromodulatory interventions targeting oscillatory neural activity to reduce pain, which could offer patients with a chronic pain condition promising new (non-pharmacological) options for pain management. The present study provides an initial suggestion that neuromodulation of somatosensory alpha activity specifically could be promising to reduce pain. Not only did the individual intervention participants show a minimally important improvement in perceived pain (i.e. > 17.50% change), but there was also an indication of a clinically relevant improvement or an improvement reflecting a verbal label of 'much improved' (i.e. > 30% change; Dworkin et al., 2008; Farrar et al., 2001). When pain intensity was known, pain intensity ratings were reduced by > 30% for two intervention participants in response to pain threshold stimuli (but not moderately painful stimuli). When pain intensity was uncertain, similarly two intervention participants demonstrated a clinically relevant reduction of intensity ratings in response to pain threshold stimuli, and one participant in response to moderately painful stimuli. A clinically relevant reduction was found more frequently for the unpleasantness ratings. When pain intensity was known, of the three intervention participants that demonstrated a reduction of perceived unpleasantness in response to pain threshold stimuli, two participants showed a reduction > 30% and the third showed a reduction of 29%. Of the three MBSR participants that demonstrated a reduction of perceived unpleasantness in response to moderately painful stimuli, one participant demonstrated a reduction > 30%, the other two showed a reduction of 28%. When pain intensity was uncertain, a clinically relevant reduction in unpleasantness ratings was only found for two intervention participants in response to moderately painful stimuli.



Finally, this indication that (based on the individual data) a clinically relevant improvement might be more prominent for perceived unpleasantness than perceived pain intensity, suggests that following a MBSR programme, change in pain experience might be present particularly for the affective dimension. This would be in line with the proposal that mindfulness meditation reduces the emotional response to sensations and improves the regulation of emotions and attention (Baer, 2003; Brown et al., 2007; Hölzel et al., 2011) and might particularly affect pain-related emotion and affect (Day et al., 2014).

One specific question posed in this study that did not receive a clear answer but deserved further investigation is whether there is an influence of uncertainty about pain intensity on the effect of mindfulness meditation on pain experience and somatosensory alpha activity. Based on the individual findings of the four intervention participants there was some suggestion that, after the MBSR training, the reduction in perceived pain was less consistently present when pain intensity was uncertain. However, overall, with only limited data available, whether or not uncertainty had an effect on the outcomes predominantly remained unclear.

There is evidence to suggest, though, that uncertainty about pain intensity not only affects perceived pain in an experimental setting (Lin et al., 2014; Ploghaus et al., 2001) but also in more clinically relevant settings. Uncertainty about pain intensity can be seen as a situation of higher threat related to pain. Höfle et al. (2013) investigated the pain response in participants viewing a needle (threatening context) versus a cotton bud (non-threatening context) approaching the hand during the anticipation of pain. They found that the amount of threat experienced during the anticipation of pain influenced not only perceived pain but also pre-stimulus somatosensory alpha activity. Uncertainty about pain intensity is also related to an enhanced capture of attention by pain. A few studies have found an effect of mindfulness meditation on attention to pain in patients with chronic pain. Garland and Howard (2013) found an effect of mindfulness meditation on attention towards cues representing threat of pain. Using a dot probe test with pain-related cues

(images related to pain, for example of severe injuries) they found that participants with a variety of chronic pain conditions demonstrated a significant attentional bias towards the pain-related cues. The participants that took part in an 8-week mindfulness meditation intervention showed a significant reduction of this attentional bias, which was not the case for the control participants. Vago and Nakamura (2011) similarly investigated attentional bias towards pain-related cues (pain words) for patients with fibromyalgia. Patients that attended an 8-week mindfulness-based intervention were compared to a control group of patients that did not have any mindfulness meditation experience. Compared to the control group, the intervention group demonstrated decreased avoidance and more efficient disengagement from the pain-related cues. Finally, in a clinical setting, uncertainty about the effectiveness of pain treatment, i.e. a context of certainty (“it does work”) versus uncertainty (“it may work”), also impacts treatment outcome (Benedetti, 2002). Pollo et al. (2001) demonstrated that uncertainty about the effectiveness of a painkiller led to a significant increase in painkillers requested over a 3-day period post-surgery: a higher amount of painkillers was needed to achieve a similar reduction of pain.

Together these findings emphasise the importance of gaining a better understanding of the potential effect of uncertainty about pain (and, in more general terms, the threat value of pain and capture of attention by pain) on perceived pain in a clinical pain setting. A better understanding of the specific conditions that lead to a more or less successful reduction of pain experience is critical for the application of MBSR in clinical pain settings.

#### **7.4.1 Evaluation of study design**

Based on the preliminary findings of this study, providing evidence for a reduction in pain experience and an increase of somatosensory alpha activity before pain onset, further study is warranted and future studies should aim to be well powered. A number of improved methodological features should also be considered in future studies, as outlined here.

In the introduction to this chapter, a number of theoretical explanations of how mindfulness meditation might influence pain experience were offered. Learning to perceive a pain as 'just' another observation of a sensation, without attaching negative thoughts and emotions to it, could result in a more neutral interpretation of pain (Brown et al., 2007). Furthermore, improved sustained attention and attentional control as a result of mindfulness practice could help people to regulate their attention, emotions, and cognitions towards pain (Hölzel et al., 2011; Malinowski, 2013). It was proposed that mindfulness meditation might in particular affect the emotional-affective dimension of pain experience.

In this study, to measure a change in pain experience after the MBSR training, two NRSs were used to assess perceived pain intensity and pain unpleasantness separately, with the intensity scale reflective of sensory-discriminative aspects and the unpleasantness scale of affective aspects of pain experience. There was some tentative evidence to suggest that an improvement of perceived pain was more prominent for perceived unpleasantness, i.e., in the affective dimension. However, based on the change in pain unpleasantness ratings solely, interpretation of the specific change in emotion, affect, or cognition after the MBSR training remains limited. Additional measures could be added to provide some insight in what might have changed in the participant's 'conscious experience' of pain, e.g., an assessment of change in perceived pain control, as a meta-analysis found a significant effect of mindfulness-based interventions on perceived pain control in patients with a chronic pain condition (Bawa et al., 2015). Also an assessment of change in pain acceptance could be considered to address the impact mindfulness meditation might have on pain experience via a change in attitude towards experience (an attitude of kindness and acceptance).

Finally, although the present study provides a systematic assessment of the changes in perceived pain intensity and unpleasantness along with neurophysiological changes following a MBSR training, some improvements could be made in the assessment of mindfulness. First, in the present study a proper assessment of previous mindfulness experience (e.g. whether they had

taken part in an MBSR intervention before) was lacking, although the MBSR training is oriented towards novices. This would be valuable information to collect in the future. Both intervention and control participants completed the CHIME, designed for the assessment of mindfulness as a quasi-trait (Bergomi et al., 2013), there was no evidence of a group or pre-post difference in the overall score on the CHIME. Thus we did not identify higher trait mindfulness after completion of the 8-week MBSR training (although this is based on the data of only two participants). To explore the effects of the mindfulness-based intervention more thoroughly, adding another measurement of mindfulness (CHIME) after another 6-8 week period of personal mindfulness practice could have been beneficial. Perhaps measuring a change in trait mindfulness immediately post-intervention was too soon. Finally, it would also be beneficial to compare the novice mindfulness meditators to experienced meditators.

The TMS (Lau et al., 2006) was also completed by the intervention participants to assess the extent to which participants achieved a mindful state after completing the 10-minute mindfulness meditation practice at Time 2. There was no clear relationship between the overall score on the TMS and the reduction in perceived pain in the four intervention participants. The overall score on the TMS for four intervention participants ranged from 26-40. Unfortunately, the TMS was only completed once by the participants, which complicated the interpretation of these scores. Future studies should ask participants to complete the TMS at another time point before the mindfulness meditation practice too, to allow for an assessment of change in the TMS score comparing before and after meditation. Kiken, Garland, Bluth, Palsson, and Gaylord (2015) did measure the TMS at several time points whilst non-clinical participants took part in an 8-week MBSR training. At each time point, participants first took part in a 10-minute mindfulness meditation practice and then completed the TMS; 75% of the participants were female and the mean age was 44.83 years. The overall score on the TMS from 0-52, with a higher total score reflecting a stronger evoked mindful state. During week 7 of the MBSR course the mean TMS score was 32.73, the mean TMS score was 23.09 at the start of the course. The four intervention participants of the present study, that were all female and had a mean age of 46.75 years, had a TMS

score of 40, 35, 29, and 26 after completing the 8-week MBSR course (mean TMS score = 32.50). Their overall TMS score after completion of the MBSR training was thus comparable with that found in the study of Kiken et al. (2015).

## **7.5 Conclusions**

Based on an individual analysis of the differences in somatosensory alpha activity and pain experience after an 8-week MBSR training course in four participants compared to four control participants, this pilot study provided a promising indication that the neurophysiological mechanism to explain the reduction of pain experience by MBSR might involve the modulation of somatosensory alpha activity before pain onset. Individual responses of the intervention participants provide an initial indication that mindfulness meditation might not only increase pre-stimulus somatosensory alpha power but also resting-state somatosensory alpha power. Furthermore, individual intervention participants demonstrated a reduction in perceived pain intensity and unpleasantness that reflected a clinically relevant improvement of pain. These early findings merit investing in a larger, well powered study.

## Chapter 8 General discussion

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This PhD thesis aimed to examine the relationship between pre-stimulus somatosensory alpha activity and pain experience. The rationale for this aim stemmed from two prior key findings: 1) that there are fluctuations in pre-stimulus somatosensory alpha activity during the anticipation of pain, possibly reflecting an attentional mechanism (Babiloni et al., 2003; Del Percio et al., 2006; May et al., 2012); and 2) that these fluctuations in pre-stimulus somatosensory alpha activity might be related to the experience of pain, with higher pre-stimulus somatosensory alpha activity related to lower perceived pain intensity (Babiloni et al., 2006; Tu et al., 2016). However, to date, evidence for this relationship is mostly correlational, limiting the interpretation of how pre-stimulus somatosensory alpha activity might affect pain experience. Moreover, as uncertainty about pain intensity also affects pain experience and possibly pre-stimulus alpha activity (Franciotti et al., 2009), this might be a confound in the relationship between pre-stimulus somatosensory alpha activity and pain experience. Therefore, to explore the relationship between pre-stimulus somatosensory alpha activity and pain experience, this thesis reported four studies, designed to examine:

- 1) If, and how pre-stimulus alpha activity might affect pain experience.
- 2) If the relationship between pre-stimulus somatosensory alpha activity and pain experience is influenced by uncertainty about pain intensity.
- 3) If the relationship between pre-stimulus somatosensory alpha activity and pain experience is influenced by fear of pain and pain catastrophising.

This final chapter is presented in three main sections addressing: (i) a summary of key findings with respect to each of the three objectives above and how these findings contribute to our understanding of the relationship between pre-stimulus somatosensory alpha activity and pain experience; (ii) limitations of the studies of this thesis; and (iii) the clinical relevance of the findings of the four studies.

## 8.1 Key findings and critical discussion of findings

*Objective 1: does pre-stimulus alpha activity affect pain experience, and if so, how?*

Study 1 (Chapter 4) attempted to replicate the finding by Babiloni et al. (2006) and Tu et al. (2016) of a negative correlation between pre-stimulus somatosensory alpha activity and pain experience. Study 1 measured pre-stimulus alpha activity with electroencephalography (EEG) over the ipsi- and contralateral somatosensory region (with respect to the stimulated hand) during the application of experimental pain stimuli, in 19 healthy pain-free participants. The findings of Study 1 indicated a marginally significant positive correlation between pre-stimulus somatosensory alpha activity and perceived pain, in the ipsi- and contralateral region. This is in contrast with the findings of Babiloni et al. (2006) and Tu et al. (2016), who both found a negative correlation between pre-stimulus somatosensory alpha activity and perceived pain intensity.

Pre-stimulus alpha power in the bilateral somatosensory region is significantly reduced for predictable moderately painful stimuli compared to non-painful stimuli before pain onset (Babiloni et al., 2003). Moreover, the findings by Babiloni et al. (2006) and Tu et al. (2016) suggest that higher pre-stimulus somatosensory alpha (i.e., less of a reduction of pre-stimulus alpha) is associated with lower perceived pain intensity. In contrast, the marginally significant correlation as found in Study 1 would suggest that higher pre-stimulus somatosensory alpha activity is associated with higher perceived pain

intensity. This difference might (in part) be explained by a difference in approach in the calculation of the alpha outcome that was used for statistical analysis. The present study used untransformed, absolute alpha power to investigate differences in pre-stimulus somatosensory alpha activity between conditions (certain and uncertain pain intensity). In contrast, Babiloni et al. (2006) did not use the average absolute alpha power over a certain time window as their outcome. Instead, they calculated the amount of change in alpha power during a period of interest compared to a baseline period to use as their alpha outcome (event-related synchronization/event-related desynchronization (ERS/ERD)). This type of calculation allows for the interpretation of changes within a condition, e.g. during the expectation of predictable pain, alpha activity was significantly decreased compared to the baseline period. The present study in contrast, aimed to investigate differences in alpha activity between conditions, allowing for conclusions on whether alpha power is higher or lower comparing conditions, e.g., the certain expectation compared to the uncertain expectation condition. It did not answer whether alpha activity was increased or decreased compared to a baseline period. Finally, Tu et al. (2016) did not use untransformed pre-stimulus somatosensory alpha power either to assess a relationship between alpha activity and pain experience, but normalised alpha outcomes (by subtracting the respective mean and dividing by the respective SD for each participant).

Nonetheless, Study 1 and those of Babiloni et al. (2006) and Tu et al. (2016) have important similarities. All three studies found a relationship between alpha and pain experience in the somatosensory region, and all identified this relationship during the final second before pain onset: from -1 to 0s in Study 1, from -1 to -0.5s (Babiloni et al., 2006), and from -0.22 to -0.03s (Tu et al., 2016). Thus, despite the difference in the direction of the relationship, the three studies all suggest a relationship between pain and alpha activity at the same location and in a similar time window before pain onset.

In addressing if and how pre-stimulus alpha activity might affect pain experience Study 1 was limited by its correlational nature. This was partly overcome by Study 3 (tACS study; Chapter 6). The findings of Study 3



confirmed the existence of a negative (not positive) relationship between pre-stimulus somatosensory alpha activity and pain experience as per Babiloni et al. (2006) and Tu et al. (2016). Study 3 was, to our knowledge, the first to demonstrate that, compared to sham stimulation, increasing somatosensory alpha activity with tACS was associated with a significant reduction of perceived pain intensity and pain unpleasantness. This provides a first indication of a causal relationship between somatosensory alpha activity and pain experience.

The preliminary findings of Study 4 (mindfulness study; Chapter 7) offer further evidence that an increase of somatosensory alpha activity before pain onset might lessen pain experience. Study 4 addressed the lack of understanding of the neurophysiological mechanism responsible for the reduction of pain following a mindfulness-based intervention. Where a modulation of pre-stimulus somatosensory alpha activity by a mindfulness-based stress reduction (MBSR) intervention had been found previously for non-painful somatosensory stimuli (Kerr et al., 2011), to our knowledge no study had yet addressed the effect of mindfulness meditation on pre-stimulus somatosensory alpha activity for painful somatosensory stimuli. Although limited, the findings of Study 4 suggested that completing an eight week MBSR course was associated with reduced perceived pain accompanied by an increase of pre-stimulus somatosensory alpha activity. Furthermore, the data also showed an increase of resting-state somatosensory alpha activity.

Although the findings for somatosensory alpha tACS (Chapter 6) and a mindfulness-based intervention (Chapter 7) were promising, the third intervention, listening to alpha binaural beats, did not demonstrate a significant reduction of pain experience (Study 2; Chapter 5). The alpha binaural beats study was based upon a small number of studies that demonstrated an increase of alpha activity during alpha binaural beats as a result of entrainment (Ecsy, 2014; Ioannou et al., 2015). However, two other studies did not find an increase of alpha activity (Gao et al., 2014; Vernon et al., 2014). Thus, evidence with respect to alpha binaural beats leading to an increase of alpha

activity were mixed. Furthermore, the studies that found an increase of alpha activity did not find an increase of somatosensory alpha specifically. However, as we did not carry out any EEG recordings during the listening to binaural beats, we cannot conclude with certainty whether or not the alpha binaural beats were successful in increasing somatosensory alpha activity.

Irrespective of whether alpha binaural beats increased somatosensory alpha activity or not, the findings of this thesis demonstrate that some neuromodulatory interventions are more successful in changing pain experience than others. Some approaches might be more effective in increasing somatosensory alpha activity (to reduce pain), which could be related to the way in which they manipulate somatosensory alpha activity. Each intervention manipulated somatosensory alpha activity via a different route. MBSR training, an endogenous manipulation of somatosensory alpha activity, provided promising tentative evidence of both an increase of somatosensory alpha activity before pain onset and a reduction of pain experience. A direct exogenous manipulation of somatosensory alpha activity by tACS also resulted in a significant reduction of pain experience. Although alpha tACS and listening to alpha binaural beats are both types of exogenous rhythmic stimulation, tACS as a type of electrical stimulation directly influences neural activity, whereas binaural beats as a type of sensory rhythmic stimulation influence neural activity indirectly via sensory pathways. The indirect exogenous method of listening to binaural beats did not result in a reduction of pain experience. To conclude, interventions that provide a direct exogenous or endogenous manipulation might be a more promising approach to increasing somatosensory alpha activity and reducing pain than an indirect exogenous manipulation of auditory stimulation.

Finally, where Babiloni et al. (2006) and Tu et al. (2016) only assessed the relationship between pre-stimulus somatosensory alpha and perceived pain *intensity*, Studies 3 and 4 suggested that pre-stimulus somatosensory alpha activity is also related to perceived pain *unpleasantness*. Interventions (tACS and MBSR) to increase pre-stimulus somatosensory alpha activity were

associated with a reduction of both perceived pain intensity and pain unpleasantness. Although perceived pain intensity and unpleasantness are related aspects of pain experience (Turk et al., 1985), perceived pain intensity and unpleasantness can be differentially affected by experimental manipulations. For example, Villemure et al. (2003) found that a change in mood was related to a change in pain unpleasantness, but not pain intensity. Perlman et al. (2010) who assessed the effects of meditation on pain experience in novice and long-term meditators, found that open monitoring meditation resulted in a significant reduction of self-reported pain unpleasantness in long-term meditators compared to novices, but no significant reduction in self-reported pain intensity was found. Studies 3 and 4 suggest that interventions increasing somatosensory alpha activity may reduce both perceived pain intensity and unpleasantness. Notably, this finding suggests that the relationship between pre-stimulus somatosensory alpha activity and pain experience not only entails the sensory dimension but also the affective dimension of pain experience.

To summarise, the first objective was to examine if, and how pre-stimulus alpha activity might affect pain experience. With an initial confirmation of the relationship between pre-stimulus somatosensory alpha activity and pain experience in Study 1, it was the findings of Studies 3 and 4 that were crucial in advancing our understanding of the relationship between pre-stimulus somatosensory alpha activity and pain experience. These two studies provided novel findings, demonstrating that manipulation of somatosensory alpha activity before the onset of pain to increase alpha results in a reduction of pain experience, thus suggesting that pre-stimulus somatosensory alpha activity and pain experience might be causally related.

*Objective 2: Is the relationship between pre-stimulus somatosensory alpha activity and pain experience influenced by uncertainty about pain intensity?*

The four studies of this thesis also examined the influence of uncertainty about pain intensity on the relationship between pre-stimulus somatosensory alpha activity and pain experience. As uncertainty about the intensity of upcoming pain affects pain experience (Lin et al., 2014; Ploghaus et al., 2001) and possibly also pre-stimulus alpha activity (Franciotti et al., 2009), uncertainty about pain intensity could be a confound in the relationship between pre-stimulus somatosensory alpha activity and pain experience. Uncertainty about pain intensity is associated with higher perceived anxiety (Ploghaus et al., 2001), higher threat value, and enhanced capture of attention by pain (Crombez et al., 1998; Morley, 2008). Thus, an influence of uncertainty about pain intensity on the relationship between somatosensory alpha activity and pain experience could provide some insight into how pre-stimulus alpha might be involved in the preparation for an anticipated painful event and the experience of pain. However, to our knowledge, no study had addressed this to date.

The findings of Study 1 firstly confirmed the influence of uncertainty about pain intensity on pain experience. In line with the findings of Lin et al. (2014) and Ploghaus et al. (2001), both perceived pain intensity and pain unpleasantness were significantly increased when anticipated pain intensity was uncertain, compared to certain. Furthermore, there was an initial indication of an influence of uncertainty on pre-stimulus somatosensory alpha activity. Statistical analysis did not show a significant main effect of uncertainty on pre-stimulus somatosensory alpha activity, only a marginally significant interaction between uncertainty, time, and somatosensory region (ipsi- and contralateral) was found. However, visual inspection of the topographies displaying the difference in alpha power when pain intensity was certain compared to uncertain suggested that pre-stimulus somatosensory alpha power was increased when pain intensity was uncertain. Importantly, alpha power was increased over the ipsilateral somatosensory region with respect to the

stimulated hand specifically: the region irrelevant to the processing of the anticipated pain stimulus. This could reflect more prominent de-activation of the irrelevant somatosensory region when pain intensity is uncertain, to facilitate processing in the relevant contralateral somatosensory region.

Study 1 showed some initial evidence that uncertainty about pain intensity had an influence on pain experience and pre-stimulus somatosensory alpha activity separately, but not on the relationship between pre-stimulus somatosensory alpha activity and pain experience directly. Comparing the effect of an intervention on pain experience (by increasing alpha) for a setting of certain and uncertain pain intensity did permit assessment of an influence of uncertainty on the relationship between alpha activity and pain. Study 3 indeed demonstrated an influence of uncertainty about pain intensity on the effect of alpha tACS: somatosensory alpha tACS was related to reduced pain experience but only when pain intensity was uncertain, rather than certain. Thus, the findings of studies 1 and 3 indicate that uncertainty about pain intensity should be considered in the relationship between pre-stimulus somatosensory alpha activity and pain experience. Finally, the findings of Study 3 suggests that interventions targeting somatosensory alpha activity may have the potential to reduce pain experience, but that a person's expectations about the intensity of pain must also be taken into account. The application of somatosensory alpha tACS might be more appropriate in clinical settings associated with higher uncertainty about pain and/or higher perceived threat.

Finally, although for the effects of alpha tACS (Study 3) an influence of uncertainty about pain intensity was present, this was not the case for the MBSR intervention (Study 4). The individual data suggested a reduction of perceived pain intensity and unpleasantness post-intervention in both the certain and uncertain condition. Thus, this suggest that the influence of uncertainty on the reduction of pain might be different for the direct exogenous modulation of alpha by tACS and the endogenous modulation of alpha by a mindfulness-based intervention.

An influence of uncertainty about pain intensity on the relationship between pre-stimulus somatosensory alpha activity and pain experience permits further interpretation of the role of pre-stimulus alpha activity in pain experience. Uncertainty is an important influence on the capture of attention by pain. It is not just (anticipated) pain that captures attention, but particularly pain that is uncertain and more threatening (Morley, 2008). The application of somatosensory alpha tACS (Study 3) only led to a significant reduction of pain experience when pain intensity was uncertain. This provides a first indication that bottom-up capture of attention might be involved in the modulation of pre-stimulus somatosensory alpha activity during the anticipation of pain.

Pre-stimulus alpha activity is considered to have a domain-independent function, i.e., a similar involvement of alpha has been found across sensory domains: pre-stimulus alpha activity is involved in the preparation for an upcoming stimulus and reflects an attentional mechanism that guides information processing (Foxe & Snyder, 2011). It has previously been shown that pre-stimulus somatosensory alpha activity is modulated by voluntary top-down direction of attention, both for non-painful (Jones et al., 2010; Van Ede et al., 2011) and painful somatosensory stimuli (Del Percio et al., 2006; May et al., 2012). The studies of this thesis suggest that pre-stimulus somatosensory alpha activity during the anticipation of pain is not only modulated by top-down attentional influences but also bottom-up attentional influences. This suggests that the guiding of processing of anticipated pain by pre-stimulus somatosensory alpha during is not just a reflecting one particular attentional mechanism, but instead a dynamic interaction of the two main attentional systems. This is in line with the attentional mechanism described in the neurocognitive model of attention to pain (Legrain et al., 2009). This model describes two main modes of attention relevant in the perception of pain, bottom-up capture of attention and top-down attentional selection (reflecting a goal-directed process that prioritises information that is relevant for the present goal). Importantly, the model also stresses the interaction of bottom-up and top-down attentional processes. Top-down attentional processes can both facilitate and inhibit the bottom-up capture of attention by pain. When attentional load for another task is high (the amount of attention invested in a task), there will be

less attentional capture by pain. In contrast, when the painful event has features in common with the features that are part of the attentional set (mental set of stimulus features that are identified as task-relevant to the participant), capture of attention by pain is likely to be enhanced. Thus, the modulation of pre-stimulus somatosensory alpha activity during the anticipation of pain might similarly reflect the 'sum' of bottom-up and top-down attentional influences; top-down influences that either enhance the or diminish the capture of attention by pain. A systematic investigation of the interplay of top-down and bottom-up attentional mechanisms has, to our knowledge, not been performed yet for pre-stimulus somatosensory alpha activity. Hauck et al. (2015) did demonstrated a modulation of alpha activity by both top-down and bottom-up influences in response to pain though (alpha after pain onset). To investigate these two influences simultaneously, painful laser stimuli were delivered on either the index or the ring finger of the left hand (site of stimulation was randomised). To assess bottom-up influences pain stimuli at high- and low-intensity were delivered, reflecting high and low bottom-up capture of attention respectively. To assess top-down influences the participants were instructed before each stimulus to direct their attention to either the index of the ring finger. This resulted in four conditions: high-intensity & attended, high-intensity & unattended, low-intensity & attended, and low-intensity & unattended. In response to the pain stimulus, alpha activity over the central region was found to be affected by both the top-down direction of attention and bottom-up capture of attention. There was a stronger decrease of alpha when the pain stimulus was attended compared to unattended. Furthermore, there was a stronger decrease of alpha when the pain stimulus was of high intensity compared to low intensity. However, the study by Hauck et al. (2015) focuses on changes in alpha activity in response to pain, i.e., after pain onset. A systematic investigation of the interplay of top-down and bottom-up attentional mechanisms has, to our knowledge, not been performed yet for pre-stimulus alpha activity. An important next step in improving understanding of how pre-stimulus somatosensory alpha activity is involved in pain processing and pain experience, would be to investigate how different attentional influences might interact in shaping the alpha response in in anticipation of pain.

To summarise, the second objective was to examine if the relationship between pre-stimulus somatosensory alpha activity and pain experience is influenced by uncertainty about pain intensity. Study 1 provided an first indication of an influence of uncertainty on pre-stimulus somatosensory alpha activity. Furthermore, Study 3 demonstrated an influence uncertainty about pain intensity on the reduction of pain experience during the application of alpha tACS. Finally, with uncertainty associated with enhanced capture of attention by pain, studies 1 and 3 together uniquely suggest that pre-stimulus somatosensory alpha activity might be influenced by the bottom-up capture of attention.

*Objective 3: Is the relationship between pre-stimulus somatosensory alpha activity and pain experience influenced by fear of pain and pain catastrophising?*

The four studies of the thesis examined the influence of pain catastrophising and fear of pain, each key components of the fear-avoidance model of chronic pain (Leeuw et al., 2007; Vlaeyen et al., 1995). Fear of pain and pain catastrophising affect pain experience for both experimental pain (Hirsh et al., 2008; Parr et al., 2012) and chronic pain (Severeijns et al., 2001; Zale et al., 2013). Moreover, pain catastrophising can affect the outcomes of pain treatment (Riddle et al., 2010; Wertli et al., 2014). Thus, given that fear of pain and pain catastrophising are important in chronic pain and might impact the efficacy of interventions to reduce pain, the relationship between fear of pain/pain catastrophising and the reduction of pain experience by the interventions alpha tACS and MBSR was assessed in Studies 3 and 4.

Study 3 provided evidence for a relationship between pain catastrophising and the efficacy of alpha tACS in reducing pain experience. Alpha tACS significantly reduced perceived pain intensity and unpleasantness when pain intensity was uncertain. Furthermore, the reduction of perceived pain intensity as a result of alpha tACS was significantly positively correlated



with pain catastrophising. This suggests that a larger reduction of pain by alpha tACS might be related to higher levels of pain catastrophising. However, this relationship did not survive correction for multiple comparisons at a significance level of .0125. The individual data of the four intervention participants in Study 4 did not suggest a relationship between fear of pain and/or pain catastrophising and the reduction of pain experience following an MBSR training.

To summarise, the third objective was to examine if the relationship between pre-stimulus somatosensory alpha activity and pain experience is influenced by fear of pain and pain catastrophising. Neither Study 3 or 4 demonstrated evidence for an influence of fear of pain. Study 3 did suggest an influence of pain catastrophising; higher levels of pain catastrophising might be related to a larger reduction of pain by alpha tACS. This suggests that alpha tACS applied over the somatosensory region might be particularly effective in reducing pain in individuals with a high pain catastrophising score.

## **8.2 Limitations**

This PhD thesis comprised four studies that were designed to collectively examine the relationship between pre-stimulus somatosensory alpha activity and pain experience. The first study assessed this relationship between pre-stimulus alpha activity and pain experience without any specific intervention. The following three studies each investigated the potential of a different intervention to reduce pain experience, to assess if, and how the manipulation of somatosensory alpha activity might affect pain experience. A number of experimental methods and measures were applied to induce and assess an experience of pain, to manipulate uncertainty about pain, and to assess the neurophysiological response during the anticipation of pain. Here, the main limitations of the methodologies applied in this thesis will be considered.

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## Pain experience

(i) Experimental pain to induce an experience of pain.

This thesis examined the relationship between alpha activity and pain experience in an experimental pain setting. Investigating clinical pain has several advantages in being able to translate this work directly to a pain population, however clinical pain is difficult to control and highly individual. The examination if, and how, interventions targeting alpha activity might affect pain (and alpha) is at an early-stage. Therefore, the emphasis here was on investigating pain experience in a standardised and controlled setting by using an experimental pain stimulus. Furthermore, applying pressure pain as the experimental pain stimulus in the studies of the thesis was intended to facilitate the translation of the findings to a clinical pain population. Pressure pain stimuli have been applied in the study of healthy and clinical populations and is the most commonly applied stimulus to assess the pain response in clinical pain populations (Plaghki & Mouraux, 2003). Nonetheless, as acute experimental pain and clinical/chronic pain are distinct phenomena, some care should be taken when generalising findings of this thesis to a clinical setting. Experimental pain is different from naturally occurring pain in fundamental ways; they differ with respect to pain duration, range of pain intensities, and controllability (Edwards et al., 2005). Experimental pain is often much more predictable and less threatening. Any conclusion on the potential of the three interventions applied in this thesis in a clinical setting is tentative and should take into account the limitations of a direct comparison between experimentally-induced acute pain and chronic pain.

(ii) To assess pain experience two rating scales were used to measure perceived pain intensity and unpleasantness

This thesis examined pain experience by assessing perceived pain intensity and unpleasantness after each pain stimulus using two rating scales.

Rating scales are commonly applied to assess pain experience; they are easy and quick to administer and are reliable and valid measures (e.g., Ferreira-Valente et al., 2011; Price et al., 1994; Williamson & Hoggart, 2005). The application of the two rating scales in this thesis allowed for an important first assessment of how pain experience might be affected by the interventions targeting alpha, with perceived pain intensity reflecting the sensory dimension and perceived pain unpleasantness the affective dimension of pain experience. Both for the alpha tACS and MBSR intervention a change in pain experience was detected using the rating scales: a reduction of perceived pain intensity and pain unpleasantness. However, the representation of pain experience by these two ratings is somewhat limited. Pain is a multidimensional (Melzack, 2001) and highly individual and subjective experience (Coghill, 2010). Assessing pain experience with a rating scale can only capture part of the information on what an individual is experiencing (Williamson & Hoggart, 2005). In line with this, in a clinical setting, a pain intensity/unpleasantness rating by a patient does not fully represent the experience and widespread impact of the chronic pain. Thus, especially when further investigating the interventions in a clinical pain setting, it should be considered to add additional measures to further explore the changes in pain experience. For instance, when further examining the MBSR intervention in a clinical setting. Assessing a change in perceived pain intensity and unpleasantness and whether this is associated with an increase of somatosensory alpha activity was an essential first step in better understanding the effect of this intervention and the neurophysiological mechanism involved. However, the theoretical mechanisms proposed to explain the effects of mindfulness on pain remain largely unconfirmed. Was there indeed a change in the interpretation of pain, a different in attitude towards pain (acceptance, self-compassion), and/or a better regulation of emotions and attention? A full understanding of not only if a mindfulness-based intervention can reduce pain, but also of the key mechanisms involved in this change is essential for further development/optimal application of mindfulness-based interventions in pain management.

To summarise, the methods to induce and assess an experience of pain as applied in the studies of this thesis were selected to address the aims of the thesis in a standardised and controlled fashion, as the studies of this thesis represent an early-stage investigation the relationship between pre-stimulus somatosensory alpha activity. However, It should be taken into account that there are limitations in the generalisation of the present findings to a clinical pain population. Moreover, further assessment of the multidimensional experience of pain beyond perceived pain intensity and unpleasantness could provide a valuable addition in interpreting the effect of the interventions in a clinical pain setting.

#### Uncertainty about pain intensity: the visual cue – pain stimulus paradigm

To examine the influence of uncertainty about pain intensity on the relationship between pre-stimulus somatosensory alpha activity and pain experience a visual cue - pain stimulus paradigm was developed for the studies of this thesis. The use of visual cues to manipulate expectations about upcoming pain is well-established method and has been applied successfully to manipulate uncertainty about pain intensity specifically. The application of visual cues to induce uncertainty about the intensity of an upcoming stimulus modulates perceived pain (Brown et al., 2008; Lin et al., 2014; Ploghaus et al., 2001). Furthermore, participants are able to correctly report which visual cue is predictive and which one is not predictive of pain intensity post-experiment (Lin et al., 2014).

An essential difference between the paradigms of these studies (Brown et al., 2008; Lin et al., 2014; Ploghaus et al., 2001) and the paradigm of this thesis relates to how the uncertain and certain trials were delivered. In the other studies trials with certain and uncertain pain intensity were intermixed. Thus, participants alternated between a state of certainty and uncertainty from trial to trial, resulting in a brief within-trial state of uncertainty. In contrast, in the four studies of this thesis, the certain and uncertain trials were delivered in separate

blocks. This resulted in an investigation of uncertainty not as a brief trial-to-trial state, but uncertainty as a more prolonged state over an entire block. The manipulation of uncertainty in this fashion also modulated perceived pain (and somatosensory alpha activity) as was found in Study 1. Furthermore, uncertainty was found to influence the reduction in perceived pain for alpha tACS. Thus, this demonstrates that inducing a more prolonged state of uncertainty effectively influenced pain experience.

Similar to the application of experimental pain stimuli and rating scales, a limitation for the use of the visual cues is present when we think about the translation of these findings to a clinical pain setting. Study 3 showed an influence of uncertainty on the outcome of the alpha tACS intervention, which suggested that uncertainty about pain should be considered when applying tACS to manage pain (i.e., the intervention might be more appropriate in some settings than others). However, there is a question of how much uncertainty as evoked with a visual cue (an experimental manipulation of uncertainty) translates to uncertainty in a clinical pain setting. Using a more prolonged state of uncertainty instead of alternating between certain/uncertain on trial-by-trial basis is likely to be more comparable with the uncertainty and threat of pain a patient might experience when having to undergo a potentially painful/unpleasant medical procedure. Nonetheless, assessing the influence of uncertainty (reflecting a higher threat value) using a manipulation more resembling of a clinical setting would be a relevant next step in the assessment of alpha tACS in a clinical pain setting. For instance, by applying a manipulation to induce higher threat of pain similar to the paradigm of Höfle et al. (2013). They investigated the pain response in participants viewing a needle (threatening context) versus a cotton bud (non-threatening context) approaching the hand during the anticipation of pain. Thus, mimicking a situation of receiving an injection. Importantly, they found that the amount of threat experienced during the anticipation of pain influenced not only perceived pain unpleasantness but also pre-stimulus somatosensory alpha activity.

### Pre-stimulus somatosensory alpha activity

To assess the relationship between pre-stimulus somatosensory alpha activity and pain experience EEG was recorded in Studies 1 and 4 of this thesis. The decision to focus on alpha activity in the pre-stimulus period specifically was driven by the literature. Fluctuations in pre-stimulus somatosensory alpha activity during the anticipation of pain, possibly reflecting an attentional mechanism had been found (Babiloni et al., 2003; Del Percio et al., 2006; May et al., 2012). Importantly, these fluctuations in pre-stimulus somatosensory alpha activity were shown to relate to pain experience, with higher pre-stimulus somatosensory alpha activity related to lower perceived pain intensity (Babiloni et al., 2006; Tu et al., 2016). Therefore, this thesis set out to explore the relationship between pre-stimulus somatosensory alpha activity and pain experience, and specifically address if, and how pre-stimulus alpha activity might affect pain experience, i.e., if a manipulation to increase pre-stimulus somatosensory alpha activity would lead to a reduction of pain experience.

EEG is a non-invasive and relatively inexpensive method to directly measure neural activity. Its biggest advantage lies in its high temporal resolution (Cohen, 2014; Davidson et al., 2000; Luck, 2005), which makes EEG particularly suitable to answer questions about quick dynamic changes in neural activity (Cohen, 2014) and the examination of oscillatory neural activity. Therefore, EEG was a suitable neuroimaging technique for the objectives of this thesis. However, a major limitation of EEG is its spatial resolution. EEG measures neural activity with a set of electrodes placed on the scalp. To focus on alpha activity in the somatosensory region in this thesis two sets of electrodes were selected to represent the ipsi- and contralateral somatosensory region (electrode locations C3, C5, CP3, CP5, and C4, C6, CP3, and CP5 respectively). These electrodes were overlapping with the electrode locations as identified by Babiloni et al. (2006) and Tu et al. (2016) where alpha activity had a significant relationship with perceived pain intensity. Tu et al. (2016) found a significant relationship for the bilateral somatosensory

scalp region with a maximum at electrode location C4, Babiloni et al. (2006) found a significant relationship at electrode location CP3 specifically. It is difficult to reconstruct the exact neuroanatomical origin of the activity as measured on the scalp. Activity measured by an electrode on the scalp reflects activity not only from regions directly below the electrode but from more distal regions as well. This limits how specific we can be in our conclusions about the EEG activity as measured over somatosensory scalp regions originating from somatosensory neural regions solely.

Although there are limitations in the certainty with which it can be concluded that the averaged alpha activity of the selected electrode locations reflects somatosensory alpha (only), there is clear support available that the alpha activity as measured over these scalp regions reflects somatosensory alpha. Tu et al. (2016) who found a significant relationship between pre-stimulus alpha and pain over bilateral somatosensory scalp regions, also carried out a fMRI study in an independent sample of participants to identify the specific brain areas whose functional state showed a similar relationship with perceived pain. The authors reported a pattern of spatial congruence between the results of the EEG and fMRI experiment. The scalp distribution of the alpha oscillations related to pain experience was congruent with the spatial distribution of a subset of regions identified in the fMRI experiment, i.e., the bilateral primary somatosensory cortex. Another approach in gaining more certainty about effectively measuring changes in somatosensory alpha activity is to select electrodes for analysis based on the EEG response to a tactile or painful somatosensory stimulus (post-stimulus alpha response). Thus, sensors demonstrating the largest response to a somatosensory stimulus were selected to examine pre-stimulus somatosensory alpha activity. For instance, Anderson and Ding (2011) identified EEG electrode locations CP3 and CP4 using this approach, in accordance with the electrode locations selected in this thesis. Finally, some studies that identified a significant pre-stimulus somatosensory alpha response applied further analysis to identify the neural source of this response. For instance, Baumgarten et al. (2016) who used MEG to measure alpha activity, also included a structural MRI scan for every participant that was used for source reconstruction analysis. They found that the significant pre-

stimulus alpha response for a tactile discrimination task that they detected at a sensor level over the somatosensory scalp region, mainly originated from a source located in the contralateral postcentral gyrus, i.e., primary somatosensory cortex.

Thus, although it is important to keep in mind the limitations in localisation that come with EEG, there is evidence to support that the changes in pre-stimulus alpha activity as measured in this thesis originate from the somatosensory cortex.

### The assessment of a reduction in perceived pain for the interventions

Three studies of this thesis each investigated the potential of a different intervention to reduce pain experience, to assess if, and how the manipulation of somatosensory alpha activity might affect pain experience. Studies 3 and 4 suggest that manipulation of somatosensory alpha activity before the onset of pain to increase alpha results in a reduction of pain experience offering a promising first indication of the potential of interventions that modulate somatosensory alpha activity in pain management. Besides the aforementioned limitation in the generalisation of the findings of this thesis to a clinical pain population, there are two other specific limitations with respect to what we can conclude about the working of the interventions as assessed in this thesis.

- (i) Long-term effects of the interventions on pain experience (and somatosensory alpha activity)

In this thesis a change in pain experience (and somatosensory alpha activity) was measured either during (binaural beats and tACS) or directly after the intervention (MBSR programme). Each of these interventions had not received much examination yet with respect to their effect on pain experience and/or the neurophysiological mechanism involved in the change in pain.



Therefore, assessing the immediate/short-term effects was considered an appropriate starting point for the exploration of the effects of these interventions targeting alpha activity. Where the findings of Studies 3 and 4 were promising, suggesting that interventions targeting somatosensory alpha could be effective in the management of pain, they are limited in so far as they only include short-term effects. Although an effect of somatosensory alpha tACS was found during tACS, the study did not measure pain experience after tACS offset, and therefore cannot answer this question. Equally, for the MBSR programme changes in pain experience and somatosensory alpha activity were only assessed once directly after the course. Further investigation, especially relevant for the clinical application the interventions (alpha tACS, MBSR), should address how long the effects on pain experience remain present. Moreover in the case of alpha tACS stimulation, future studies should also explore whether multiple sessions of stimulation might enhance long-term effects.

(ii) A behavioural assessment only of the effects of alpha tACS and alpha binaural beats

Study 4 (MBSR) examined both changes in somatosensory alpha activity and perceived pain. Studies 2 and 3 (alpha binaural beats and alpha tACS) only assessed changes in perceived pain. For the application of binaural beats and tACS very little (or no) evidence was available from the existing literature on their effectiveness in reducing pain. Studies 3 and 4 served as a first exploration of the effectiveness of these two interventions to reduce pain experience online, i.e., to reduce pain during listening to binaural beats/tACS stimulation. Thus, these studies served as an initial behavioural exploration to inform the conduct of further studies that include EEG recording. However, not recording EEG in the studies of this thesis does introduce some limitations in the interpretation of the findings. For instance, alpha tACS was applied over the somatosensory region to increase alpha. A reduction of pain was found for the application of somatosensory alpha tACS suggesting that an increase of

somatosensory alpha activity was indeed present. This is further supported by a number of EEG studies that detected an increase of alpha activity for tACS (Kasten et al., 2016; Neuling et al., 2013; Vossen et al., 2015; Zaehle et al., 2010). However, based on the present data this cannot be determined with certainty. An obvious next step would be to also assess changes in alpha power directly, by recording EEG. This would allow us to confirm whether somatosensory alpha power is increased comparing before and after alpha tACS, and whether there are differences in the effect of alpha tACS on somatosensory alpha power during a certain and uncertain setting. Similarly, recording EEG during listening to binaural beats could provide a more conclusive answer on why the alpha binaural beats were not effective in reducing pain online, in contrast with the offline reduction of pain experience as found by Ecsy et al. (2016) and Ecsy (2014).

#### Number of participants and statistical power

There is one final limitation to discuss with respect to the interpretation the findings of the PhD thesis. This limitation is based on the number of participants included in the studies of the thesis. Two studies in which statistical analysis was applied included a relatively small number of participants (Study 1, Chapter 4; Study 2, Chapter 5). This introduced a risk that for these studies statistical power was reduced. Statistical power refers to the probability that a statistical test will detect an effect assuming that an effect is present. When participant numbers are low a study can be underpowered, i.e., one cannot be fully confident that an effect that exists in the data will be detected (Field, 2009).

In the first study of the thesis (Chapter 4) 30 participants took part in the experiment. However, due to technical challenges during data collection a relatively large amount of datasets had to be excluded from statistical analysis. Only 19 datasets were included in the final analysis of pre-stimulus somatosensory alpha activity. Although it was considered to collect more

datasets to increase statistical power, based on the time constraints of the PhD project it was eventually decided to prioritise data collection for the other studies of the thesis. The reduced statistical power has implications for the pre-stimulus alpha results of Study 1. Although visual inspection of the TFRs and topographies provided a strong suggestion of an influence of uncertainty about pain intensity on pre-stimulus somatosensory alpha activity, no statistically significant effect of uncertainty was found. A possible explanation for this is that the study was underpowered. Participant numbers were relatively low and considerable variability was present in the data (Figure 4.3). Thus, further well-powered investigation is warranted to confirm the influence of uncertainty on pre-stimulus somatosensory alpha activity. This also applies to the marginally significant positive correlation between pre-stimulus somatosensory alpha activity and perceived pain that was found in Study 1.

Nevertheless, this study did provide significant evidence for an effect of uncertainty on perceived pain intensity and unpleasantness (the behavioural outcomes were based on  $N = 30$ ). Thus, Study 1 did confirm the effectiveness of the visual cue - pressure stimulus paradigm to manipulate expectation about pain intensity, which justified the application of the paradigm for the other studies of the thesis.

The statistical analysis of Study 2 (alpha binaural beats) was based on the data of 17 participants. It was expected that a reduction in pain ratings would be present during binaural beat stimulation compared to white noise (online effect), in line with an offline effect of alpha binaural beats (after auditory stimulation offset) as found by Ecsy et al. (2016) and Ecsy (2014). However, in Study 2 no evidence for an effect of listening to binaural beats on perceived pain was found, nor a trend towards an effect. The findings of Study 2, together with mixed evidence for the effectiveness of binaural beats to increase alpha power from previous research (Ecsy et al., 2016; Ecsy, 2014; Gao et al., 2014; Ioannou et al., 2015; Vernon et al., 2014), put to question whether alpha binaural beats are effective in increasing alpha activity and reducing pain. However, Ecsy and colleagues (2014, 2016) found a significant effect of binaural beats based on the data of 32 participants. Therefore, the lack of an

effect of alpha binaural beats in Study 2 could be related to the lower number of participants that was included, i.e., Study 2 might have lacked statistical power to detect an effect of alpha binaural beats. Thus, some caution should be exercised when disregarding alpha binaural beats as an intervention to reduce pain based on the findings of Study 2. Further replication with a larger sample size would be required to provide a more conclusive answer on the effectiveness of alpha binaural beats to reduce pain.

To conclude, a smaller number of participants in some of the studies of the thesis should be taken into account with respect to the results of these studies. Some caution should be exercised with respect to interpretation of the findings and a more conclusive answer would require a fully-powered follow-up.

### **8.3 Clinical implications**

Many people experience severe and widespread negative effects of chronic pain throughout their lifetime (Breivik et al., 2006; Phillips et al., 2008; Van Hecke et al., 2013). Unfortunately, many patients are not satisfied with their pain management (Breivik et al., 2006); conventional treatment options to manage chronic pain only demonstrate a modest improvement of pain and minimal improvement of physical and emotional functioning (Turk et al., 2011). As an alternative to currently available treatment Jensen et al. (2008) emphasised the potential of neuromodulatory interventions targeting oscillatory neural activity to reduce pain. As pre-stimulus somatosensory alpha activity has been related to pain experience, with higher pre-stimulus alpha activity related to lower perceived pain intensity (Babiloni et al., 2006; Tu et al., 2016), in this thesis we focused on the modulation of somatosensory alpha activity and its potential to manage pain. We expected that neuromodulatory interventions with potential to increase somatosensory alpha activity before the onset of pain might result in a reduction of pain experience. There was some initial evidence that interventions can modulate pre-stimulus somatosensory alpha activity. Kerr

et al. (2011) found a modulation of pre-stimulus somatosensory alpha activity as a result of a mindfulness meditation intervention, but during the anticipation of a tactile stimulus.

This PhD thesis addressed the effect of neuromodulatory interventions, including mindfulness meditation, on somatosensory alpha activity during the anticipation of pain and its relationship with pain experience. The three interventions investigated in the thesis - alpha binaural beats, alpha tACS, and mindfulness meditation – were applied not only to advance the understanding about the relationship between pre-stimulus somatosensory alpha activity and pain experience, but also to provide a first exploration of the potential of these neuromodulatory interventions in the management of chronic pain.

Two interventions supported the potential of reducing pain via an increase of somatosensory alpha activity: alpha tACS and mindfulness meditation. The application of alpha tACS had been shown previously to increase alpha activity (Helfrich et al., 2014; Vossen et al., 2015; Zaehle et al., 2010). However, the application of alpha tACS to reduce pain experience had not been investigated yet. Study 3 showed a significant reduction in pain experience as a result of alpha tACS over the somatosensory region, providing novel evidence for the application of somatosensory alpha tACS as an intervention to manage pain.

In contrast, for mindfulness meditation there was already some evidence to support its potential to reduce pain (e.g. Hilton et al., 2017; Kabat-Zinn, 1982; Zeidan et al., 2010). However, here a clear understanding about the neurophysiological processes involved was largely lacking. Study 4 provided preliminary evidence for both a reduction in pain experience and an increase of somatosensory alpha activity before the onset of pain (pre-stimulus and resting-state alpha) as a result of the 8-week MBSR course. This provided an initial indication that the effects of a mindfulness-based intervention on pain experience might be the result of a modulation of somatosensory alpha activity before pain onset. Together the findings from the tACS study and mindfulness meditation study support the potential of neuromodulatory interventions that target somatosensory alpha activity in the management of pain. Finally, the

findings of the PhD thesis demonstrate that some neuromodulatory interventions are more successful in changing pain experience than others. Although the findings of the alpha tACS study (Chapter 6) and mindfulness meditation study (Chapter 7) were promising, the third intervention investigated (listening to alpha binaural beats; Chapter 5) did not demonstrate a significant reduction of pain experience. Thus, the application of binaural beats does not seem favourable as an option to manage chronic pain.

When evaluating the effectiveness of interventions in pain management, it is important to take into account individual characteristics. Patients with chronic pain condition are not a uniform group, but instead have considerable differences in physical and psychological characteristics (Turk, 2005). The outcome of pain treatment is influenced by patient characteristics, in particular psychological characteristics (McCracken & Turk, 2002; Turk, 2005; Vlaeyen & Morley, 2005), and context (Benedetti, 2002). Thus, in this thesis the influence of some psychological characteristics and context on the reduction of pain by the interventions was assessed, in order to explore the optimal application of the interventions and/or the most suitable group of patients for a certain intervention.

With respect to context it was investigated if expectations about pain intensity influenced intervention outcome, specifically uncertainty about pain intensity. Study 3 demonstrated a significant influence of uncertainty about pain intensity on the effect of alpha tACS: somatosensory alpha tACS was only found to significantly reduce pain experience when pain intensity was uncertain, not when pain intensity was known. This suggests that interventions targeting somatosensory alpha activity may have the potential to reduce pain experience, but that a person's expectations about the intensity of pain must also be taken into account. The application of somatosensory alpha tACS might be more appropriate in certain clinical settings associated with higher uncertainty about pain and/or higher perceived threat.

With respect to individual characteristics we investigated how fear of pain and pain catastrophising might influence intervention outcome. Study 3

pointed to an association between pain catastrophising and the reduction of pain by alpha tACS. A larger reduction of pain was related to higher levels of pain catastrophising. This suggests that alpha tACS applied over the somatosensory region might be particularly effective in reducing pain in individuals with a high pain catastrophising score. Where others found higher pain catastrophising to be related to a less favourable outcome when undergoing knee surgery (Riddle et al., 2010) or receiving conventional treatment for low back pain (including physical therapy and cognitive behavioural therapy) (Wertli et al., 2014), the application of a neuromodulatory intervention such as alpha tACS might be particularly beneficial for these patients with higher pain catastrophising.

Together the findings on uncertainty and pain catastrophising in relation to effects of the alpha tACS intervention support the general recommendation of matching treatment with individual patients and treatment context (Turk, 2005; Vlaeyen & Morley, 2005), and provide an initial indication that factors such as uncertainty about pain, higher perceived threat, and pain catastrophising are important to include in any future evaluation of the potential of neuromodulatory interventions targeting somatosensory alpha activity in a clinical setting.

## **8.4 Future directions**

The findings of this thesis offer a promising start in the investigation of the potential of interventions that modulate somatosensory alpha activity in pain management but further work is needed to investigate the effectiveness of these interventions in a clinical pain setting. To start, a more fundamental question should be addressed: if and how somatosensory alpha activity might be involved in the pain experience of patients with a chronic pain condition.

There is some evidence that patients with chronic pain show differences in alpha activity compared to pain-free controls. The dominant peak in the EEG spectrum (the frequency at which EEG power is maximum), usually present

somewhere within the alpha frequency range (8-12Hz), was found to have a significantly lower frequency in patients with chronic pain, for EEG recorded during rest (Boord et al., 2008; De Vries et al., 2013; Lim et al., 2016; Sarnthein et al., 2006). For example, Sarnthein et al. (2006) demonstrated a significantly lower peak frequency for patients with chronic neurogenic pain, pain initiated by a lesion or dysfunction of the peripheral or central nervous system. Similarly, a significantly lower alpha peak frequency was found in patients with pain following spinal cord injury (Boord et al., 2008), patients with fibromyalgia (Lim et al., 2016), and patients with abdominal pain as a result of chronic pancreatitis (De Vries et al., 2013). Crucially, there has also been a first indication of a relationship between alpha activity over somatosensory and frontal regions and chronic pain experience. Camfferman et al. (2017) recently demonstrated a significant negative relationship between alpha power during rest and chronic pain intensity in a group of 103 patients with a variety of chronic pain conditions (significant moderate negative correlations for electrode locations F3, F4, CP3, and CP4; based on the 10-20 system). Thus, they demonstrated that somatosensory alpha activity might also play a role in the experience of chronic pain and that the modulation of somatosensory alpha activity might be a promising means of reducing chronic pain. But the evidence on the role of (pre-stimulus) somatosensory alpha activity in chronic pain experience is limited. Gaining a better understanding of how changes in somatosensory alpha activity are related to pain experience in patients with chronic pain would allow for more optimal application of neuromodulatory interventions to manage pain.

This thesis aimed to examine somatosensory alpha activity before pain onset and its relationship with pain experience specifically. This aim was founded on key literature demonstrating the involvement of pre-stimulus somatosensory alpha activity in the preparation for an upcoming pain stimulus and a relationship with perceived pain. However, future work should also explore the wider involvement of neural oscillatory activity in pain experience. Pain experience does not solely depend on processing in a single brain region,



it is the result of processing within a widespread neural network, and neural oscillations are responsible for the integration of neural activity across this network (Ploner, Sorg, & Gross, 2016). Considering alpha activity's role in guiding information processing by suppressing the processing of irrelevant information to facilitate the processing of relevant information, alpha activity could be involved not just in guiding processing within the somatosensory cortex but also in guiding the communication between the somatosensory cortex and other functionally connected brain regions that are part of the pain-related neural network. Future work should address the role of pre-stimulus (somatosensory) alpha activity throughout the pain-related network, in particular in regions such as the anterior insula cortex and cingulate cortex that have been found involved in the anticipation of pain as well (Ploghaus et al., 1999; Wiech et al., 2010).

In line with this, where the four studies focused on changes in somatosensory alpha power, to address the communication between regions of the pain-related neural network it would be important to investigate phase-based alpha outcomes too. An assessment of phase coherence or synchronisation in the alpha band between the somatosensory region and other regions of the pain-related neural network would be a key future direction in better understanding the preparation for an anticipated painful event and its relationship with pain experience. The phase of neural oscillations is related to the exact timing of neural activity, and phase consistency or synchronisation is thought to reflect the timing of communication between neural regions (Sauseng & Klimesch, 2008). Similarly, phase consistency has been proposed to reflect connectivity between neural regions, and as reflecting a mechanism of neural integration across neural networks (Bruns, 2004). As such, phase consistency has been pointed out as an essential process in the support of complex cognitive processing, which requires integration of activity in widespread neural networks (Engel & Singer, 2001; Fries, 2005; Lachaux et al., 1999). This type of analysis could for instance assist in investigating if the effect of uncertainty about pain intensity on pre-stimulus somatosensory alpha activity as found in this thesis and the effect of uncertainty on pre-stimulus alpha activity in the anterior insula as found by Franciotti et al. (2009) indeed reflect a

common underlying mechanism (of capture of attention and/or threat detection).

Finally, where the thesis focused on the role of neural oscillatory activity in the alpha frequency-band specifically, oscillatory activity at other frequencies has also been implicated in the coordination of neural processing resulting in an experience of pain (e.g., beta and gamma oscillations), as discussed in detail in a recent review by Ploner et al. (2016). For example, Tu et al. (2016) not only found a significant relationship between pre-stimulus oscillatory activity and pain experience in the alpha-frequency range but also in the gamma-frequency range. Furthermore, Ploner et al. (2016) also discuss how neural oscillations from different frequency ranges can interact in the processing of pain, for example alpha and gamma oscillations. In fact, Tu et al. (2016) found that, although pre-stimulus alpha activity and gamma activity both predicted perceived pain intensity separately, pre-stimulus alpha activity and gamma activity together were significantly better in predicting subsequent perceived pain, suggesting a synergy of the two in neural processing resulting in an experience of pain. However, to date there is little understanding of the relationship between oscillations at different frequencies in the neural processing of pain and pain experience. Thus, future work should address the interaction of neural oscillatory activity across different frequency ranges in pain experience and consider the differential roles of activity in the different frequency ranges.

## **8.5 Conclusions**

The four studies of this thesis together advance our understanding of the relationship between pre-stimulus somatosensory alpha activity and pain experience. Actively manipulating somatosensory alpha activity before the onset of pain using alpha tACS resulted in a significant reduction of pain experience, when pain intensity was uncertain. Furthermore, preliminary results showed that a reduction of pain experience was accompanied by an increase of somatosensory alpha activity before pain onset (both pre-stimulus and

resting-state alpha) as a result of mindfulness meditation. Together these findings showed that pre-stimulus somatosensory alpha activity affects pain experience and provide a first indication of causality. Further understanding of the relationship between pre-stimulus somatosensory alpha activity and pain experience came from the finding that this relationship is influenced by uncertainty about pain intensity. With uncertainty about pain intensity reflecting higher perceived threat and an enhanced capture of attention, this thesis provides initial evidence for an influence of bottom-up capture of attention on pre-stimulus somatosensory alpha activity and the experience of pain. Finally, this thesis also provides valuable first evidence for the potential of neuromodulatory interventions targeting somatosensory alpha activity in the management of pain.

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