UNIVERSITY OF LIVERPOOL

Effects of pain catastrophising on behavioural and cortical responses to pain-related stimuli

Thesis submitted in accordance with the requirements of the University of Liverpool for the degree of Doctor in Philosophy by Xiaoyun Li

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List of abbreviations

In order of use:

fMRI	Functional magnetic resonance imaging
CSQ	Coping Strategies Questionnaire
PCS	Pain Catastrophizing Scale
SI/SII	Primary/ Secondary somatosensory cortex
PCC	Posterior cingulate cortex
PFC	Prefrontal cortex
rACC	Rostral anterior cingulate cortex
EEG	Electroencephalograph
VBM	Voxel based morphometry
DLPFC	Dorsolateral prefrontal cortex
CBT	Cognitive-behavioural therapy
MCC	Mid-cingulate cortex
PET	Positron emission tomography
ERP	Event-related potential
LPP	Late positive potential
DARTEL	Diffeomorphic anatomical registration using exponentiated lie algebra
EOG	Electrooculagraphic
EKG	Electrocardiographic
EMG	Electromyogram
VEP	Visual-evoked potential
AEP	Auditory-evoked potential
SEP	Somatosensory-evoked potential
LEP	Laser-evoked potential
MEG	Magnetoencephalography
GA	Genetic algorithm
MUSIC	Multiple signal classification algorithm
LORETA	Low resolution brain electromagnetic tomography algorithm
LAURA	Local autoregressive average algorithm

CLARA	Classical LORETA analysis recursively applied algorithm
RF	Radio frequency
TR	Time to repeat
TE	Time to echo
High-Cat	High pain catastrophisers
Low-Cat	Low pain catastrophisers
FPQ-III	Fear of Pain Questionnaire - III
STAI-S	State anxiety
STAI-T	Trait anxiety
ANOVA	Analysis of variance
IAPS	International Affective Picture System
IRI	Interpersonal Reactivity Index
SD	Standard deviation
GM	Grey matter
WM	White matter
MNI	Montreal Neurological Institute
CSF	Cerebrospinal fluid
TIV	Total intracranial volume
GLM	General linear model
FDR	False discovery rate
EM	Eye movement
RT	Reaction time
PHG_L	Left parahippocampal gyrus
PHG_R	Right parahippocampal gyrus
IPL	Inferior parietal lobule

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Effects of pain catastrophising on behavioural and cortical responses to pain-related stimuli

Xiaoyun Li

Abstract

Pain catastrophising is an exaggerated negative mental set brought to bear during actual or anticipated pain experience (Sullivan et al., 2001b). People with high pain catastrophising were reported to perceive stronger pain intensity, attribute more pain to others, and solicit higher levels of social support from others when exposed to pain, relative to low pain catastrophisers (Sullivan et al., 2001b, Quartana et al., 2009). Three important models of pain catastrophising, the appraisal model, the attentional model, and the communal coping model, have been proposed to investigate the influence of pain catastrophising on pain-related outcomes. However, the neural basis of pain catastrophising in the social-emotional context among healthy people is poorly understood. This thesis utilised neuroimaging methods and novel experimental paradigms to explore effects of pain catastrophising on behavioural and cortical responses to pain-related stimuli in healthy people. It also investigates the associations between pain catastrophising and structural brain features. A comprehensive review of previous experimental findings was performed to identify novel research questions. Behavioural, eye movement, EEG and MRI data for 6 unique studies were collected.

Chapter One features a review of relevant theories, studies, and findings pertaining to pain catastrophising. The specific research problems and hypotheses investigated in the thesis are explicitly described. Chapter Two describes the theory of the EEG, MRI and eye tracking methods used in the experimental chapters of the

thesis. Chapter Three outlines the methods and materials used for each individual study.

Chapter Four describes the experimental findings of the thesis. In the first study, a paradigm using a varying level of background noise was applied to evaluate the sensitivity to pain cues in high and low pain catastrophisers. No significant differences were found. In the second and third study, the eye tracking method and a dot-probe paradigm were used to measure the attentional processing to pain-related stimuli. High pain catastrophisers responded to probes after pain scenes slower compared to low pain catastrophisers. In the fourth study, ERP data revealed that high pain catastrophisers exhibited differences in ERP components and source activation patterns during the observation of pain pictures. The first four studies of this thesis reported that high pain catastrophisers attributed stronger pain to pain in others. In the fifth study, LEP data showed that high pain catastrophisers reduced perceived pain during viewing of comforting hand postures, and displayed enhanced ipsilateral operculo-insular activation to pictures not showing comforting gestures. In the final study of the thesis, a morphological analysis of cortical and subcortical structures was performed using high-resolution T1-weighted MR images. It demonstrated that alterations to the morphology of selected cortical regions and the dorsal striatum were associated with pain catastrophising.

Chapter Five discusses the findings of each individual study in light of previous research and the implications and inferences that can be drawn from the data. Chapter Six represents a general discussion of the main findings of the thesis. This chapter examines how the findings of each individual study relate to the theories of pain catastrophising. The limitations of the thesis and the implications of the findings for future research are also discussed.

Declaration

No part of this work has previously been submitted in support of another application for a degree or qualification at this or any other University or institute of learning.

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Chapter One

General Introduction

1.1 Pain and antecedents of pain

1.1.1 Antecedents of pain

The International Association for the Study of Pain defined pain as ‘‘an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage’’ (International Association for the Study of Pain Task Force on Taxonomy, 1994, p. 210). This definition takes into consideration that pain is always subjective, a body sensation, and an unpleasant affective experience, and has no absolute relation with tissue damage.

It has been emphasised that the perception of pain is not only related to the noxious input, but also is critically influenced by psychological variables (Wiech and Tracey, 2009). For example, the majority of studies using mood induction on experimentally-induced pain, such as cold pressor pain, report that positive mood attenuates the perception of pain (Weisenberg et al., 1998, Meagher et al., 2001), whereas negative mood heightens pain perception (Wunsch et al., 2003, Kenntner-Mabiala and Pauli, 2005). Experimental data also addresses the influence of emotions/ moods on pain perception. Ploghaus et al. (2001) performed a functional magnetic resonance imaging (fMRI) study using noxious thermal stimulations, and found that high anxiety could elicit stronger pain when a low thermal intensity stimulation was conducted. In addition, clinical studies suggested that increased pain sensitivity was associated with the high co-morbidity between pain and mood disorders, such as post-traumatic stress disorders (Lang et al., 2013, Takeda et al.,

2013) or major depressive disorder (Bair et al., 2003). Recently, a clinical longitudinal study found that the onset of depression and anxiety had the probability to increase the number of pain locations and heighten chronic pain severity (Gerrits et al., 2013). In conclusion, negative moods, such as anxiety and depression, may play an important role in pain perception.

1.1.2 Attitudes toward pain

An attitude is an expression of favour or disfavour towards a person, a place, an object, or an event (Banaji and Heiphetz, 2010). It can be formed from an individual past and present. Allport (1935) defined the attitude as ‘‘a mental and neural state of readiness, organised through experience, exerting a directive or dynamic influence upon the individual’s response to all objects and situations with which it is related’’ (p. 810). The attitude was the most distinctive and indispensable concept in contemporary social psychology (Allport, 1935). Social psychologists conceive that attitudes consist of cognitive, affective, and behavioural components (Forgas et al., 2011). Particularly, the term ‘affect’ commonly refers to a broader concept of general mood. Also, affect can influence attitudes (Ajzen, 2001). For instance, a study about mood effects found that attitudes influenced intentions to eat low-fat food in the context of negative mood (Armitage et al., 1999). Moreover, self-esteem is considered as a primary attitude for self evaluation. Evidence suggests that low self-esteem could prospectively predict depressive symptoms and induce more anxiety during a confrontational interview (Banaji and Heiphetz, 2010).

Indeed, Jensen et al. (1999) proposed that pain attitudes played a central role in predicting pain behaviour and pain perception. Negative pain attitudes, such as attitudes toward pain-related harm, have been associated with increased pain

intensity, pain behaviour (Shen et al., 2013), pain catastrophising, heightened depression and pain disability (Turner et al., 2000, Wong et al., 2011). Pain catastrophising is one of psychological factors mediating pain experiences. In the last two decades, pain catastrophising has received great attention as an important factor of pain experience (Sullivan et al., 1995, Sullivan and Neish, 1999, Sullivan et al., 2001b, Turner and Aaron, 2001, Quartana et al., 2009). The overall aim of the thesis is to investigate effects of pain catastrophising on behavioural and cortical responses to pain-related events in healthy people. It also looks into the correlations between the structural brain alterations and pain catastrophising.

1.2 Pain catastrophising

1.2.1 The definition of catastrophising

The term catastrophising was formally introduced by Ellis (1962), a founder of rational-emotional therapy. An example of a catastrophising attitude is: "How terrible the situation is; I positively cannot stand it!" Subsequently, Beck (1976) incorporated the concept of catastrophising into the cognitive theory of depression. According to Beck's theory, catastrophising was described as a maladaptive cognitive style, in which information was misinterpreted so that negative outcomes were expected (Beck, 1976, 1979, Beck and Emery, 1985). Here are two examples. (1) A teenage is too afraid to start driving training, due to he believes he would get himself into an accident. (2) A staff made a mistake at work and corrected since noticed. However, he worried that someone might find out and he might got fired. Such thoughts are tied to the perception of oneself as vulnerable and as being subject to danger over which one has insufficient control. It also has been suggested that

catastrophising is a risk factor for anxiety. For example, social anxiety disorder was related to catastrophic thinking about the consequences (Hofmann et al., 2005).

1.2.2 The concept of pain catastrophising

Historically, a few fundamental sources have outlined the concept of pain catastrophising (Spanos et al., 1979, Rosenstiel and Keefe, 1983, Chaves and Brown, 1987, Sullivan et al., 2001b). The early work of Chaves and Brown (1987) addressed catastrophising as a tendency to magnify pain information or exaggerate the threat value of pain. Spanos et al. (1979) employed a cold pressor task to measure catastrophising and classified high pain catastrophisers as individuals who expressed more worries about pain and excessively focused on pain stimuli. Finally, Rosenstiel and Keefe (1983) discussed catastrophising in terms of helplessness and the maladaptive coping approach with pain. On the basis of the previous conceptualisations of pain catastrophising, Sullivan et al. (2001b) defined the concept of pain catastrophising as "an exaggerated negative mental set brought to bear during actual or anticipated pain experience".

1.2.2.1 Assessment of pain catastrophising

To quantify pain catastrophising, Rosenstiel and Keefe (1983) developed a self-report instrument - the Coping Strategies Questionnaire (CSQ) with seven subscales, including a catastrophising subscale. The catastrophising subscale reflected helplessness and pessimism in the context of failure to cope with pain-related events. However, this instrument has not fully addressed catastrophising in both aspects of cognition and affectivity. Therefore, Sullivan et al. (1995) postulated a three-dimensional model of pain catastrophising. The Pain Catastrophizing Scale (PCS) has 13-items focusing on factors of magnification, rumination, and

helplessness. Magnification is a tendency to magnify the pain-related events. Rumination is related to inability to constrain pain-related thoughts. Helplessness indicates a failure to cope with negative events. A number of studies utilised confirmatory factor analysis to assess the validity of the PCS in healthy, pain-free volunteers (Sullivan et al., 1995, Osman et al., 1997, Sullivan and Neish, 1999, Sullivan et al., 2001a), chronic pain patients (Sullivan et al., 1998, Van Damme et al., 2002a), gender (Sullivan et al., 2000b), diverse culture groups, and non-English speakers (Severeijns et al., 2002, Van Damme et al., 2002a, Yap et al., 2008). Subsequently, various versions of Pain Catastrophizing Scale have been developed to evaluate pain catastrophising in different populations, such as children (Crombez et al., 2003, Goubert et al., 2006), adolescents (Tremblay et al., 2008), and significant others (Cano et al., 2005). Relative to CSQ which primarily focused on the helplessness component (Rosenstiel and Keefe, 1983), the PCS evaluates broader dimensions of pain catastrophising (Sullivan et al., 1995).

1.2.3 Pain catastrophising and the pain-related outcomes

1.2.3.1 Experimental induced pain

It has been well documented that pain catastrophising correlates with pain intensity, pain related interference and disability, and emotional distress (Sullivan et al., 2001b, Quartana et al., 2009). Sullivan et al. (1995) conducted a laboratory study using a cold pressor test and found that high, compared to low, pain catastrophisers reported stronger pain intensity. In addition, high, compared to low, pain catastrophisers experienced more thought intrusions during cold presser tests, especially when required to suppress their thoughts about pain (Sullivan et al., 1997). Sullivan et al. (1999) has also found that people with high pain catastrophising

reported less pain when they were required to disclose worries about dental pain rather than to suppress the distress during the dental hygiene treatment. A study in chronic musculoskeletal pain patients revealed that patients with high pain catastrophising scores showed little changes in pain threshold and tolerance from first to second cold pressor test when focusing on sensory words, whereas their pain threshold and tolerance showed reductions during focusing on emotional words (Michael and Burns, 2004). It was also reported that children with frequent catastrophic thoughts expressed higher pain during a pressure pain procedure, regardless of the observer was a stranger or their parent (Vervoort et al., 2008).

1.2.3.2 Clinical pain

The relationship between catastrophising and clinical pain has been reported in diverse patient groups, such as, chronic pain associated with spinal cord injury (Turner et al., 2002), musculoskeletal injury (Martel et al., 2008, Wideman et al., 2009), osteoarthritis (Keogh and Eccleston, 2006, Sullivan et al., 2009), whiplash injury (Vangronsveld et al., 2007, Vangronsveld et al., 2008), rheumatoid arthritis (Lefebvre and Keefe, 2002), low back pain (Van Damme et al., 2002a, Goubert et al., 2004a, Peters et al., 2005, Swinkels-Meewisse et al., 2006), postsurgical pain (Pavlin et al., 2005), and fibromyalgia (Van Damme et al., 2002a, Geisser et al., 2003).

Pain catastrophising has been associated with a wide range of pain responses, such as, greater consumption of analgesics (Jacobsen and Butler, 1996), longer hospitalisation (Gil et al., 1992), and higher frequency of pain behaviour performance (Keefe et al., 2000). In clinical studies, catastrophising has been suggested to be related to stronger pain severity among patients with fibromyalgia

(Burgmer et al., 2011), osteoarthritis (Sullivan et al., 2009), and low back pain (Peters et al., 2005). Longitudinal studies also suggest that pain catastrophising may influence long-term effects of pain. For example, high levels of pain catastrophising have been suggested to predict enhanced pain intensity at a 12-month follow-up after total knee replacement (Edwards et al., 2009).

Previous studies also indicated that pain catastrophising, together with depression, affected the long-term pain-related outcomes, such as pain severity and disability (Keefe et al., 2003, Edwards et al., 2006). Pain catastrophising is strongly associated with self-reported physical limitations, reduced likelihood of returning to work, and physical impairment in chronic pain patients (Evers et al., 2003, Goubert et al., 2004a, Gauthier et al., 2006). Pain catastrophising also has an association with heightened disability (Sullivan et al., 2002a). In addition, long-term work disability can be predicted by pain catastrophising in patients with musculoskeletal injuries over timeframes of up to 1 year (Wideman and Sullivan, 2011). The magnification subscale of PCS was strongly correlated with post-surgery pain and functional limitations in patients with osteoarthritis six weeks after a total knee arthroplasty (Sullivan et al., 2009).

1.2.3.3 Fear-avoidance model

The beliefs and attitudes toward pain can affect the experiences of both acute and chronic pain. These beliefs and attitudes also may increase the likelihood of acute pain becoming chronic. Lethem et al. (1983) first proposed the fear-avoidance model to explain the relationship between fear/anxiety and chronic pain. Based on Lethem et al.'s model, Vlaeyen et al. (1995, 2000) suggested a cognitive-behavioural model of fear of movement/(re)injury (Fig. 1.1) to explain how acute low back pain

patients develop a chronic pain problem with a chain of events. The fear of movement/(re)injury model states that when pain is perceived individuals typically can employ two different coping responses to pain based on their previous pain experiences - acceptance or avoidance (Lethem et al., 1983, Vlaeyen et al., 1995, Leeuw et al., 2007, Haythornthwaite, 2013). For majority of individuals, pain is considered as temporary, undesirable and unpleasant, but not catastrophic. In this case, individuals are more likely to confront their pain (acceptance of pain) and have strong motivation to return to normal life. Such a positive response has been reported to be associated with lower pain intensity, less pain-related distress and avoidance, and less disability (McCracken, 1998, Thompson and McCracken, 2011).

On the other hand, in a significant minority of individuals, catastrophising enters the chain of events. Pain catastrophising leads to pain-related fear, such as fear of pain or fear of movement/(re)injury, and thereafter initiates a fear-avoidance cycle that promotes and maintains depression, activity limitations and disability. The fear avoidance model addresses the role of pain catastrophic interpretations following the pain experience, and subsequent fear and hypervigilance to pain. Previous studies have already found associations between fear-avoidance model and pain catastrophising (Crombez et al., 1999, Sullivan et al., 2002b, Boersma et al., 2004, Goubert et al., 2004b, Smeets et al., 2006, Vangronsveld et al., 2008, Woods and Asmundson, 2008). Healthy people with high pain catastrophising avoided strenuous muscle exercises (Sullivan et al., 2002b). Studies of chronic musculoskeletal pain suggested that reduction of fear of movements via graduated performance of feared movements had successfully reduced activity avoidance (Boersma et al., 2004, Woods and Asmundson, 2008). Crombez et al. (1999) also reported a correlation between disability and fear of pain in low back pain patients. In general, reduced fear

of pain and pain catastrophising has been suggested to be associated with less disability (Smeets et al., 2006, Vangronsveld et al., 2008).

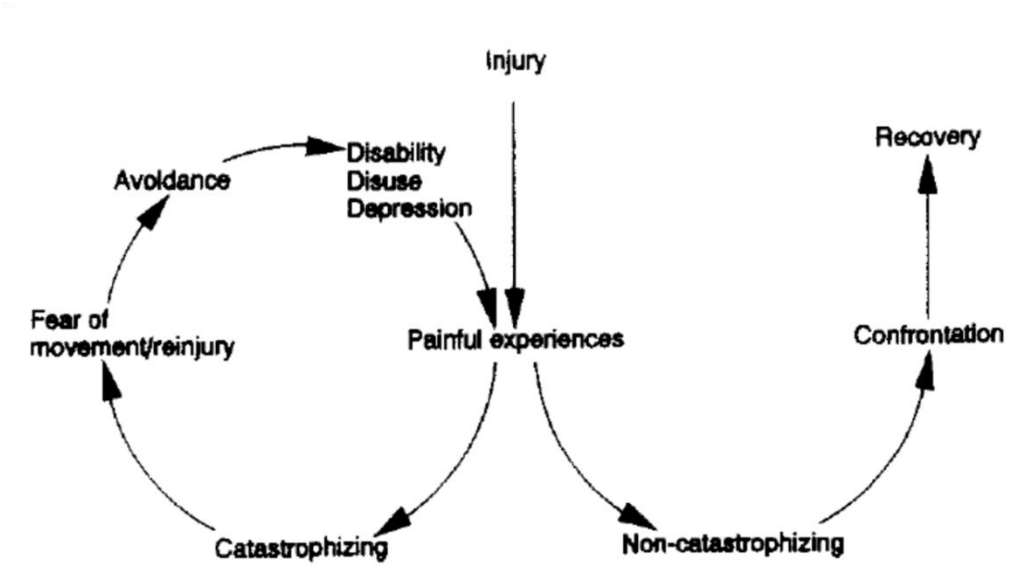

Fig.1.1 Cognitive-behavioural model of fear of movement or (re)injury. Adapted from ‘‘Fear of movement/(re)injury in chronic low back pain and its relation to behavioural performance’’ by Vlaeyen et al., 1995, Pain, 62, 363-372, Fig. 1.

1.2.4 Theories of pain catastrophising

1.2.4.1 Appraisal model

Jensen et al. (1991) have pointed out that pain catastrophising may be related to the concept of appraisal. Appraisal has been framed in the context of the transactional stress and coping model (Lazarus and Folkman, 1984). Lazarus and Folkman (1984) stated that primary appraisal concerns judgements about whether a potential stressor was irrelevant, benign-positive or stressful, whereas secondary appraisals involved in the beliefs about coping opinions and the possible effectiveness. According to this model, Severejins et al. (2004) proposed the appraisal model of pain catastrophising. In this model, magnification and rumination may reflect attention towards and evaluation of a threatening painful stimulus

(primary appraisal), whereas helplessness may reflect a maladaptive ability to cope with pain (secondary appraisal). In support of appraisal model of pain catastrophising, Williams et al. (2011) found a positive correlation between threat appraisal of pain and catastrophising in children suffering induced visceral discomfort. Of particular interest was that children with high pain catastrophising level showed more symptom complaints when the parents verbally expressed their child's symptoms. Other studies suggested that pain catastrophising was associated with other appraisal constructs, like self-efficacy (Sullivan et al., 2001b).

1.2.4.2 Attentional model

Excessive attention to pain is one of the key features of pain catastrophising. Researchers proposed that pain catastrophisers amplify the pain experience through exaggerating a threat value of pain stimuli or pain sensations (Eccleston and Crombez, 1999, Sullivan et al., 2001b, Quartana et al., 2009). Indeed, the attentional model of pain catastrophising is rooted in the cognitive-affective model elaborated by Eccleston and Crombez (1999), which addressed selected attention for pain. The authors suggest that when attention is interrupted by noxious stimuli, a current action is shifted towards an escape from a noxious stimulus. In support of this hypothesis, a study of a tone discrimination task during salient pain stimulation suggested that pain catastrophising may be involved in the process of attentional interruption (Crombez et al., 1998a).

Van Damme et al. (2002b, 2004) used a cueing paradigm to investigate the attentional effects on pain among high and low pain catastrophisers. Results showed that individuals with high pain catastrophising had difficulty disengaging from pain-related events, and showed increased attentional bias towards pain-related

information. In addition, their findings also suggested that high pain catastrophisers had difficulty utilising uncertain information about the occurrence of pain, indicating that high pain catastrophisers may overestimate the probability to experience pain (Van Damme et al., 2004). Clinical findings contributed to this suggestion by demonstrating that chronic back pain patients with high pain catastrophising may habitually overpredict the intensity of forthcoming experienced pain before exposure to a potentially stressing movement (Goubert et al., 2002).

To address the role of attention in pain catastrophising, previous studies showed that pain catastrophising enhanced attentional bias towards pain-related events (Sullivan et al., 1997, Crombez et al., 1998a, Sullivan and Neish, 1999, Goubert et al., 2004b, Michael and Burns, 2004, Vancleef and Peters, 2006). Laboratory data reported that high pain catastrophisers experienced more pain when suppressing distress (Sullivan et al., 1997, Sullivan and Neish, 1999), and showed more vigilance to threatening information (Crombez et al., 1998a, Goubert et al., 2004b). In addition, pain catastrophisers decreased their threshold and tolerance of cold pain sensitivity when attention was distracted by negative affective information (Michael and Burns, 2004), and enhanced attentional interference on the auditory discrimination task during electrocutaneous stimulation (Vancleef and Peters, 2006). Pain catastrophising has also been shown to be associated with enhanced attention to pain in low back pain patients (Quartana et al., 2007).

1.2.4.3 Communal coping model

Sullivan et al. (2001b) proposed that pain catastrophising represented an interpersonal manner of coping with pain. The communal coping model (Keefe et al., 1989, Sullivan et al., 2001b, Turner and Aaron, 2001, Turner et al., 2002) has

been suggested as an explanatory framework of pain catastrophising. According to this model, people with strong pain catastrophising are likely to minimise their pain-related emotional distress through maximising social proximity, or seeking supports or empathic responses from solicitous partners and their social environment. Hence, in order to maximise the probability of drawing others' attention, pain catastrophisers might subconsciously engage in a high frequency of pain behaviours, and amplify pain experience and negative outcomes, such as emotional distress and disability. In turn, pain catastrophisers, inadvertently accelerate and aggravate pain severity and pain-related disability.

In support of the communal coping model, Sullivan and Neish (1999) recruited a group of undergraduate students and investigated them using a dental hygiene procedure. They found that high pain catastrophisers could benefit from disclosure of pain-related emotions. Several studies reported that high, compared to, low pain catastrophisers displayed exaggerated pain behaviours, such as facial expression of pain, in the presence of an observer during experimental pain (Sullivan et al., 2004, Vervoort et al., 2008), or in the presence of a physician during the medical examination (Tsui et al., 2012).

A study of patients with a spinal cord injury reported that chronic pain patients living with a spouse or partner have a higher probability of catastrophising (Giardino et al., 2003). In a study of patients with gastrointestinal cancer pain, caregivers of patients who catastrophised perceived greater levels of pain and provided higher levels of instrumental support (Keefe et al., 2003). Cano et al. (2009a) suggested that pain catastrophising was associated with perceived entitlement to pain-related support. However, the relationship between pain

catastrophising and social support may also feature, in addition to supportive behaviour, punishing and critical responses from spouses or partners of pain catastrophisers (Keefe et al., 2003, Boothby et al., 2004, Cano, 2004, Buenaver et al., 2007). For example, Boothby et al (2004) examined the relationship between pain catastrophising and spouse's responses to pain in chronic pain patients. They found that pain catastrophising did not correlate with solicitous support from partners, rather with punishing responses from spouses. Further, Cano (2004) performed a hierarchical regression analysis to test the interaction between pain duration and catastrophising in chronic pain patients. Their study showed that pain catastrophising was associated with positive spouse responses during comparatively short period of pain, whereas it was associated with punishing spouse responses in the long term. In addition, Lackner and Gurtman (2004) used a circumplex model of interpersonal behaviour and showed that pain catastrophising was associated with a submissive interaction style with a high dependency and demand for support.

1.2.5 Individual differences of pain catastrophising – effects of gender

A number of studies have reported gender differences in pain catastrophising. Females score higher than males in pain catastrophising in both clinical (Jensen et al., 1994, Keefe et al., 2000) and healthy (Sullivan et al., 1995, Sullivan et al., 2000a, Sullivan et al., 2000b, Edwards et al., 2004) populations. Gender differences among healthy volunteers were also observed in the subscales of rumination and helplessness, with females reporting higher scores than males (Sullivan et al., 1995, Osman et al., 2000). Similar findings were reported in another two studies using a cold pressor test (Sullivan et al., 2000a, Sullivan et al.,

2000b). In a patient population, Osman et al. (2000) found that females only scored higher on the rumination subscale than males.

It has been suggested that pain catastrophising could partially mediate gender differences in pain intensity. Sullivan et al. (2000b) examined the gender differences in pain and catastrophising and found that gender effects on pain or pain behaviour no longer existed when pain catastrophising was statistically controlled. Similar findings were reported by Weissmann-Fogel et al. (2008) who showed that statistically significant effects of gender on diffuse noxious inhibitory controls disappeared after controlling for pain catastrophising. Goodin et al. (2009) suggested that females may reduce efficacy of diffuse noxious inhibitory controls due to catastrophising on pain-related events. However, results of hierarchical regression analyses indicated that pain threshold, tolerance, and intensity were consistently predicted by fear of pain rather than catastrophising after controlling for gender before and after a cold pressor test (Hirsh et al., 2008). Thorn et al. (2004) employed the path-analytic model to demonstrate that gender differences in catastrophising and pain responses to cold pressor pain were partially mediated by the Masculinity-Femininity personality trait. In accordance with Thorn et al. (2004), path analysis by Dixon et al. (2004) revealed that gender differences in pain perception were largely attributable to emotional vulnerability through catastrophise thinking during a cold pressor test.

A recent literature review of 10 years of laboratory research in healthy people addressed the relationship between pain and gender (Racine et al., 2012a). They concluded that females compared to males have lower pressure pain thresholds and less thermal and pressure pain tolerances. In line with these

findings, numerous studies have shown that in comparison with males, females reported enhanced pain intensity (Sullivan et al., 2000a, Sullivan et al., 2000b, Keogh and Herdenfeldt, 2002, Edwards et al., 2004, Thorn et al., 2004), reduced pain threshold and tolerance (Keogh and Herdenfeldt, 2002, Edwards et al., 2004, Thorn et al., 2004), and greater overt pain behaviour (Sullivan et al., 2000a, Edwards et al., 2004). In addition, gender differences in the application of coping strategies have been found in both adults (Keogh and Herdenfeldt, 2002) and adolescents (Keogh and Eccleston, 2006). Data suggested that females benefited from emotional focusing, such as relying on more social support and positive self-statements, whereas males employed behavioural distraction to cope with pain (Jensen et al., 1994).

Findings on gender differences in pain perception (Racine et al., 2012a) shed light on the greater proneness to catastrophising in females than males. Racine et al. (2012b) summarised the gender effects on pain experience in four aspects: biological, psychological, social, and the past history. Firstly, the experimental evidence suggests those biological factors including hormonal (estrogens, stress hormones, etc.) and physiological (blood pressure regulation, heart rate, etc.) factors may contribute to gender differences in pain intensity (al'Absi et al., 2000, 2002, Aloisi, 2003, Dixon et al., 2004, Aslaksen et al., 2007). For instance, stress hormones may attenuate pain perception (al'Absi et al., 2000, 2002). Compared to males, females reported higher pain intensity and lower levels of stress hormones during a cold pressor test (al'Absi et al., 2000, 2002). Secondly, pain catastrophising rather than depression and anxiety has been shown to mediate gender differences in pain (Sullivan et al., 2000b, Dixon et al., 2004, Thorn et al., 2004, Hirsh et al., 2008, Weissman-Fogel et al., 2008, Racine et al., 2012b).

Thirdly, the role of gender expectancies on pain is an important determinant of pain responses between genders (Bartley and Fillingim, 2013). The female role is stereotypically associated with a greater perception of pain. Previous studies suggested that both genders believed that females were willing to report pain more than males (Robinson et al., 2001), and that such gender expectancies may influence pain perception (Fillingim et al., 2002, Robinson et al., 2003). Finally, only a limited number of studies indicated that past pain-related experiences may influence pain sensitivity in females but not in males (Fillingim et al., 1999, 2000, Fillingim and Edwards, 2005). Taken together, aforementioned studies suggest that females report greater pain intensity and engage in catastrophising more than males.

1.2.6 Neural correlates of pain catastrophising

1.2.6.1 Functional differences of pain catastrophising

The advent of non-invasive functional neuroimaging techniques such as functional magnetic resonance imaging opened the possibility for evaluation of the neural circuits involved in the experience of pain, including the sensation of pain and pain-related psychological variables (Tracey, 2008, Lee and Tracey, 2013). Over the past ten years, only a few studies have addressed the neural correlates of pain catastrophising during experimental pain (Gracely et al., 2004, Seminowicz and Davis, 2006, Lloyd et al., 2008, Jensen et al., 2010, Burgmer et al., 2011, Vase et al., 2012, Lin et al., 2013). In a study of fibromyalgia patients employing blunt pressure pain, Gracely et al. (2004) found that pain catastrophising was associated with a range of cortical activation in the regions of somatosensory cortex (SI/SII), inferior parietal cortex, thalamus, posterior cingulate cortex (PCC), prefrontal cortex (PFC),

and cerebellum. Especially, activations in the rostral anterior cingulate cortex (rACC) and left lentiform were found in patients with high pain catastrophising. Moreover, a study of chronic low back pain patients during intense tactile stimulation reported that the magnitude of PCC and parietal cortex activations negatively correlated with catastrophising scores in a group of patients not displaying pain behaviour (Lloyd et al., 2008). However, other studies in fibromyalgia patients showed that greater cortical activation during experimental pain was modulated independently of pain catastrophising (Jensen et al., 2010, Burgmer et al., 2011).

As far as healthy people are concerned, Seminowicz and Davis (2006) reported that pain catastrophising positively correlated with pain-related brain responses in the rACC, insula, PFC, putamen, and hippocampus/parahippocampal gyrus during mild pain. In contrast, a different pattern emerged during intense pain with lower pain catastrophising scores being associated with greater cortical activations in the prefrontal regions, posterior parietal cortex and amygdala. A recent study showed a similar pattern of correlations using functional neuroimaging with electrical stimulation of tooth pulp (Lin et al., 2013). The authors found augmented hippocampus activation in people with high levels of catastrophising.

Vase et al. (2012) reported in an electroencephalography (EEG) study associations between pain catastrophising scores and the amplitude of the mid-latency somatosensory evoked potential originating in the secondary somatosensory cortex. Taken together, previous neuroimaging and electrophysiological studies highlight the role of pain catastrophising in amplification of cortical activation during noxious stimulation.

1.2.6.2 Structural brain characteristics of pain catastrophising

Voxel-based morphometry (VBM) can be used to analyse anatomical MR images in order to quantify macroscopic alterations in the grey and white matter of the brain (Ashburner and Friston, 2000). Three VBM studies have illustrated associations between pain catastrophising and structures of grey matter in chronic pain patients (Schweinhardt et al., 2008, Blankstein et al., 2010, Seminowicz et al., 2013). Female patients with chronic vulvar pain have demonstrated local grey matter density increases paralleling PCS scores in the left hippocampus/ parahippocampal gyrus (Schweinhardt et al., 2008). A reduced volume of the dorsolateral prefrontal cortex (DLPFC) was found in the irritable bowel syndrome patients with high levels of pain catastrophising (Blankstein et al., 2010). A recent study in chronic pain patients following cognitive-behavioural therapy (CBT) demonstrated associations between grey matter density and pain catastrophising in the right hippocampus and right DLPFC (Seminowicz et al., 2013). Conversely, this study also reported grey matter volume expansions with decreased pain catastrophising in the right SII/SI/posterior parietal cortex, left DLPFC, left inferior frontal gyrus and pregenual anterior cingulate cortex after CBT (Seminowicz et al., 2013). Furthermore, a diffusion tensor imaging study involving patients with irritable bowel syndrome reported negative correlations between PCS scores and fractional anisotrophy in white matter in the right mid-anterior cingulum (Chen et al., 2011).

1.2.7 Interim integrative summary

Previous studies suggested that pain catastrophising was associated with pain and pain-related outcomes in both healthy and clinical populations. According to the attentional model, high pain catastrophisers may over-react to pain and augment their

attentional bias towards pain-related events. The communal coping model states that catastrophisers communicate their pain experiences to solicit emotional and social support, or empathic responses from others to minimise their emotional distress, although the probability of achievement of coping goals might be limited. Pain catastrophisers have been also shown to report stronger pain and higher demands of social support from others. Furthermore, several neuroimaging studies suggested that pain catastrophising may regulate cortical activity in regions involved in sensory, attentional, and affective processing of pain.

However, cognitive and neural mechanisms underlying pain catastrophising still remain poorly understood. Firstly, it is unclear whether high pain catastrophisers would show greater sensitivity to pain cues in the absence of physical pain, such as vicarious pain or pain in others. Secondly, previous studies usually examined attentional processing indirectly by measuring the manual reaction times. Therefore, the entire course of attentional process has not been addressed in previous pain catastrophising studies. Thirdly, the neural basis of pain empathy in pain catastrophisers is not understood well. Further, the neural network of enhanced soliciting of social support in high pain catastrophisers has not been unveiled. Last but not least, previous studies focused on the structural brain alterations associated with pain catastrophising in the clinical population. It is not known whether such correlations exist in healthy people. Therefore, the present thesis also addressed associations between the brain structure and pain catastrophising in healthy people.

1.2.8 Attentional factors

1.2.8.1 Attentional processing and pain

It is largely accepted that pain can be modulated by the sensory and affective aspects of attention. The allocation of attentional resources to perceptual processes is based on the relevant information for internal goals as well as the stimulus salience (Legrain et al., 2009a). Two models of attentional processing have been proposed to illustrate the role for attention on pain: top-down and bottom-up processes (Legrain et al., 2009a). Top-down modulation of attention by pain is an intentional and goal-directed process. Attention modulates perception and cognition by allocating attention to relevant events. Thereby, it may amplify behavioural and physiological responses to relevant events and attenuate responses to irrelevant events (Corbetta and Shulman, 2002). The bottom-up model corresponds to an involuntary capturing of attention by pain. Independent of intentional control, attentional capturing is often imposed by salient stimuli (Yantis, 2000). The salience of stimuli refers to their novelty, intensity and their potential threat value (Yantis, 2008).

Top-down attention is also referred to as endogenous or sustained attention, whereas bottom-up attention is commonly typified as exogenous or transient attention (Carrasco, 2011). However, there are important differences between both types of attention. Endogenous attention is under clear voluntary control. Although exogenous cues might orient attention to their spatial location automatically, the action of orienting (exogenous) attention can be endogenously modulated in accord with task demands (Lupiáñez et al., 2001). In addition, top-down attention is called sustained, since subjects typically direct their top-down attention at objects, features, or regions in space for sustained periods of time, whereas bottom-up attention is transiently captured (Hein et al., 2006). In accordance with the cognitive-affective model (Eccleston and Crombez, 1999), pain-related events may automatically

capture attention and interrupt the current action. Then, an individual may preferentially cope with pain in order to escape from the bodily threat.

Neuroimaging studies have suggested that insular cortex and mid-cingulate cortex (MCC) are involved in the bottom-up attentional processes (Peyron et al., 2000). Accumulating neuroimaging studies have supported the attentional function of MCC (Davis et al., 1997, Derbyshire et al., 1998, Peyron et al., 1999, Downar et al., 2002). A PET study using a factorial design to investigate the attentional component of pain response found that MCC was activated as a part of attention network involving the prefrontal and posterior parietal cortices (Peyron et al., 1999). The MCC was also activated in other attentional studies requiring sustained attention in the absence of pain, such as the Stroop test (Peyron et al., 2000). Laser-evoked potential studies showed that the P2 component, likely to be generated in MCC, was engaged in attention to pain, with novel and salient stimuli eliciting larger P2 amplitudes (Garcia-Larrea et al., 1997, Garcia-Larrea et al., 2003, Legrain et al., 2009b). The early N1 nociceptive-evoked responses, generated in the operculo-insular cortex (Garcia-Larrea et al., 2003), have been related to bottom-up capturing of attention by pain (Iannetti et al., 2008, Legrain et al., 2009b).

It has been suggested that top-down model can modulate the bottom-up mechanism of attention for pain (Legrain et al., 2009a, Legrain et al., 2012). EEG studies found decreased P2 amplitudes of laser evoked potentials during a distraction task (Legrain et al., 2005). When participants were required to direct more attention to the visual task, the novelty effect on P2 was reduced. Neuroimaging studies complemented the results by showing a reduction of activation to painful stimuli in

the regions of MCC and operculo-insular cortex when attention was highly demanded in the primary visual task (Seminowicz et al., 2004, Bingel et al., 2007).

1.2.8.2 Alterations in attentional processing in high pain catastrophisers

Previous studies have employed the attentional model to explain effects of pain catastrophising on pain perception. Van Damme et al. (2002b, 2004) carried out two typical attentional experiments involving pain catastrophising, and indicated that high, compared to low, pain catastrophisers showed an attentional bias to pain itself or to the threat of pain. Attentional bias, defined as selective attention towards concern-related information in an individual's environment (Roelofs et al., 2002, Schoth et al., 2012), has been well documented in different clinical groups, such as, anxiety (Bar-Haim et al., 2007), depression (Donaldson et al., 2007), heavy alcohol drinkers (Miller and Fillmore, 2010), and smokers (Wertz and Sayette, 2001). Attentional bias to pain has also been addressed in studies with experimentally induced pain (Van Damme et al., 2007, Van Damme et al., 2010), as well as the absence of pain (Pincus et al., 1998, Keogh et al., 2001, Khatibi et al., 2009, Beck et al., 2011, Asmundson, 2012, Crombez et al., 2013). Evidence for the role of attentional bias has also been demonstrated in the context of pain catastrophising (Sullivan et al., 1997, Crombez et al., 1998b, Michael and Burns, 2004, Vancleef and Peters, 2006). Michael and Burns (2004) used the cold pressor test and an information focus manipulation, and found that high pain catastrophisers paid more attention to pain-related affective words.

It has been suggested that the prolonged experience of inescapable pain may lead to a high level of bodily awareness and high levels of symptom reporting in chronic pain (Aldrich et al., 2000). Laboratory data found that high pain

catastrophisers displayed hypervigilance to pain-related threat (Crombez et al., 1998a, Goubert et al., 2004b). A study of fibromyalgia patients also suggested that they reported heightened vigilance to pain than patients with low back pain according to the self-report instruments (Crombez et al., 2004). They found that catastrophic thinking about pain positively correlated with vigilance to pain.

1.2.9 Empathy for pain

1.2.9.1 Neural basis of pain empathy

Empathy is a capability to perceive and respond to other's feelings, which are induced by observing or imagining another person's affective state (Goubert et al., 2005, de Vignemont and Singer, 2006, Singer and Lamm, 2009, Decety, 2011, Bernhardt and Singer, 2012). Preston and de Waal (2002) proposed an integrative Perception-Action Model of empathy, which suggested that observation or imagination of another person in a particular emotional state automatically activates a representation of that state in the observer, with its associated autonomic and somatic responses. In support of the Perception-Action Model of empathy (Preston and de Waal, 2002), the discovery of mirror neuron systems provided a neural mechanism for action observation. Neurons in the ventral premotor and parietal cortices were activated during execution and observation of actions in monkeys (Gallese et al., 1996). Growing evidence suggests that a similar neural system exists in the human brain (Grafton et al., 1996, Gallese et al., 2004). Subsequent neuroimaging studies demonstrated that similar networks of brain regions are activated by observing a variety of states including pain (Singer et al., 2004, Jackson et al., 2006), disgust (Phillips et al., 1997, Wicker et al., 2003), touch (Keysers et al.,

2004, Blakemore et al., 2005, Ebisch et al., 2008), fear (de Gelder et al., 2004), and emotional facial expression (Carr et al., 2003).

Pain is a highly complex and subjective experience influenced by memories, emotional, pathological and cognitive factors. Pain, of course, can be shared with others. Furthermore, observing vicarious pain can induce supportive behaviour or unpleasant feelings, and can even be perceived as painful by observers themselves (Bernhardt and Singer, 2012). Two fMRI studies investigated the cortical responses to self-experienced pain and pain observed in others (Singer et al., 2004, Singer et al., 2006). One of the studies found that shared neural circuits in the regions of ACC, anterior insula, brainstem, and cerebellum were activated in both 'self' and 'others' conditions during the noxious pain stimulation (Singer et al., 2004). Similar activations were reported in fair players observing others in pain (Singer et al., 2006). Viewing human hands or feet in the painful situation has been shown to activate the pain empathy network (Jackson et al., 2005, Jackson et al., 2006, Cheng et al., 2007, Gu and Han, 2007, Morrison et al., 2007). A recent meta-analysis on 32 fMRI studies of empathy for pain concluded that the most consistent activated regions were bilateral anterior insula and anterior mid-cingulate cortex (Lamm et al., 2011). The consistency of activations in the neural networks elicited by both the experience of pain to oneself and the knowledge of vicarious pain supports the Perception-Action model that empathy for pain involves shared representations, with experience of pain.

Event-related potential (ERP) studies of empathy for pain also suggest that empathic response can be modulated by affective and cognitive processes (Fan and Han, 2008, Han et al., 2008, Decety et al., 2010, Li and Han, 2010, Ibáñez et al.,

2011). The ERP results illustrated the temporal dynamics of empathy for pain with an early automatic processing component (110 – 160 ms) over the frontal area and a late cognitive evaluative component, such as P3, over the centro-parietal regions during a pain judgement task presenting painful and non-painful picture stimuli. A recent ERP study also proposed that the long-lasting and late ERP positivity (late positive potential, LPP) engaged in the processes of empathy-related self-regulation with larger LPPs to painful pictures (Ikezawa et al., 2013).

1.2.9.2 Viewing pain in others and pain catastrophising

Goubert et al. (2005) proposed that empathy was profoundly affected by top-down processes driven by the observer's knowledge and other dispositions, like the observer's pain catastrophising. The role of observer judgement of pain has been well documented (Prkachin et al., 1994, Martel et al., 2011). In support of the communal coping model, young adults with high pain catastrophising, compared to those with low pain catastrophising, attributed stronger pain to people exposed to a cold pressor test (Sullivan et al., 2006b). Similar findings have been reported by Martel et al. (2008) showing healthy people viewing chronic pain patients lifting canisters. Their results suggested that pain estimates were influenced by the observer's level of catastrophising, with high pain catastrophisers estimating more intense pain in others and having a higher accuracy of pain judgements. In addition, parents' catastrophising about children's pain has been associated with overestimation of their children's pain (Goubert et al., 2009a, Esteve et al., 2013) and expression of greater negative feelings (Goubert et al., 2008). For parents with high pain catastrophising, viewing their children in pain may lead them to elicit discouragement and

solicitousness responses (Caes et al., 2012b, Vervoort et al., 2012, Esteve et al., 2013).

1.3 Problems and hypotheses

1.3.1 Effects of pain catastrophising on the classification of ambiguous pain

Previous studies suggested that pain catastrophising was involved in attentional bias towards pain-related events (Chapter 1.2.3.2 and 1.2.7.2). Pain catastrophising has been suggested to be associated with vigilance to a pain threat (Crombez et al., 1998a, Goubert et al., 2004b). Hypervigilance to pain cues and increased pain catastrophising were previously identified in fibromyalgia patients (Crombez et al., 2004). In addition, van Damme et al. (2004) suggested that high pain catastrophisers were struggling to employ uncertain information about occurrence of pain. These studies suggested that high pain catastrophisers might be particularly sensitive to pain cues in the presence of noise. Therefore, I have designed a study presenting information about pain cues masking with a varying level of background noise.

- Research question 1: Does pain catastrophising influence the detection threshold for pain cues presented in a noisy background?

My thesis investigated the sensitivity to initial pain cues in high and low pain catastrophisers during viewing of scrambled pictures containing pain, negative emotional scenes, and neutral objects. The following hypothesis was tested:

- High-, compared to low, pain catastrophisers will identify pain scenes in scrambled pictures at a higher scrambling level (i.e., high level of background noise).

1.3.2 Effects of pain catastrophising on attention to pain in others

Studies reviewed in Chapter 1.2.7.2 suggest that pain catastrophising is associated with attentional bias to pain-related stimuli and to hypervigilance to pain. The visual probe task has been frequently adopted for the investigation of attentional bias (Asmundson, 2012, Crombez et al., 2013). In a visual probe paradigm, pairs of visual stimuli are presented simultaneously and compete for attention. Response times to a series of probes are measured. Typically, a shift of attention towards the location of pain-related stimuli relative to neutral stimuli can be observed, indicating attentional bias towards pain (Keogh et al., 2001, Boston and Sharpe, 2005, Khatibi et al., 2009, Schoth and Liossi, 2010, Beck et al., 2011). Vervoort et al. (2011a, 2012) used dot-probe and visual search paradigms, and found that parents who catastrophised about children's pain strongly attended to child's pain more strongly than non-catastrophising parents. Recent studies using the dot-probe paradigm showed that chronic pain patients and their caregivers with high levels of fear selectively shifted attention towards pain faces (Khatibi et al., 2009, Mohammadi et al., 2012).

Eye-tracking allows for the recording of the pattern, orientation and duration of eye movements (Kimble et al., 2010). It has the advantage of distinguishing spatial and temporal patterns of visual attention (Derakshan et al., 2009), and provides a continuous and non-invasive measurement of attention to visual stimuli. Recently, Yang et al. (2012) utilised eye tracking in a dot-probe paradigm to investigate the visual attention to pain in people showing high and low fear of pain. Their findings suggested that attentional bias towards pain words in high pain-fearful people occurred during the very early stages of visual information processing. Using the same paradigm, Vervoort et al. (2013a) investigated effects of pain

catastrophising on attention to facial expression of pain. Low pain catastrophisers initially directed their attention more quickly to pain rather than to neutral faces. Healthy volunteers with high pain catastrophising showed decreased tendency for an initial orienting to pain faces, and did not show preference for pain faces during the first fixation period. Interestingly, people reporting high catastrophising and pain sensitivity demonstrated longer fixation durations for both neutral and pain facial expressions.

The knowledge about how pain catastrophising regulates attentional bias to others' pain is limited. The methodology employed in previous studies did not evaluate the entire duration of attentional processing, such as the initial attention allocation and attentional maintenance. The present thesis explores the attentional processing and bias towards pain in others in high and low pain catastrophisers using the eye tracking method.

- Research question 2: Does pain catastrophising modulate attentional bias for pain in others?

The present study utilised the visual probe task to analyse the attentional effects in high and low pain catastrophising people during viewing pictures depicting imminent (e.g. a syringe tip in contact with the skin) or highly probable pain (e.g. a knife cutting a cucumber while thumb likely to be cut as well) and graphically matched pictures with less likelihood of pain being inflicted. The following hypothesis was tested:

- High-, compared to low, pain catastrophisers will attribute stronger pain to pain scenes, will allocate attention more quickly, and dwell on visual pain stimuli longer.

It has been suggested that attention can be captured by emotional information (Browning et al., 2010). Attentional bias towards negative stimuli has been demonstrated in previous studies involving anxiety and depression (Fox et al., 2005, Mathews and MacLeod, 2005). Pain-related stimuli can also capture attention due to their negative emotional value rather than specifically due to pain information itself. Therefore, to identify whether attentional processing specifically for pain or generally to negative affective information in high pain catastrophisers, negative emotional stimuli those not containing pain were employed in the second eye tracking study. The following hypothesis was tested:

- High-, compared to low, pain catastrophisers will show attentional bias towards pain scenes and not towards negative emotional stimuli.

1.3.3 Pain catastrophising effects on the cortical responses to viewing pain in others

Chapter 1.2.8.2 reviewed behavioural responses to pain in others in high and low pain catastrophisers. High pain catastrophisers attributed stronger pain to people exposed to a cold pressor task (Sullivan et al., 2006b). It has also been shown that the level of pain catastrophising may influence estimation of other people's pain and manifest in soliciting social support (Goubert et al., 2009a, Caes et al., 2012b, Vervoort et al., 2012, Esteve et al., 2013). Event-related potential (ERP) technique has been shown to be effective for evaluating neurophysiological responses to emotional stimuli (Lopes da Silva, 2005). As mentioned in Chapter 1.2.8.1, ERPs have differentiated pictures depicting scenes with high risk of pain and those involving comparatively low risk of pain in healthy people (Fan and Han, 2008, Decety et al., 2010, Li and Han, 2010, Ibáñez et al., 2011). This type of pictures has been also shown in fMRI studies to activate bilateral insula and anterior cingulate

cortex and other regions of the brain (Singer et al., 2004, Jackson et al., 2005, Jackson et al., 2006, Singer et al., 2006, Cheng et al., 2007, Gu and Han, 2007, Akitsuki and Decety, 2009, Lamm et al., 2011).

The neural basis of viewing greater pain in others in context of pain catastrophising is poorly understood.

- Research question 3: Are the cortical processes associated with observation of pain in others affected by pain catastrophising?

In this thesis, ERPs were recorded to analyse the cortical activation processes underlying viewing pain in others in groups of high- and low-pain catastrophisers during passive viewing of pain and non-pain pictures. The following hypothesis was tested:

- High-, compared to low, pain catastrophisers will attribute stronger pain to pain scenes, and manifest stronger activation in cortical regions mediating emotional processing and attention.

1.3.4 Pain catastrophising effects on the cortical responses to laser stimulation during viewing of comforting hand postures

The communal coping model postulates that pain catastrophisers are likely to mitigate their pain and pain-related emotional distress through soliciting social support by communicating their pain to others (Chapter 1.2.3.3). It has been suggested that chronic pain patients with high pain catastrophising perceived greater levels of support from their spouse or partner (Keefe et al., 2003, Boothby et al., 2004, Cano, 2004, Buenaver et al., 2007). Previous research showed that several pain

processing regions, such as anterior cingulate cortex and insula, responded to physical pain and vicarious pain, such as viewing pictures depicting pain in others (Peyron et al., 2000, Ploner et al., 2002, Garcia-Larrea et al., 2003, Singer et al., 2004, Jackson et al., 2005, Jackson et al., 2006, Singer et al., 2006). Affective touch can modulate behavioural and neural responses to observed human tactile interactions (Bufalari and Ionta, 2013). Skin-to-skin contact is crucial for social-interaction sub-serving non-verbal communication of intentions and emotions. A study of patients with heritable disorders suggested patients reported similar subjective pleasantness ratings to physical touch and vicarious touch (Morrison et al., 2011b).

In the context of the communal coping model, high pain catastrophisers are more dependent on soliciting social support (Keefe et al., 1989, Sullivan et al., 2001b, Turner et al., 2002). Therefore, it is likely that high, compared to low, pain catastrophisers will show reduced cortical activity to pain when viewing comforting hand postures compared to non-comforting hand gestures.

- Research question 4: Are the cortical responses to noxious stimulation during observation of comfort-giving scenes affected by pain catastrophising?

EEG recordings and noxious laser stimulation were used in the present thesis to investigate the cortical responses to experimental pain during viewing hand postures depicting a comforting touch, touch, and non-touch in high and low pain catastrophisers. The following hypothesis was tested:

- High-, compared to low, pain catastrophisers will report smaller pain and manifest diminished cortical activation during viewing of comfort-giving hand postures.

1.3.5 Pain catastrophising and structural features of cortical and subcortical brain regions in healthy people

VBM studies have reported a reduced grey matter volume in rACC, insular cortex, orbitofrontal cortex, DLPFC, temporal cortex, thalamus, and parahippocampal gyrus in chronic pain patients (Apkarian et al., 2004, Schmidt-Wilcke et al., 2005, Schmidt-Wilcke et al., 2006, Kuchinad et al., 2007, Schmidt-Wilcke et al., 2007, Davis et al., 2008, May, 2008, Valfrè et al., 2008). May (2008) suggested that the decreases of grey matter volume in these brain areas may refer to a failing inhibition of pain in chronic pain populations. The morphological findings associated with pain catastrophising in chronic pain patients (described in Chapter 1.2.5.2) are partially consistent with the aforementioned studies. Methodological issues surrounding tissue classification or arbitrary smoothing could also affect the validity of VBM findings (Jones et al., 2005, Smith et al., 2006, Patenaude et al., 2011). VBM is not suited for the study of deeper regions such as basal ganglia structures. Alternative methods, such as geometric shape analysis of subcortical structures may be preferable to VBM in identification of subtle morphological alterations (Patenaude et al., 2011). This method can identify the location and direction of complex morphological alterations through direct measurement of geometric shape in selected subcortial regions more precisely than VBM (Patenaude et al., 2011).

Further, knowledge of structural brain features associated with pain catastrophising in healthy people is limited. Therefore, my thesis also focused on relationships between volume and shape of cortical and subcortical structures and pain catastrophising in healthy people.

- Research question 5: Is pain catastrophising in healthy people associated with volume and shape changes in specific brain regions?

The method of VBM based on Diffeomorphic Anatomical Registration using Exponentiated Lie algebra (DARTEL) (Ashburner, 2007), and a novel technique of geometric shape analysis of subcortical structures have been employed. The following hypothesis was tested:

- Pain catastrophising scores in healthy people will correlate with volume and shape changes in pain processing regions.

Chapter Two
Theoretical basis of methods

2.1. Principles of electroencephalography

2.1.1. Physiological basis of EEG

The human cerebral cortex contains about 100 billion neurons (Sanei and Chambers, 2009). Each neuron consists of cell body, axon, and dendrites. Neurons respond to stimuli and transmit information along the axons and dendrites. The neuronal electrical activation mainly includes two forms – action potentials and postsynaptic potentials (Luck, 2005, Mulert and Lemieux, 2010, Lopes da Silva and Van Rotterdam, 2011). An action potential, mediated by the sodium and potassium voltage - gated ion channels, is a temporary change in the membrane potential such that the intracellular potential suddenly decreases (depolarisation), producing a spike, and then quickly returns to the resting membrane potential (repolarisation) (Sanei and Chambers, 2009). However, action potentials mostly last between 1 and 2 milliseconds. Scalp electrodes cannot detect action potentials as EEG signals due to the short latency (Koester, 1991). Instead, postsynaptic potentials, originating from the extracellular current flow, make up the EEG potentials. This kind of neural activity stems from the summation of extracellular currents from numerous individual neurons. To allow the potential summation to take place, the events need to be relatively slow, lasting tens or even hundreds of milliseconds. After an action potential travels along the fibre, excitatory or inhibitory neurotransmitters release into the synaptic cleft and act on corresponding receptors on the postsynaptic membrane, causing the changes of ion channels and leading to a build-up of

electrical potentials across the cell membrane. The summation of electrical currents that flow through the extracellular space is directly responsible for the generation of field potentials attributing to scalp potentials (Buzsáki et al., 2003, Luck, 2005, Mulert and Lemieux, 2010). Especially, there is a large number of similarly oriented pyramidal cells in the cortex. The main neurons which generated the synaptic potentials, fire in synchrony to produce currents in the long apical dendrites to form coherent magnetic fields. In this way, the voltage fluctuations of these neurons can be detected by EEG systems (Lorente de No, 1947, Sanei and Chambers, 2009, Mulert and Lemieux, 2010).

2.1.2. EEG signal acquisition and processing

Generally, an EEG recording consists of the measurement and amplification of fluctuating electrical potentials over time (Maus et al., 2011). Acquiring EEG signals from the brain has become vital for diagnosis and monitoring of a variety of diseases, such as epilepsy (Thompson and Ebersole, 1999), depression with cognitive impairment (Brenner, 1999), delirium (Jacobson and Jerrier, 2000, Onoe and Nishigaki, 2004), and Alzheimer's disease (Koenig et al., 2005).

In a conventional EEG, electrodes are placed on the scalp with a conductive gel, paste or liquid. To allow comparisons among clinical and research studies, the International 10–20 system for standardised electrode placement has been widely utilised, which is based on relative distance measurements using internationally recognised anatomical landmarks (nasion, inion, left, and right mastoids) on the skull (Jasper, 1958, Pizzagalli, 2007). This system ensures that labelling the positions of individual electrode is consistent across laboratories. EEG data mainly contains three components: event-related potentials, EEG background signals, and artifacts. EEG

amplifiers amplify the EEG signal and attenuate noise. The resulting amplified EEG signals are digitised, and the digital recording is used for display and analysis purposes. EEG signals represent the potential differences between two electrodes, usually an active electrode and a reference electrode, meaning that the scalp potentials are reference-dependent (Luck, 2005). Reference electrodes can be placed on different sites of scalp. For instance, the average mastoids reference creates a zero-resistance electrical bridge between the hemispheres and references the active site to the average of bilateral mastoid electrodes. However, the drawback of this method is that it may drift away effective reference from the midline if the electrical resistance at each electrode differs (Luck, 2005). Therefore, the common average reference has been proposed as a reference-independent option (Lehmann, 1987). This method relies on the principle that electrical events produce both positive and negative poles. The integral of these potential fields in a conducting sphere sums to zero. Therefore, subtracting the common average reference from each channel will result in a reference-free EEG signals (Nunez et al., 1997, Michel et al., 2004).

2.1.2.1. Volume conduction problem

EEG signals can be detected due to the process of current flow between a generator dipole in the brain and a scalp EEG electrode. The flowing currents in the electrically conductive medium of the brain are called volume conduction. The voltage difference depends on the localisation and orientation of the dipole and the conductivity and resistance of the scalp, skull, cerebrospinal fluid layer and brain, referred to as volume conductor (Luck, 2005). Mathematical rules can be employed to understand the influence of volume conduction on the measures from the scalp. For example, as electricity spreads out through the conductor, the deeper the source dipole is located, the more difficult it is to detect (Klein and Thorne, 2007).

However, various algorithms have been developed and improved to eliminate or reduce effects of volume conduction (Michel et al., 2004). For instance, realistic head shaped volume conductor models have been shown to improve the accuracy of the source localisation (Fuchs et al., 2007). In realistic head models using a boundary element method or finite element method, the segmentation of an anatomical MRI scan including the interfaces is taken into account to restrict the solution space to structures where putative EEG sources can actually arise (Gonçalves et al., 2000, Michel et al., 2004, Fuchs et al., 2007).

2.1.2.2. Filtering

Filtering is necessary during EEG data acquisition and before or after averaging of event-related potentials (Luck, 2005). In terms of the ability to suppress or pass various different frequencies, four most common filters can be classified. The high-pass filters pass high frequencies and attenuate low frequencies; the low-pass filters remove high frequencies and pass the low frequencies. The bandpass filters constitute the combination of the high-pass and low-pass filters, which suppress both frequencies and only pass the intermediate range of frequencies. A special type of filter is the notch filter having a frequency of 50/60 Hz, this is employed to remove the narrow range of frequencies generated by line currents (Litt and Cranstoun, 2003, Edgar et al., 2005, Luck, 2005). Filter settings can help to enhance or attenuate brain activity above and below selected frequencies. Of particular importance is that high-frequency artifacts are mainly from muscle and low-frequency artifacts from movement rather than brain activity (Litt and Cranstoun, 2003). In addition, filters can distort EEG signals and event-related potential waveforms (Luck, 2005). Therefore, a well-designed filter setting should be applied during EEG data acquisition and during processing of EEG signals.

2.1.2.3. Artifact rejection in EEG analysis

During the EEG signal acquisition, various artifacts are recorded by EEG equipment, which do not originate from brain activity and which can contaminate EEG recordings. Artifacts are generally classified into two types: physiological and non-physiological artifacts (Klem, 2003, Luck, 2005). Physiological artifacts usually arise from sources within the body but not the brain, such as electrooculographic activity (EOG), electrocardiographic activity (ECG), electromyographic activity (EMG) and respiration. For instance, the EOG is a steady potential (approximately 0.40− 1 mV) difference with the positive pole localised to the cornea and the negative pole to the retina. This electrical potential is detected by the electrodes surrounding the eyeball, and its voltage is greater than the cerebral potentials. When the eye movement occurs, the artifact generated by the EOG is detected (Klem, 2003). Another type of artifact may originate from poor electrode-to-skin contact, or electronic noise from alternating current electrical appliance (causing a 50 Hz artifact in the recording). Such issues can be solved by manually discarding the contaminated trails following visual inspection. Alternatively, independent component analysis approach can by employed (Jung et al., 2000). With this approach, EOG or ECG artifacts, for instance, can be separated and extracted from the EEG signal in order to clean the data (Luck, 2005).

2.1.3. Quantitative analyses of EEG

2.1.3.1. Event-related potential analysis

Event-related brain potentials (ERPs) are time-locked voltage fluctuations induced within the brain during specific sensory, motor, and cognitive processes. ERPs are typically triggered by an internal or external event or stimulus, and appear

as brain potentials, such as, visual, auditory, or somatosensory evoked potentials. They are utilised to investigate cognitive processing by measuring brain activity (Friedman and Johnson, 2000, Curran et al., 2006, Fabiani et al., 2007, Sanei and Chambers, 2009). ERP analysis has been employed for evaluation of brain functions and the clinical diagnosis of neuropsychiatric disorders, such as, depression (Hansenne et al., 1996), phobia (Miltner et al., 2005), and generalised anxiety disorder (Turan et al., 2002).

Although ERPs are small voltages (1-30 μV) relative to spontaneous EEG activity, ERP waveforms can be isolated by means of averaging techniques to generate a robust averaged waveform. A mean ERP waveform contains positive and negative voltage deflections, which reflect relatively independent underlying or latent components (Luck, 2005). The ERP waveform can be quantitatively measured in terms of amplitude (i.e., how the component responds in terms of the size of the deflection to experimental variables), latency (i.e., the time point at which peak occurs), and scalp distribution (i.e., the pattern of voltage gradient of a component over scalp and time) (Johnson, 1992). Compared to fMRI and PET, ERP technique is considered to be a non-invasive and comparably inexpensive means of evaluating neuronal activity. ERP technique provides excellent temporal resolution and can detect electrical changes over the course of milliseconds (Schneider and Strüder, 2009). However, due to the small amplitude of an ERP, it requires a large number of trials for averaging. Another disadvantage of ERP technique is its poor spatial resolution relative to hemodynamic measures. Because a given pattern of ERP data can be explained by infinite internal ERP generator configurations, it is difficult to localise exactly where ERPs are generated (Luck, 2005). Fortunately, the scalp distribution of the ERP components can provide complementary information to

amplitude and latencies for solving the problems of source localisation (Friedman and Johnson, 2000, Michel et al., 2004). ERPs, hence, are typically qualified with spatiotemporal voltage patterns to identify the temporal and spatial alternations of different sources (Handy, 2005).

ERPs can be classified with regard to the sensory modality as visual-evoked potentials (VEP), auditory-evoked potentials (AEP), and somatosensory-evoked potentials (SEP). Also, they can be classified according to the latency at which their components occur after the onset of stimulus. The short latency components (< 100 ms) usually are generated during early information processing stages and highly sensitive to physical properties, such as stimulus modality, intensity, duration, or repetition rate. Evoked potential components displaying predominantly sensory information are called exogenous components. In contrast, the long latency (> 100 ms) components usually depend on complex tasks involving psychological stimuli, such as novelty and memory recall. They are considered as the endogenous components, and engage higher-order functional processing (Luck, 2005). Since ERPs generation is a continuous process, ERPs are widely used to examine both exogenous and endogenous components.

2.1.3.2. Visual event-related potential

A visual evoked potential is an evoked potential caused by a visual stimulus, such as the checkerboard pattern on a computer screen. There are a few typical VEP components, such as P1, N1 and P300. P1 component typically appears around the lateral occipital electrodes at 60–90 ms after the onset of stimulus peaking at 100–150 ms (Luck, 2005). P1 wave likely originates in the extrastriate visual cortex (Clark and Hillyard, 1996), and is sensitive to the allocation of spatial attention

(Mangun and Hillyard, 1988, Fu et al., 2001), and to the subject's state of arousal (Vogel and Luck, 2000). The P1 component is followed by N1, originating in parietal and lateral occipital cortex, and typically peaking at 150-200 ms (Luck, 2005).The enhancement of N1 relates to the processes of discrimination (Vogel and Luck, 2000). The P300 component at the central-parietal area is thought to involve the higher-order processes associated with memory and decision-making (Hopfinger and West, 2006).

2.1.3.3. Laser evoked potential

Pain is a complex sensory, cognitive and affective phenomenon, hence, it intrinsically involves both physical and psychological stimulus attributes. Laser-evoked potentials (LEPs) have been introduced as a non-invasive tool for evaluating the function of central nociceptive pathways, by firing cutaneous Aδ and C-fiber without eliciting responses from Aβ mechanoreceptors (Bromm and Treede, 1987, Bromm et al., 1991, Treede and Kunde, 1995). LEPs are frequently applied in both basic and clinical research (Bromm et al., 1991, Kakigi et al., 1991, Treede et al., 1991, Garc ́ıa-Larrea et al., 1997, Garcia-Larrea et al., 2002, Iannetti et al., 2003, Mouraux and Iannetti, 2009).

The majority of the LEP response is formed by a negative-positive biphasic deflection (N2-P2), peaking at ~200–350 ms after stimulating the dorsum of the hand, and maximal at the scalp vertex (Bromm and Treede, 1987). A majority of laser-evoked potential studies reported the time window of the N2-P2 component (see Fig. 2.1) was consistent with the latency times of ACC activation, although slightly variable across studies (Tarkka and Treede, 1993, Bromm and Chen, 1995, Valeriani et al., 1996, Lenz et al., 1998a, Lenz et al., 1998b, Valeriani et al., 2000,

Bentley et al., 2002, Bentley et al., 2003, Lorenz and Garcia-Larrea, 2003). The generator of the N2-P2 dipole is remarkably located in the mid-portion of ACC (caudal anterior cingulate cortex), corresponding to Brodman's area 24 (BA 24) (Garcia-Larrea et al., 2003).

The N2-P2 complex is preceded by an earlier N1 component around the temporal region contralateral to the stimulated side, peaking at ~150–160 ms (Treede et al., 1988). It has been suggested that this smaller negative wave overlaps with the larger subsequent N2 component in time and space (Treede et al., 1988, Kunde and Treede, 1993). Both EEG and MEG studies have proposed that the N1 component was generated in the parietal operculum (SII) or posterior insular region (Tarkka and Treede, 1993, Bromm and Chen, 1995, Kakigi et al., 1995, Valeriani et al., 1996, Frot and Mauguière, 1999, Ploner et al., 1999, Kakigi et al., 2000, Kanda et al., 2000, Ploner et al., 2002, Frot and Mauguière, 2003). In accordance with electrophysiological studies, most imaging studies with laser stimulation reported bilateral distribution of increased cerebral blood flow in opercular-insular cortex (see (Peyron et al., 2000) for a review). Frot et al. (1999) used intracortical recordings and found a time lag of about 15 ms for ipsilateral N1 LEP component compared with the contralateral side, and concluded that bilateral opercular activation did engage into the early phase processing of LEPs.

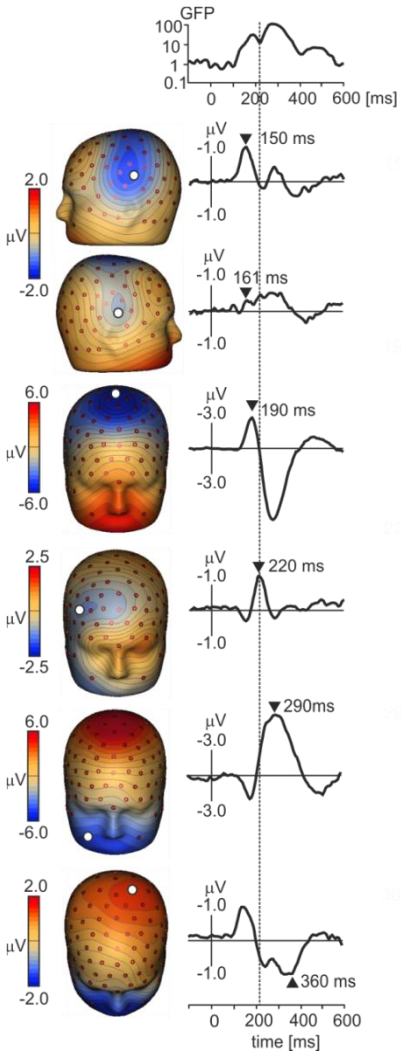

Fig.2.1 The isopotential maps and potentials at select electrodes of grand average of LEPs at six time points: 150 ms (N1 potential, top row), 161 ms, 190 ms (N2 potential), 220 ms (N220 potential), 290 ms (N3 potential), and 360 ms (P3 potential, bottom panel). The global field power is also shown. The vertical line crossing all panels indicates the peak latency of the N220 potential. Adapted from ‘‘Emotional modulation of experimental pain: a source imaging study of laser evoked potentials’’ by Stancak and Fallon, 2013, Frontiers in Human Neuroscience, 7, Fig. 1A.

In a spatial discrimination task using a laser oddball paradigm, a posterior distributed laser evoked P3 component (360–600 ms) is separated from P2 component, according to the latency and topographical dissimilarities (Towell and Boyd, 1993, Kanda et al., 1996, Siedenberg and Treede, 1996, Legrain et al., 2002, Legrain et al., 2003). This component is functioning as similar to the cognitive P300 wave, as known for the auditory P3 (Donchin and Coles, 1988) or somatosensory P3

(Becker et al., 1993). For instance, Kanda et al. (1996) observed stronger amplitudes of P3 component elicited by the rare stimuli in different modalities, such as, nociceptive, somatosensory, and auditory. Both EEG (Valeriani et al., 1996) and MEG (Watanabe et al., 1998) data suggested the P3 component was generated in the medial temporal region, which was located around the amygdala and hippocampi. Indeed, an fMRI study with laser stimulation showed evidence that bilateral amygdala and hippocampus where involved in pain processing (Bingel et al., 2002), while greater hippocampal activation is found during an unexpected pain stimulation (Ploghaus et al., 2000), or during painful stimulation associated with anxiety (Ploghaus et al., 2001). A recent EEG study with laser evoked potentials during affective sounds supports these results and the N3 component, peaking at 419 ms, was generated in the medial temporal cortex (Stancak et al., 2013).

2.1.4. EEG source localisation

2.1.4.1. Basis of source localisation methods

Brain activity contains both temporal and spatial characteristics. Although EEG shows excellent temporal resolution, the spatial resolution of EEG is limited due to blurring effects of the volume conduction. To improve the spatial resolution of EEG, source localisation has been employed. To identify localised sources the voltage potential distribution over the cortices is measured to estimate the current sources inside the brain that best fit the EEG data (Luck, 2005, Grech et al., 2008). The procedure of EEG source localisation works by estimating the positions and orientations of the underlying source dipoles on the basis of the specified electric potential or magnetic field recordings from the scalp, which is called inverse (Hämäläinen et al., 1993, Luck, 2005) or ‘‘underdetermined’’ problem. As for

source localisation, two main approaches are overdetermined/ equivalent dipole models (Scherg, 1990, Scherg and Buchner, 1993) and underdetermined/ linear distributed source models (Hämäläinen and Ilmoniemi, 1994, Fuchs et al., 2001). In the equivalent current dipole model, it is assumed that scalp EEG potentials are generated by one or few focal sources. Depending on a priori knowledge, the best source location can be found by computing the surface electric potentials, using a forward solution. However, during dipole modelling it is difficult to determine the a priori exact number of dipole sources. Considering this intrinsic limitation, the distributed model has received increased attention. In the linear distributed model, all possible source locations are considered simultaneously. Thus, there is no priori assumption on the number of the dipoles in the brain (Michel et al., 2004, Pizzagalli, 2007). When using source models, regularised solutions are required to solve the ill-posed inverse problem with many possible solutions. EEG source localisation is not only used in cognitive neuroscience research (Keeser et al., 2011, Valentini et al., 2012a), but also applied in clinical neuroscience (Park et al., 2002, Paquette et al., 2009). In the next subsections, three common approaches are introduced.

2.1.4.2. Equivalent current dipole approaches

2.1.4.2.1. Genetic algorithm (GA)

GA is an optimisation algorithm based on the mechanics of natural evolution. It is effective in rapidly searching the global solution. In GA, an initial population of individuals represents a possible solution to an optimisation problem. The process is governed by selection, mutation and crossover. According to the principle of fitness function, the GA obtains the optimal solution after a series of iterative computations. In this case dipoles are modelled as a set of parameters that determine the orientation

and the location of the dipole and the error between the projected potential and the measured potentials is minimised by GA techniques (McNay et al., 1996, Grech et al., 2008).

2.1.4.2.1. Multiple signal classification (MUSIC) algorithm

MUSIC aims to estimate the possible number of underlying sources. The principle of MUSIC is to decompose the signal in order to identify underlying components in the time series data (Mosher and Leahy, 1998, Michel et al., 2004). In MUSIC, a single-dipole model within a three-dimensional head volume conductive model is scanned and projections onto an estimated signal subspace are computed. This method can solve the generalized eigenvalue problem in a way that the solution offers the best-fitting orientation of the dipole. However, a major problem of MUSIC is to choose the correct location of the source projecting to the signal subspace. To solve this problem, Mosher and Leahy (1999) improved the MUSIC algorithm to a recursively applied and projected MUSIC (RAP-MUSIC). This method uses each successively located source to form an intermediate array gain matrix, and projects both the array manifold and the signal subspace estimate into its orthogonal component, and thus additional fictitious source will not be found.

2.1.4.3. Linear distributed approaches

2.1.4.3.1. Low resolution brain electromagnetic tomography (LORETA) algorithm

LORETA is one of the inverse solutions for localising the electrical activity in the brain based on scalp potentials from EEG recordings. It computes a unique three-dimensional distribution of the generating electrical neuronal activity based on the maximum smoothness of the solution (Pascual-Marqui et al., 1994, Pascual-

Marqui, 1999). In LORETA, the solution space is restricted to cortical gray matter and hippocampus, as determined in the digitized Talariach atlas provide by the Montreal Neurological Institute (MNI; Brain Imaging Centre) standard brain template (Pascual-Marqui, 2002). LORETA is based on the electrophysiological and neuroanatomical constraints, and shares a good validation with numerous studies (Pascual-Marqui, 2002, Yao and Dewald, 2005), thus it is widely accepted for the application of source modelling. However, because of the potential for an over-smoothed function, LORETA method has been criticised as not suitable for focal source estimation (Michel et al., 1999, Grave de Peralta Menendez and Gonzalez Andino, 2000).

2.1.4.3.2. Local autoregressive average (LAURA) algorithm

LAURA attempts to incorporate biophysical laws as constraints in the norm minimisation approach (Michel et al., 2004, Grech et al., 2008). According to the Maxwell equations of electromagnetic theory, the strength of each source decreases with the inverse of the cubic distance for vector fields and with the inverse of the squared distance for potential fields. Thus, this method assumes that the activity will decrease (or regress) according to these laws when the source is away from the measuring point. LAURA incorporates these biophysical laws in terms of a local autoregressive average with coefficients depending on the power and the distance from the point (Grave de Peralta Menendez et al., 2001, Grave de Peralta Menendez and Gonzalez Andino, 2002, Grave de Peralta Menendez et al., 2004). Consequently, two attributes determine the activity at any solution point: one is fixed by the biophysical laws, and the other is free and is determined from the data. The advantage of LAURA is that it makes no a priori assumptions regarding the number of sources and their localisations, and can deal with multiple simultaneously active

sources (Michel et al., 2001). It estimates 3D current density distributions using a realistic head model with a solution space equally distributed within the grey matter of the MNI standard brain. LAURA algorithm has been utilised for localising the cortical activity in clinical studies, such as, epilepsy (Groening et al., 2009, Elshoff et al., 2012), and neuroscience studies, such as, multisensory processing (Senkowski et al., 2007), or pain (Stancak and Fallon, 2013).

2.1.4.3.3. Classical LORETA analysis recursively applied (CLARA) algorithm

CLARA is an iterative application of the LORETA algorithm with an implicit reduction of the source space in each iteration to make distributed source images more focal (Hoechstetter et al., 2010). It benefits from the combination of discrete and distributed source analysis by employing distributed source analysis with a shrinking of the source space. Compared to the LORETA method (Pascual-Marqui et al., 1994), CLARA is better suited to detect the hidden sources of neural activity with deblurred images (Hämäläinen et al., 2011a, Ortiz-Mantilla et al., 2012, Valentini et al., 2012a, Valentini et al., 2012b, Wang et al., 2013).

2.2 Principles of magnetic resonance imaging

2.2.1. Basic principles and physics of MRI

Magnetic resonance imaging (MRI) is a non-invasive medical imaging technique contributing to research and clinical applications. MRI signals are acquired by measuring the activity of protons, which most commonly uses the hydrogen atom, because it contains a solitary proton and processes a significant magnetic moment. An abundance of hydrogen protons exists in the human body. They spin along their axis, yielding a large aggregate magnetic moment, which is

referred to as a net magnetic field caused by the spinning angular momentum of H^+ hydrogen ions (Narasimhan and Jacobs, 2002, Westbrook et al., 2005). When a participant is placed in a strong magnetic field, the protons spin, and align in parallel to the static external magnetic field (longitudinal magnetisation) (Hendee and Morgan, 1984). In the MR scan, a radio-frequency (RF) pulse with the precessional frequency, called the Larmor frequency, is applied perpendicular to the static magnetic field, which phenomenon is termed as resonance. The energy of the hydrogen, arisen from the RF pulse, causes the magnetic moment of protons to tilt in the main magnetic field, and induces magnetisation that converts into a transverse plane (transverse magnetisation) (Hendee and Morgan, 1984, Deichmann et al., 2010).

Due to the limited duration of precession, once the RF pulse is removed, the tilted magnetisation vector tends to realign with the static magnetic field. This recovery process of longitudinal magnetisation is associated with the release of energy of hydrogen nuclei and is termed spin-lattice or longitudinal relaxation (Hendee and Morgan, 1984, Westbrook et al., 2005, Deichmann et al., 2010). The time required for the magnetic moment of the nuclei to return to equilibrium is known as T1 (Hendee and Morgan, 1984). Simultaneously, but independently, the precessing tilted magnetic moment tends to break apart through a spin dephasing process. This decay of coherent transverse magnetisation is due to the energy exchange of adjacent nuclei, named spin-spin or transverse relaxation. The time of the dephasing process is known as T2 (Hendee and Morgan, 1984, Narasimhan and Jacobs, 2002). Both relaxations are separate processes, however, T2 never exceed T1 (Hendee and Morgan, 1984). T1 and T2 relaxation times vary in different tissues. As the Larmor frequency of hydrogen in lipids is lower than that of hydrogen in water,

lipids, relative to water, have a shorter T1 and T2 (Hendee and Morgan, 1984, Westbrook et al., 2005). Therefore, MR images of soft-tissue contrast can be manipulated widely depending on the timing parameters. By altering the repetition time (i.e. the interval of the entire pulse sequence, TR) or echo time (i.e., the time between RF pulse and response signal, TE), it is possible to alter or weight the image contrast for particular tissues. Short TRs and TEs produce T1-weighted images, in which substances with a short T1 (i.e., lipids) appear brighter. Alternatively, T2-weighted images are obtained by long TRs and TEs.

Spatial information about the presence of protons from the MR signal is captured by superimposing the magnetic field gradients, which can alter the magnetic field resulting in a change in resonance frequency or phase (Narasimhan and Jacobs, 2002). This causes a distribution of the proton's Larmor frequency in a horizontal direction throughout the time mapped onto a frequency spectrum, known as frequency encoding. Alternatively, the gradient field causes spins with different Larmor frequencies to dephase and further spatial information is encoded into a specific sequence of phase accumulation. This is known as phase encoding (Narasimhan and Jacobs, 2002, McRobbie et al., 2007, Deichmann et al., 2010). By tailoring the RF pulse with a same frequency used to excite proton spins, the gradient duration and magnitude, and combining frequency and phase encoding, pulse frequencies are designed to focus on selective space of the image (Narasimhan and Jacobs, 2002). This process of reconstruction is similar to that used in computerised tomography. Mathematically, MR signal is decomposed by performing a Fast Fourier Transformation, which permits signal to be decomposed into a sum of sine waves each of different frequency, phases and amplitudes, to identify the proton intensities across the image (McRobbie et al., 2007). The frequency and phase

encoding also undergo the process of Fast Fourier Transformation, resulting in the computation of an image by considering the intensity and location of MR signal (Narasimhan and Jacobs, 2002).

2.2.2. High-resolution T1-weighted structural images

T1-weighted anatomical magnetic resonance images display higher spatial resolution and are routinely acquired in neuroimaging studies. The contrast of a T1-weighted image depends on the differences in the T1 time between lipids and water (Westbrook et al., 2005). A short TE and TR can enhance the T1 contrasts between tissues. For instance, lipid-based tissues with a short T1 generate stronger proton density and brighter signals than water-based tissues with a long T1. Due to the excellent display of boundaries between tissues, T1-weighted images are known as anatomical scans (McRobbie et al., 2007). In addition, T1-weighted images show a high contrast between grey and white matter. Thus, T1-weighted images can be used for tissue classification and bias correction (Ashburner and Friston, 2005). It also can be employed to evaluate the change in the density of grey matter, e.g., in voxel-based morphometry studies of alterations of grey and white matter brain structures (Ashburner and Friston, 2000), or to assess subcortical alterations to geometric shape (Patenaude et al., 2011).

2.3. Eye tracking technique

2.3.1. Principles of eye tracking

Eye tracking is an approach for measuring the eye positions at a given time, and/ or the pathway in which eyes are shifting from one location to another (Poole and Ball, 2005). According to the ‘‘eye-mind’’ hypothesis, proposing a relationship

between what the eyes are gazing at and what the mind is engaged with (Just and Carpenter, 1980), eye movements can provide a dynamic trace of where individual's attention is focusing on in relation to the visual display. In general, there are two types of eye tracking techniques: one type measuring the position of the eye relative to the head, and another measuring the direction of visual attention (so-called ''point-of-regard'') (Duchowski, 2007). The first analytical techniques were proposed for the detection of eye movement through direct contact with the cornea, which were considered an invasive tool (Andreassi, 1989). Later, electrooculography (EOG) became one of the most common technologies for eye movements recording (Oster and Stern, 1980). This technique relied on the indirect measurement of the corneo-fundal potential with electrodes mounted on the skin around the eye. In the twentieth century, such as the eye gaze tracking techniques (e.g. the corneal reflection technique), more accurate and less intrusive techniques have been developed (Poole and Ball, 2005). Measuring eye movement metrics, such as fixations, saccades, gazes, and pupil size, can unveil the amount of processing being applied to targets at the point-of-regard. Fixations are defined as the moments when the eyes are relatively stationary, which moments corresponding to visual information encoding. Saccades are the quick eye movement between fixations. Gaze is the measurement of the amount of fixation durations within the area of interest (Poole and Ball, 2005). Eye tracking approaches have been used in a wide variety of disciplines, such as cognitive science (Jones et al., 2012), linguistics (Dickey et al., 2007) and clinical research (Kimble et al., 2010).

2.3.2. Eye tracker

An eye tracker is a non-invasive electronic device allowing accurate tracking of eye positions and pupil diameters relative to a flat surface. The most popular used

design for measurement of the point-of-regard is the video-based eye tracker. This method employs the pupil-centre corneal-reflection method to extract the eye position from video images (Duchowski, 2007, Hansen and Ji, 2010). The apparatus typically consists of a desktop computer and a table-mounted infrared camera next to or beneath a display monitor. In operation, infrared light firstly illuminate the eye to generate strong corneal reflections, causing the bright pupil effect which enhances the camera's image of the pupil (Fig. 2.2). Once the image processing software identifies and locates both the centres of the pupil and the corneal reflection, the vector between them is measured. A simple calibration procedure is routinely needed before any eye tracker recording, in order to relate individual's point-of-regard to locations in the computer screen (Goldberg and Wichansky, 2003, Poole and Ball, 2005). Eye tracking techniques attribute detailed, quantitative data to the entire testing procedure, rather than are limited to general measurement. It also can be utilised with different cognitive techniques, like EEG and fMRI, for cross-discipline research (Holsen et al., 2008, Fan et al., 2013). However, due to strong individual differences (i.e. eye colour), such disadvantages can cause the failure of calibration and the reduction of contaminated data (Goldberg and Wichansky, 2003).

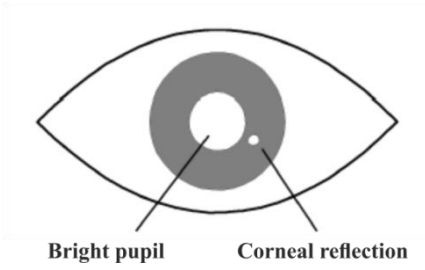

Fig.2.2 Corneal reflection and bright pupil as seen in the infrared camera image. Adopted from ''Eye tracking in human-computer interaction and usability research: current status and future prospects'' by Poole and Ball, 2005, *Encyclopedia of human computer interaction (Ghaoui, C., ed)*, pp 211-219, Fig. 1.

Chapter Three

Methods & Materials

3.1. Experiment 1: Effects of pain catastrophising on the classification of ambiguous pain

3.1.1. Subjects

One hundred and forty nine female students of Psychology at the University of Liverpool were screened using the Pain Catastrophizing Scale (PCS, mean ± SD = 19.8 ± 8.9, Med = 19 (Sullivan et al., 1995)). Subjects were excluded if they reported a history of neurological or psychiatric diseases or chronic pain. This study employed the cut-off points of upper and lower third PCS scores (Sullivan et al., 1995) for grouping subjects as high or low pain catastrophisers. A score of > 24 indicates high pain catastrophisers (High-Cat), and a score of < 15 indicates low pain catastrophisers (Low-Cat). A total of 85 healthy students with 42 High-Cat and 43 Low-Cat people participated in this study in exchange for course credit after giving informed consent. The study was approved by the Research Ethics Committee of the University of Liverpool. All subjects had normal or corrected-to-normal vision. All but 4 subjects had right-hand dominance according to self-report.

3.1.2. Materials

Three sets of 15 grey photographs of Pain, Negative, and Neutral were used (Fig. 3.1). Pain pictures were similar to those used in previous studies (Jackson et al., 2005, Jackson et al., 2006, Gu and Han, 2007, Lamm et al., 2007a, Akitsuki and Decety, 2009), displaying hands or feet in a situation which may cause physical pain (e.g., a knife slicing a cucumber and threatening to also cut a finger, or a hand

trapped in a door). Both Negative emotional and Neutral pictures were selected from the International Affective Picture System (IAPS) (Lang et al., 2008).Negative emotional pictures, abbreviated as Negative pictures, showed human being displaying sadness (e.g., crying or attending a funeral). Neutral pictures showed objects (e.g. a cup of coffee or a clock). It is known that the emotional state and arousal of the observer may be affected by hue, brightness and saturation of the picture colours (Valdez and Mehrabian, 1994). Therefore, all selected pictures were transformed into grey images (8-bit), by means of Corel PHOTO-PAINT X6 (Corel Corporation, Ottawa, Canada). Pictures in the three categories (Pain, Negative, Neutral) were graphically equivalent in terms of colour, contrasts, objects shown and view angles. The luminance of pictures in the three categories were equal according to an one-way ANOVA for repeated measures ($F(2,44) = 0.04$, $p = 0.996$. All pictorial stimuli were sized at 425 × 319 pixels (72 dpi).

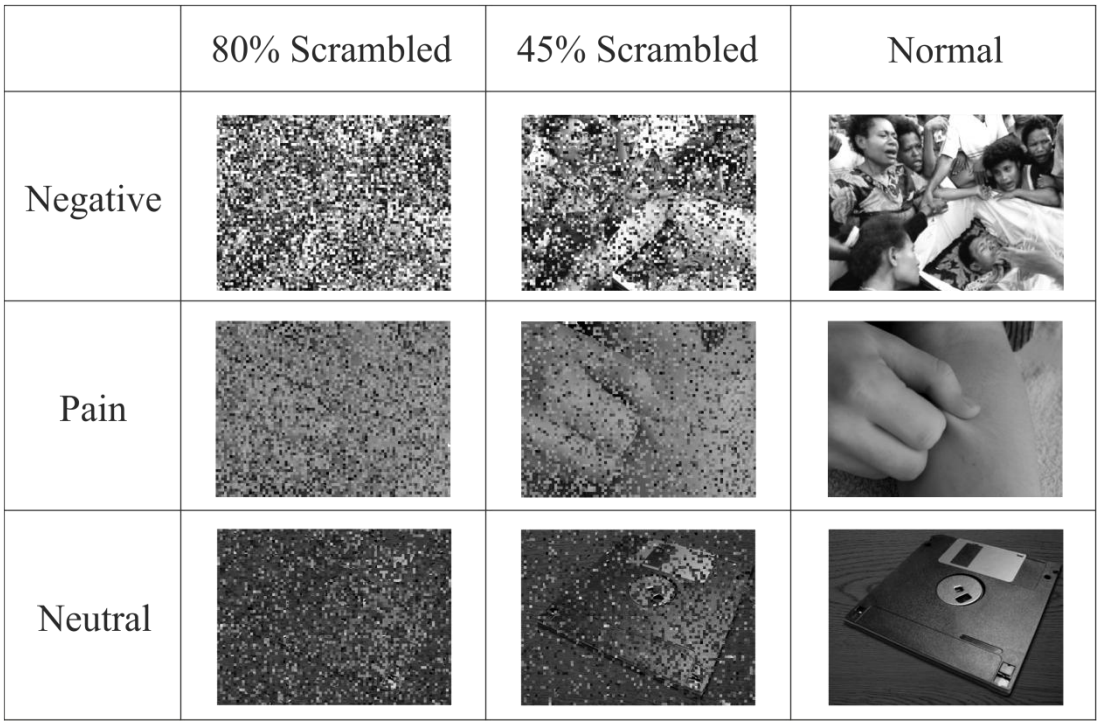

Fig. 3.1 Sample stimuli scrambled at 80%, 45%, or 0%.

3.1.3. Procedure

Upon arrival at the laboratory, subjects were required to complete the Fear of Pain Questionnaire – III (FPQ-III (McNeil and Rainwater, 1998)), and State-Trait Anxiety Inventory (STAI (Spielberger et al., 1983)).

Subjects sat in a sound and light attenuated room and viewed a 19 inch LCD computer monitor (60 Hz refresh rate) placed 0.7 m in front of them. At the beginning of each trial, a grey picture scrambled initially at 80% was centrally presented against a black background. Pictures were presented with the scrambling effect decreasing 2% per step, and each picture was displayed for 1.5 s. Subjects pressed the button when the original unscrambled picture emerged, or when they were able to identify the stimulus category. Subjects were required to select one from four options ('Not sure', 'Object', 'Pain', and 'Emotion') to classify the picture appropriately. Next, a nine-point rating scale with anchors, ''not certain at all'' (1) and ''very certain'' (9) was presented to evaluate the certainty of the subject's decision, in form of nine horizontally aligned white rectangles appearing on light yellow background. If the 'Pain' option was selected, subjects were required to evaluate the pain contained in the picture (1 = 'no pain at all', 9 = 'worst possible pain'). If the 'Object' or 'Emotion' options were selected, subjects were instructed to rate the valence of the picture content with 1 representing 'neutral' and 9 representing 'very unpleasant'. Each scale was presented till perceived a response or till a 10-second period elapsed. Fifteen pictures per block consisting of five Pain, five Negative, and five Neutral pictures, with a total of three blocks, were presented in randomised order. Before the experiment, subjects performed six practice trials, with two pictures of each category, to familiarise themselves with the task. These six

trials were contained different pictures to the experimental trials, and were excluded from the data analysis.

At the end of the experiment, subjects rated the photographs in terms of emotional valence and arousal using the 9-point Likert-style Self Assessment Manikin scales (Bradley and Lang, 1994). In addition, subjects rated the complexity of the picture content using a 9-point numeric scale ranging from 1 (not complex at all) to 9 (very complex). Another Pain Catastrophizing Scale was required to fill up in order to evaluate subject's pain catastrophising after the experiment.

3.1.4. Data analysis

The detection threshold, error rate, and decision confidence for Pain, Negative and Neutral pictures were tested for differences between pain catastrophising groups, measured in a two-way ANOVA for repeated measures with the between-subject factor of group (high vs. low pain catastrophisers), and the within-subject factor of picture type. Subjective ratings of valence, arousal, and picture complexity were also analysed using mixed 2×3 repeated measures ANOVAs. The P-values from the ANOVA analyses were adjusted with Greenhouse-Geisser correction to avoid violation of the sphericity assumption, due to the picture factor including more than 2 levels. Student's paired-sample t-test was used to compute the contrasts between two picture conditions. Student's independent samples t-test was used to evaluate the group differences in questionnaires. In order to reduce the risk of type one error in multiple comparisons, Bonferroni-Šidák's adjustments of P values were applied. A 95% confidence level was employed throughout. Statistical analyses were carried out in SPSS 20.0 (SPSS Inc., New York, USA).

3.2. Experiment 2: Effects of pain catastrophising on attention to pain in others: an eye movement study

3.2.1. Subjects

Seventy female students of Psychology at the University of Liverpool were screened using the Pain Catastrophizing Scale (PCS (Sullivan et al., 1995)) approximately 1 week prior to the experiment. Subjects were excluded if they reported a history of neurological or psychiatric diseases or chronic pain, or who required prescription eye glasses and could not wear contact lenses instead. Nineteen subjects scoring greater than 24 of the Pain Catastrophizing Scale and seventeen subjects scoring below 15 were selected and grouped as high and low pain catastrophising groups, respectively. The upper and lower thirds of the distribution of PCS scores were used as the cut-off points. Thus, thirty-six female subjects aged 18.9 ± 2.0 years (mean ± SD, High-Cat: 19.3 ± 2.8, Low-Cat: 18.6 ± 0.7) participated in the study for course credit exchange after giving their informed consent. The study was approved by the Research Ethics Committee of the University of Liverpool. All but five subjects had right-hand dominance according to self-report.

3.2.2. Materials and equipment

Visual stimuli consisted of 20 pairs of photographs with one photograph displaying hands or feet in situations implying pain (Pain, e.g., a knife slicing a cucumber and threatening to also cut a finger, or a hand trapped in a door), and one graphically matched control photograph not implying any pain (Non-Pain, e.g., a knife slicing a cumber with a knife safely away from the finger), similar to those used in previous studies (Jackson et al., 2005, Jackson et al., 2006, Gu and Han,

2007, Lamm et al., 2007a, Akitsuki and Decety, 2009). All pairs of Pain and Non-Pain photographs were graphically equivalent in terms of colour, contrasts, objects shown and view angles. Visual stimuli were presented using Inquisit version 3.0 software (Millisecond Software, Seattle, USA) on a 23-inch computer. The EYE-TRAC D6 Desktop mounted camera (Applied Science Laboratories, Bedford, MA, USA), which was used to record horizontal eye movements during the task, was employed simultaneously with the presentation of visual stimuli.

3.2.3. Procedure

Upon arrival at the eye tracking lab subjects provided their informed consent and completed a battery of questionnaires including Interpersonal Reactivity Index (IRI (Davis, 1980)), Fear of Pain Questionnaire – III (FPQ-III (McNeil and Rainwater, 1998)), and State-Trait Anxiety Inventory (STAI (Spielberger et al., 1983)). These questionnaires were used to evaluate any differences in empathic concern, fear to pain, and anxiety trait between high and low pain catastrophisers.

Subjects sat in the sound and light attenuated room and viewed the computer screen placed about 1 m in front of them. The remote camera for eye tracker was underneath the computer screen. Subjects were required to rest the chin and forehead on the brace and keep their heads as still as possible during the experiment. Their hands were rested on a table placing on the keyboard. The eye position was calibrated by displaying nine white dots on the screen in a 3×3 array (with the first one dot at the top left and the last one at the bottom right), and participants were required to look at each dot in turn while their gaze direction was recorded.

This experiment was organized into four blocks. The experiment started with the presentation of instruction, which illustrated the whole procedure and the

judgment task (e.g., pain judgment). In the visual probe task, each trial (Fig. 3.2) began with a 500 ms resting interval with a black fixation cross on a grey background. Then, a pair of matched images implying Pain and Non-Pain scenes was presented on the left and right sides of the grey background for 2000 ms. Subjects' eye movements were recorded during this period. After a 500 ms break, one of the Pain or Non-Pain images was displayed on the middle of the screen randomly for 1000 ms until the subject gave a manual response. During the response interval, the following instruction was presented in the centre of the screen "Press A if the picture was pain related, L if non-pain related", indicating participants were required to identify the single picture by pressing the button ''A'' if the picture implied pain or the button ''L'' if the picture implied non-pain. Once the key was pressed or after 3000 ms picture onset, the probe image was removed from the screen and next trial was started. Between blocks, subjects were allowed to rest for one minute. The total of 20 pairs was presented repeatedly in random order in each of four blocks totalling 80 trials. Pain scenes were present on the left and right sides of the screen in counterbalance during the whole experiment.

At the end of the experiment, subjects rated the photographs in terms of emotional valence and arousal using 9-point Likert-style Self Assessment Manikin scales (Bradley and Lang, 1994). In addition, subjects rated the pain attributed to each scene using a 9-point numeric scale ranging from 1 (no pain at all) to 9 (worst possible pain).

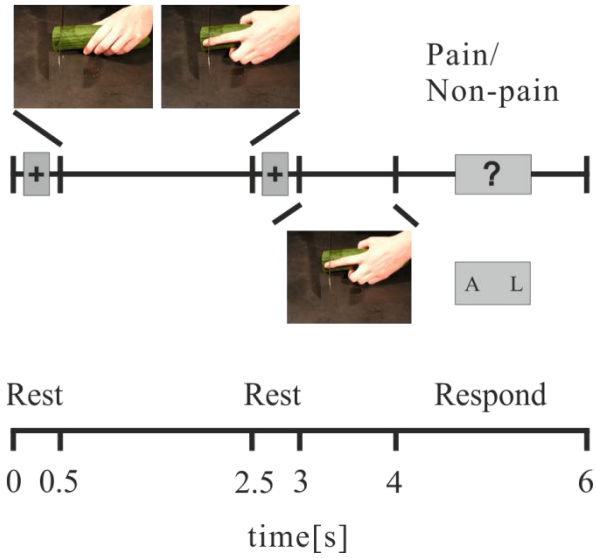

Fig. 3.2 Flowchart of the eye movement experiment. The figure displays one trial of the visual probe task, starting with a 0.5 s rest and continuing with a pair of pictures (Pain vs. Non-Pain) for 2 s. After half second break, a pictorial probe (Pain or Non-Pain picture) presents for 1 s and was followed by a response period of 2 s during which participants pressed the keyboard button 'A' or 'L' to identify whether the probe picture implicating a Pain or Non-Pain scene.

3.2.4. Data reduction and analysis

Eye movement data were analysed using ASL Results software (Applied Science Laboratories, Bedford, MA, USA). For each trial, gaze position was recorded at a sampling rate of 120 Hz during the 2000 ms in which the Pain and Non-Pain picture pairs were presented. Three regions of interest were occupied in Pain photographs, Non-Pain photographs, and the region in between the pictures. Eye movement data were excluded if fixations did not direct to any of these three regions of interest. If eye movements were stable within 1˚ of visual angle for 100 ms or longer, this was classified as a fixation to that position, the duration of which was recorded. The fixation latency was computed as the interval between the onset of the pictorial stimuli and the first fixation onset. Fixation was defined as being gazing at the left or right pictures if they were 1˚ wide of the central position on the horizontal plan.

Fixations on either picture in each pair were identified when the following 3 conditions were satisfied: (1) subjects gazed in the central region before the picture onset, (2) saccades occurred at least 100 ms after picture onset (fixations with shorter latencies are unlikely to be related to the pictures, and may instead reflect express saccades or anticipatory eye movements) (Fischer and Weber, 1993), (3) subjects fixated on either picture rather than the central position during the picture presentation (Mogg et al., 2003, Field et al., 2004, Yang et al., 2012). Due to calibrated failure, eye movement data of eight subjects were missing (≥ 50%) and excluded. Therefore, data from 28 subjects (13 High-Cat and 15 Low-Cat subjects) were retained for data analysis.

A 2×2 between-groups design evaluated effects of group (High-Cat vs. Low-Cat) and picture type (Pain vs. Non-Pain) on five eye movement indices (direction bias of initial gaze, first fixation latency, first fixation duration, and average fixation duration). Subjective ratings of valence, arousal, and pain were analysed using mixed 2×2 repeated measures ANOVAs. Student's independent samples t-test were used to evaluate the group differences in the questionnaires. In order to reduce the risk of type one error in multiple correlations, Bonferroni-Šidák's adjustments of P values were applied. A 95% confidence level was employed throughout, using the Greenhouse-Geisser correction. Statistical analyses were carried out in SPSS 20.0 statistical analysis package (SPSS Inc., New York, USA).

3.3. Experiment 3: Effects of pain catastrophising on attention to pain in others: a second eye movement study

3.3.1. Subjects

Eighty-three female students of Psychology at the University of Liverpool were screened using the Pain Catastrophizing Scale (PCS, mean ± SD = 20.2 ± 9.0, Med = 19 (Sullivan et al., 1995)). Subjects were excluded if they reported a history of neurological or psychiatric diseases or chronic pain, or who required prescription eye glasses and could not wear contact lenses instead. Following the criteria of grouping in Study 1, twenty subjects scoring greater than 24 of the Pain Catastrophizing Scale and eighteen participants scoring below 15 were selected and grouped as high (High-Cat) and low pain catastrophising groups, respectively. Thus, thirty-eight female subjects aged 20.9 ± 3.3 years (mean ± SD, High-Cat: 19.7 ± 2.6, Low-Cat: 22.2 ± 3.5) participated in the study for course credit exchange after giving their informed consent. The study was approved by the Research Ethics Committee of the University of Liverpool. All but one subject had right-hand dominance according to self-report.

3.3.2. Materials and equipment

Twenty Pain and 20 graphically matching Non-Pain pictures and 20 Negative emotional pictures were used to create 20 Pain– Non-Pain picture pairs, 20 Pain– Negative picture pairs, and 20 Negative– Non-Pain picture pairs. Pain and Non-Pain pictures were used as same as those in Experiment 2. Negative emotional pictures (abbreviated as 'Negative') were selected from the International Affective Picture System (IAPS) (Lang et al., 2008). Compared to Pain pictures, Negative pictures did not contain bodies, injuries and wounds (e.g. a sinking ship). All

pictures were graphically equivalent in terms of colour, contrasts, objects shown and view angles. Visual stimuli were presented with the same equipment that was employed in Experiment 2.

3.3.3. Procedure

Upon arrival at the eye tracking lab subjects provided their informed consent and completed questionnaires the same as those in Experiment 2. Experimental settings for subjects, such as, eye position calibrations, were the same as the Experiment 2 (See Section 3.2.3 for details).

This experiment was organized into 4 blocks. The experiment started with the presentation of instruction, which illustrated the whole procedure and the judgment task (e.g. pain judgment). In the dot-probe task, each trial (Fig. 3.3) began with a black fixation cross on a grey background for 1 s, which was replaced by the display of a pair of pictures, side by side, for 2 s. Immediately after the offset of the picture pair, a black dot probe ('•') was presented in the position of one of the preceding pictures, until participants responded via a key press. Subjects were instructed to press the button ''A'' if dot probe appeared on the left side or the button ''L'' if on the right side, as quickly as possible. Each probe appeared until a response or for 1.5-second maximum. Eye movement data were recorded during each trial, beginning immediately before the onset of fixation cross and terminating immediately after participants made a response.

In the whole experiment, the total of 60 pairs was presented repeatedly in each of four blocks totalling 240 trials. Within each block the trials were presented in a new random order for each participant, so that the picture type position varied over trials. Four different presenting combinations were using the target pictorial stimuli

and dot probe appearing in the left or right positions of the computer screen. Two combinations included the target picture and the probe in the same position of the computer screen (i.e. once in the left side of the computer screen and once in the right side of the screen), which were considered as the congruent trials. Another two combinations were comprised of the target stimuli and the probe in the opposite position of the computer screen (i.e. one in the left side and the other in the right side), considered as the incongruent trials (MacLeod et al., 1986, Haggman et al., 2010).

At the end of the experiment, subjects rated the photographs in terms of emotional valence and arousal using 9-point Likert-style Self Assessment Manikin scales (Bradley and Lang, 1994). In addition, subjects rated the pain attributed to each scene using a 9-point numeric scale ranging from 1 (no pain at all) to 9 (worst possible pain).

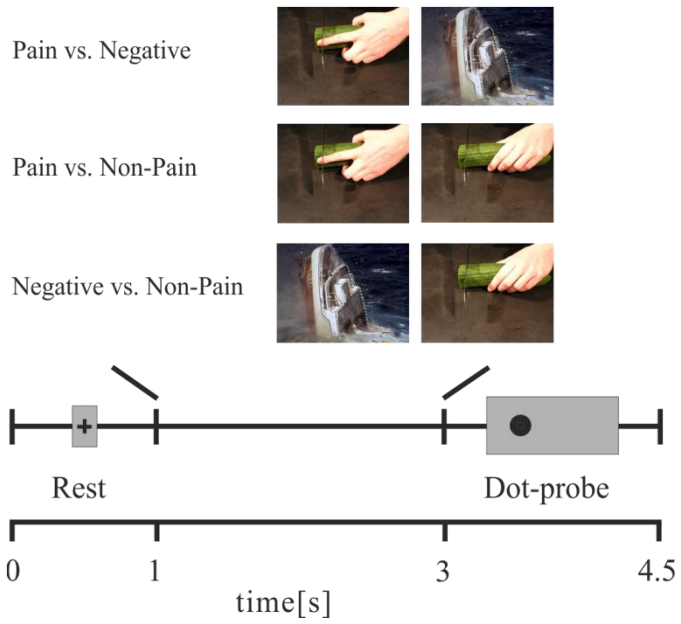

Fig. 3.3 Flowchart of the second eye movement experiment. The figure displays one trial of the visual probe task, starting with a 1 s rest and continuing with the presentation of a picture pair (i.e. Pain vs. Non-Pain) for 2 s, and followed by a dot-probe response period of 1.5 s during which participants pressed the keyboard button 'A' or 'L' to identify whether the black dot probe appeared on the left or right side.

3.3.4. Data reduction and analysis

Eye movement data were analysed with a same protocol and procedure as Experimental 2 (See Section 4.2.4 for details). Data from 32 subjects (17 High-Cat and 15 Low-Cat subjects) were retained for data analysis.

Based on the previous studies (Mogg et al., 2003, Gao et al., 2011, Yang et al., 2012), a 2×3 between-groups design evaluated effects of group (High-Cat vs. Low-Cat) and types of picture pair (Pain– Non-Pain vs. Pain– Negative vs. Negative– Non-Pain) on eye movement bias in attention orientation (initial gaze direction bias and first fixation latency bias), attention maintenance (first fixation duration bias and average fixation duration bias), and attention re-engagement. Subjective ratings of valence, arousal, and pain were analysed using mixed 2×3 repeated measures ANOVAs. All p-values from ANOVA analyses were adjusted with Greenhouse-Geisser correction to avoid violation of the sphericity assumption. Student's independent samples t-test were used to evaluate the group differences in the questionnaires. In order to reduce the risk of type one error in multiple correlations, Bonferroni-Šidák's adjustments of P values were applied. A 95% confidence level was employed throughout. Statistical analyses were carried out in SPSS 20.0 statistical analysis package (SPSS Inc., New York, USA).

3.4. Experiment 4: Pain catastrophising effects on the cortical responses to viewing pain in others

3.4.1. Subjects

Ninety-nine female students of psychology from the University of Liverpool were initially screened using the Pain Catastrophizing Scale (PCS, mean ± SD = 19.1 ± 9.8) (Sullivan et al., 1995) approximately 2 weeks prior to the experiment. All students were informed that this questionnaire concerned their thoughts and feelings when they were experiencing pain. Students were excluded if they reported a medical condition associated with pain or any neurological or psychiatric disease, or had abnormal visual ability. Subjects having PCS scores greater than 24 or lower than 15 were classified as high- (High-Cat) and low (Low-Cat) pain catastrophisers, respectively. The cut-off points were the 66.7% and the 33.3% percentiles of PCS scores. Thirty females (15 High-Cat vs. 15 Low Cat) aged 20.3 ± 2.7 years (mean ± SD, Low-Cat: 21.1 ± 3.5, High-Cat: 19.4 ± 1.1) participated in the EEG experiment for course credits. All participants gave their informed consent according to Declaration of Helsinki. The study was approved by the Research Ethics Committee of the University of Liverpool. All but three subjects had right-hand dominance according to self-report.

3.4 2. Procedure

Subjects sat in a sound and light attenuated room and viewed a 19 inch LCD computer screen placed 0.7 m in front of them whilst holding a response keypad in both hands. Subjects were informed to picture the pain which they may observe in photographs to be presented on a computer screen. The experiment was organised into 4 blocks each lasting 7.3 min. Each trial (Fig. 3.4) began with a 4 s resting

interval during which subjects viewed a black fixation cross on a grey background. In each trial, a picture was presented on the grey background for 3 s followed by a resting interval of 2 s and a 2 s response epoch. During the response epoch, a black question mark was displayed prompting the participant to press one of two buttons if the picture was implying pain and the other button if pain was not implied in the scene. The side of the button associated with pain was balanced across subjects. In each of four blocks, 20 pain and 20 graphically matching non-pain scenes were presented. The scenes were similar to those used in previous studies (Jackson et al., 2005, Jackson et al., 2006, Gu and Han, 2007, Lamm et al., 2007a, Akitsuki and Decety, 2009), and displayed hands or feet in the situations representing implied pain, such as a knife slicing a cucumber and threatening to also cut a finger, or a tip of a syringe needle placed on the forearm. The non-pain scenes were graphically matched to pain scenes but contained no potential pain threat, such as a tip of a pen placed on the forearm, as illustrated in Fig. 3.4. Pairs of pain and non-pain pictures were graphically equivalent in terms of colour, contrast, objects, and viewing angles. The sets of 20 pain and 20 non-pain pictures were presented at random in each of four blocks totalling 80 trials for each picture type. At the end of the experiment, subjects were instructed to rate the valence (‘‘neutral’’ - ‘‘very unpleasant’’) and arousal (‘‘neutral’’ – ‘‘very arousing’’) of every picture using 9-point Likert-style Self Assessment Manikin scales (Bradley and Lang, 1994). In addition, participants rated the pain attributed to each scene using a 9-point numeric scale ranging from 1 (no pain at all) to 9 (worst possible pain). Participants also completed the Interpersonal Reactivity Index (IRI) (Davis, 1980) to evaluate any differences in empathic concern between high and low pain catastrophisers. The IRI measures four scales of empathic behaviour such as empathic concerns or perspective taking.

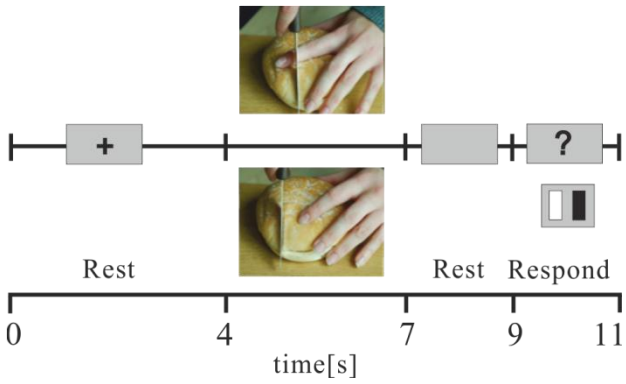

Fig. 3.4 Flowchart of the pain observation experiment. The figure illustrates one trial of the experiment, beginning with rest (4 s) and continuing with visual presentation of a pain or non-pain scene for 3 s, followed by another rest period of 2 s, and a response period of 2 s during which subjects pressed left or right button on a response pad to indicate whether the photograph depicted a pain or non-pain scene.

3.4.3. Data recordings

EEG was recorded continuously using the 128-channel Geodesics EGI System (Electrical Geodesics, Inc., Eugene, Oregon, USA) with the sponge-based Geodesic Sensor Net. The sensor net was aligned with respect to three anatomical landmarks including two pre-auricular points and the nasion. The electrode-to-skin impedances were kept below 50 kΩ and at equal levels in all electrodes. The recording bandpass filter was 0.1−100 Hz, and the sampling rate was 250 Hz. The electrode Cz was used as the reference.

3.4.4. Data pre-processing

EEG data was processed using BESA (Brain Electric Source Analysis) v. 6.0 program (MEGIS GmbH, Munich, Germany). Data was spatially transformed into reference-free data using common average reference method (Lehmann, 1987). The oculographic and, when necessary, electrocardiographic artifacts were removed by principal component analysis (Berg and Scherg, 1994). Data was visually inspected for the presence of any movement or muscle artifacts, and epochs contaminated with

artifacts were excluded. Event related potentials (ERPs) were computed separately for high- and low-pain catastrophisers responses to pain- and non-pain- trials by averaging respective epochs in the interval ranging from 200 ms before stimulus onset to 1400 ms after stimulus onset. The baseline period ranged from -200 ms to 0 ms relative to the onset of visual stimulus. ERP signals were bandpass-filtered from 0.5 to 40 Hz. Evoked potentials from four blocks were averaged. The average number of epochs used was 58.4 ± 10.7 during pain scenes and 59.1 ± 11.2 during non-pain scenes.

3.4.5. Source dipole analysis

To evaluate the differences in event-related potentials between High-cat and Low-Cat groups during two conditions (i.e. viewing pain vs. non-pain pictures) and to localise the cortical regions potentially showing significant differences related to pain catastrophising, the source localisations were estimated using CLARA (Classical LORETA Analysis Recursively Applied) (Hoechstetter et al., 2010), as implemented in BESA v. 6.0 program. CLARA is a novel iterative source analysis method which operates by performing a weighted LORETA (Low Resolution Electromagnetic Tomography Analysis) on each iteration, followed by source space reduction. Compared to the standard LORETA method (Pascual-Marqui et al., 1994), CLARA reduces the blurring of the estimated sources while maintaining the advantages of a predefined distributed source model, thus making it easier to obtain a relative focal distribution of source activation (Hämäläinen et al., 2011b, Valentini et al., 2012a, Valentini et al., 2012b). It combines the advantages of discrete and distributed source analysis by employing distributed source analysis with a shrinking of the source space. A default minimum regularisation cut-off parameter was used.

The source image was expressed as current density within a standard MRI image (nAm/cm^3). The ellipsoid head model was used, and the conductivities were set as follows: skin = 0.33 S/m, skull = 0.0042 S/m, cerebrospinal fluid = 1.0 S/m, and brain parenchyma = 0.33 S/m.

The source dipole model was built by applying CLARA to grand average EEG waveforms comprising all subjects and both conditions. Here employed the iterative application of the LORETA algorithm to explain the potential changes occurring in the time epoch of -200 ms to 1400 ms. Four clusters have been detected to operate during this interval. One equivalent source dipole was placed to the spatial maximum of each CLARA cluster and orientation was fitted at the fixed dipole location. The four dipole solution accounted for 96% of variance in ERP data, and proved to be stable across conditions and subjects. Source locations were transformed to approximate Talairach coordinates using BESA v. 6.0 program.

To evaluate statistically the effects of pain catastrophising on ERPs, the grand average source dipole model was used to compute individual source waveforms during viewing of pain and non-pain pictures in High-Cat and Low-Cat groups. The source waveforms were exported by fixating the source dipole locations and refitting the orientations of all four dipoles in each subject and condition, similar to previous studies (Tarkka and Treede, 1993, Schlereth et al., 2003, Gutschalk et al., 2005, Stancák et al., 2011).

A MATLAB v. R2011a program (The MathWorks, Inc., USA) was employed to analyse the average source waveforms in each of four source dipoles for pain and non-pain pictures in High-Cat and Low-Cat groups. In each source, intervals of interest have been determined by identifying the latencies in which the

source dipole activation displayed significant main effects (i.e. group or picture type effect) or interactions (i.e. group × picture type) with a $P \leq 0.05$ using nonparametric permutation-based two-way mixed-effect model ANOVAs (Maris and Oostenveld, 2007). Mean source activations were extracted for all participants and both conditions in each interval of interest per each source. A two-way mixed-effect measures ANOVA, involving one within-subject factor (pain vs. non-pain pictures) and one between-subject factor (High-Cat vs. Low-Cat groups), was performed in each interval of interest in SPSS 20.0 (SPSS Inc., New York, USA).

3.4.6. Statistical analysis

Subjective ratings of valence, arousal and pain were analysed using mixed 2×2 mixed-effect measures ANOVAs. Scale values obtained from IRI in High-Cat and Low-Cat groups were compared using a Student's independent samples t-test. Pearson's correlation coefficients were computed to evaluate associations between the differences between pain and non-pain pictures in source dipole components and the differences in subjective scales. In order to reduce the risk of type one error in multiple correlations, Bonferroni-Šidák's adjustments of P values were applied. A 95% confidence level was employed throughout. Statistical analyses were carried out in SPSS 20.0 statistical analysis package.

3.5. Experiment 5: Pain catastrophising effects on the cortical responses to laser stimulation during viewing of comforting hand postures

3.5.1. Subjects

Eighty female students of Psychology at the University of Liverpool were initially screened using the Pain Catastrophizing Scales (PCS, mean ± SD = 16.7 ± 10.0, Med = 19 (Sullivan et al., 1995)). All students were informed that this questionnaire was concerned the thoughts and feelings when they were in pain. Students were excluded if they reported a medical condition associated with pain or neurological and psychiatry diseases. The study followed the cut-off scores for catastrophisers proposed by Sullivan et al. (1995) to classify participants (> 24 high pain catastrophisers (High-Cat) and < 15 low pain catastrophisers (Low-Cat)). A total of 24 healthy students with 12 subjects per each group aged 20.5 ± 3.3 years (mean ± SD, High-Cat: 19.8 ± 3.0, Low-Cat: 21.1 ± 3.5) were selected to participate in the study in exchange for course credit, after giving informed consent. The study was approved by the Research Ethics Committee of the University of Liverpool. All subjects had normal or corrected-to-normal vision. All but 5 subjects had right-hand dominance according to self-report.

3.5.2. Procedure

Upon arrival at the EEG laboratory subjects were required to complete the Interpersonal Reactivity Index (IRI (Davis, 1980)) and State-Trait Anxiety Inventory (STAI (Spielberger et al., 1983)).

Subjects sat in a sound and light attenuated room and viewed a 19 inch LCD computer monitor placed 0.7 m in front of them. Both of the subject's hands rested

on a wooden desk. The right hand was enclosed in a black box, and a circle of 3 cm in diameter was drawn on the dorsolateral part of the hand. The left hand was holding the mouse. The experimenter held the hand piece of the laser stimulator and orientated the laser beam by changing pseudo-randomly the target spot within the defined area on the hand, in order to avoid sensation or fatigue of primary nociceptive afferents. The experimenter and the participant were required to wear goggles to protect their eyes away from the laser beam.

The experiment was organized into four blocks each lasting seven minutes. Each trial (Fig. 3.5) began with a 4 s resting interval during which subjects viewed a black fixation cross on a grey background. In each trial, a photograph was presented on the grey background for 4 s. After a 1s onset of the photograph, a laser stimulation was given randomly on the right hand. Each photograph was followed by a resting interval of 2 s and a 4 s evaluation period during which the subject was required to evaluate the pain perceived from the laser stimulation. An eight-point rating scale with anchors ,‘‘no pain at all” (0) and “worst possible pain” (7) was presented in form of eight horizontally aligned dark grey rectangles appearing on a light grey background. Subjects rated the intensity of their pain by repeatedly clicking a computer mouse with their left hand. Three different types of images with 40 photographs per type were presented in random order in four blocks, totalling 120 trials. Before the experiment, subjects were informed that there were three types of photographs, with three hands shown in each. The single right hand (painful hand) was in the same uncomfortable situation as subject’s painful hand. A pair of hands (comfort hands) offered different degrees of comfort-giving. In the Non-Touch condition, the comforting hands did not touch the painful hand; in the Touch condition, the comforting hands only touched the dorsolateral part of the painful

hand; and in the Comfort condition, the comforting hands were fully holding the painful hand.

At the end of the experiment, subjects rated the photographs in terms of comforting, empathy and pleasantness using a 9-point numeric scale ranging from 1 ('neutral' or 'no empathy displayed') to 9 ('highly comforting', 'high empathy displayed', or 'very pleasant').

Laser stimuli were applied using an Nd-YAP laser stimulator (Stim1324, El.En., Italy). The pulse duration was 2 ms, and the beam diameter was 4 mm. The intensity of the laser stimuli was adjusted individually, prior to the first block by incrementing the stimulus intensity from 1.25 to 1.75 J. The intensity which produced a moderate pain sensation, rated 3−4 on an 8-point rating scale, was used throughout. To ensure the stimulation intensity was as close as possible to the beginning intensity, the calibration procedure was repeated between blocks if necessary. These stimulus parameters were optimised to produce a sharp pricking pain mediated by Aδ fibres.

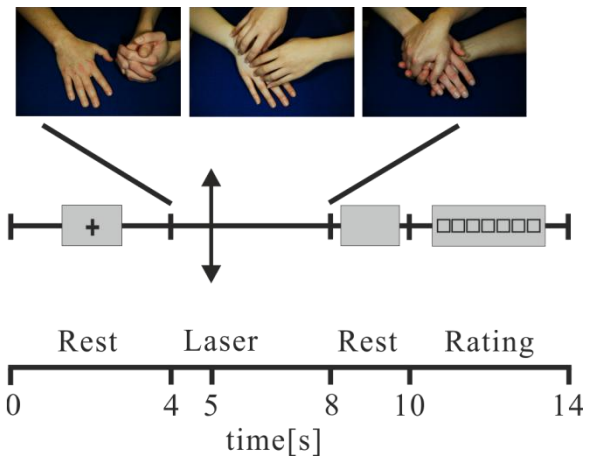

Fig. 3.5 Flowchart of the comfort-giving experiment. The figure illustrates one trial of the experiment, beginning with a 4 s rest and continuing with a visual display of a Non-Touch, Touch or Comfort photograph for 4 s, followed by another 2 s rest period, and a response period of 4 s during which subjects repeatedly clicking the computer mouse for evaluating their pain intensity with their left hand. Laser stimulation was given after 1 s onset of the visual stimuli.

3.5.3. Data recordings

EEG was recorded continuously using the 128-channel Geodesics EGI System (Electrical Geodesics, Inc., Eugene, Oregon, USA) with the sponge-based Geodesic Sensor Net. The sensor net was aligned with respect to three anatomical landmarks including two pre-auricular points and the nasion. The electrode-to-skin impedances were kept below 50 kΩ and at equal levels in all electrodes. The recording bandpass filter was 0.1−400 Hz, and the sampling rate was 1000 Hz. Electrode Cz was used as the reference.

3.5.4. Data pre-processing

EEG data was processed using BESA v. 6.0 (MEGIS, Germany). Data were spatially transformed into reference-free data using the common average reference method (Lehmann, 1987). The oculographic and, when necessary, electrocardiographic artifacts were removed by principal component analysis (Berg and Scherg, 1994). Data were visually inspected for the presence of any movement or muscle artifacts, and epochs contaminated with artifacts were excluded. Evoked related potentials (ERPs) were computed separately for high- and low-pain catastrophisers responses to Comfort-, Touch- and Non-Touch trials by averaging their respective epochs. Then, grand averaged EEG waveforms comprised of all subjects and all three types of pictures were constructed.

For the analysis of ERPs to picture stimuli, each epoch started 300 ms before and ended 1700 ms after the pictorial stimuli, with the baseline ranging from -300 ms to 0 ms relative to the onset of pictorial stimulus. Evoked potentials from four blocks were averaged. The average number of trials used was 28.1 ± 7.7 (mean ± SD) for Comfort photographs, 29.3 ± 6.9 for Touch photographs, and 26.3 ± 8.2 for Non-

Touch photographs. It has been known for a high-pass filter to remove the slow wave activity (i.e. LPP) from the data. Studies with emotional visual stimuli recommended a 0.1 Hz high-pass filter for obtaining a sustained LPP (Hajcak et al., 2007, Schupp et al., 2007, Hajcak and Olvet, 2008, Foti et al., 2009, Hajcak and Dennis, 2009). Therefore, in order to detect the early fast components and the slower frequency activity, two bandpass filters were employed for the ERP analysis – 0.1 - 30 Hz and 2 - 40 Hz.

For LEPs, each epoch started 200 ms before and ended 1000 ms after the laser stimulus onset, with the baseline ranging from -200 ms to 0 ms relative to the onset of laser stimulus. ERP signals were bandpass-filtered from 1 to 40 Hz. Evoked potentials from the four blocks were averaged. The average number of trials used was 33.2 ± 4.5 (mean ± SD) for Comfort photographs, 33.8 ± 4.5 for Touch photographs, and 31.1 ± 5.7 for Non-Touch photographs.

3.5.5. Source dipole analysis of ERPs to picture stimuli

To evaluate the differences in event-related potentials between High-cat and Low-Cat groups during three conditions (i.e. viewing Comfort, Touch, and Non-Touch pictures) and to localise the cortical regions potentially showing significant differences related to pain catastrophising, the source localisations were estimated using the Multiple Source Probe Scan (MSPS) for model validation and the Local Auto-Regressive Average (LAURA) toolbox for source localization (Grave de Peralta Menendez et al., 2001, Michel et al., 2004), as implemented in BESA v. 6.0. LAURA is a method for distributed linear inverse solutions comprising biophysical laws as constraints, and contains a depth weighting term and a representation of a local autoregressive function (Grave de Peralta Menendez et al., 2001, Grave de

Peralta Menendez et al., 2004, Michel et al., 2004). It estimates 3D current density distributions using a realistic head models with the Montreal Neurological Institute's (MNI) template brain. LAURA deals with multiple simultaneously active sources and makes no a priori assumption about the number of activated sources and their locations. A default minimum regularisation cut-off parameter was used. The source image was expressed as current density within a standard MRI image (nAm/cm^3).

The source dipole model was built by applying MSPS and LAURA to grand averaged EEG waveforms comprising all subjects and all three conditions. This study employed the spatial weighting of the LORETA algorithm to explain the potential changes occurring in the time epoch of -300 ms to 1000 ms. Six clusters were found to operate during this interval. One equivalent source dipole was placed in the spatial maximum of each LAURA cluster, and orientation was fitted at the fixed dipole location. The six dipole solution accounted for 95.1% of variance in the ERP data, and proved to be stable across conditions and subjects. Source locations were transformed to approximate Talairach coordinates using BESA v. 6.0. For source localization, the ellipsoid head model was used, and the conductivities were set as follows: skin = 0.33 S/m, skull = 0.0042 S/m, cerebrospinal fluid = 1.0 S/m, and brain parenchyma = 0.33 S/m.

3.5.6. Source dipole analysis of LEPs

Laser evoked potentials (LEPs) were analysed using multiple source dipole analysis (Scherg and von Cramon, 1986). This method requires building a model encompassing several equivalent source dipoles placed into different cortical regions. As there are many alternative solutions of the inverse problem (Hämäläinen et al., 1993), CLARA (Classical LORETA Analysis Recursively Applied

(Hoechstetter et al., 2010)), as implemented in BESA v. 6.0, was employed for the estimation of the source localizations. It combines the advantages of discrete and distributed source analysis by employing distributed source analysis with a shrinking of the source space (Hämäläinen et al., 2011b, Valentini et al., 2012a, Valentini et al., 2012b). A default minimum regularisation cut-off parameter was used. The source image was expressed as current density within a standard MRI image (nAm/cm^3).

The source dipole model was built by applying CLARA to grand averaged EEG waveforms comprising all subjects and all three conditions. Here it employed the iterative application of the LORETA algorithm to explain the potential changes occurring in the time epoch of -200 ms to 1000 ms. Six clusters were found to operate during this interval. One equivalent source dipole was placed in the spatial maximum of each CLARA cluster and orientation was fitted at the fixed dipole location. The six dipole solution accounted for 92.9% of variance in LEP data, and proved to be stable across conditions and subjects. Source locations were transformed to approximate Talairach coordinates using BESA v. 6.0.

3.5.7. Statistical analysis

To evaluate effects of pain catastrophising on ERPs and LEPs, the grand average source dipole model was used to compute individual source waveforms during viewing of Comfort, Touch, and Non-Touch pictures in High-Cat and Low-Cat groups. The source waveforms were exported by fixing the source dipole locations and refitting the orientations of all six dipoles in each subject and condition, similar to previous studies (Tarkka and Treede, 1993, Schlereth et al., 2003, Gutschalk et al., 2005, Stančák et al., 2011).

A MATLAB v. R2011a program (The MathWorks, Inc., USA) was employed to analyse the average source waveforms in each of six source dipoles for three picture types in High-Cat and Low-Cat groups. In each source, intervals of interest were determined by identifying the latencies in which the source dipole activation displayed significant main effects (i.e. group or picture type effect) or interactions (i.e. group × picture type) with a $p \leq 0.05$ using nonparametric permutation-based 2×3 mixed-effect model ANOVAs (Maris and Oostenveld, 2007). Mean source activations were extracted for all participants and three conditions in each interval of interest in each source. A two-way mixed-effect measures ANOVA, involving one within-subject factor (Comfort, Touch, and Non-Touch pictures) and one between-subject factor (High-Cat vs. Low-Cat groups), was performed in each interval of interest in SPSS 20.0 (SPSS Inc., New York, USA).

Subjective ratings of pain, comforting, empathy, and pleasantness were analysed using mixed 2×3 mixed-effect measures ANOVAs. All p-values from ANOVA analyses were adjusted with the Greenhouse-Geisser correction to avoid violation of the sphericity assumption. Student's paired-sample t-test was used to compute the contrasts between two picture conditions. Pearson's correlation coefficients were computed to evaluate associations between the source dipole components of each condition and the corresponding subjective pain ratings to laser stimulation. A Student's independent samples t-test was used to evaluate the group differences in IRI and STAI scales. In order to reduce the risk of type one error in multiple correlations, Bonferroni-Šidák's adjustments of P values were applied. A 95% confidence level was employed throughout. Statistical analyses were carried out in SPSS 20.0 (SPSS Inc., New York, USA).

3.6. Experiment 6: Pain catastrophising and structural features of cortical and subcortical brain regions in healthy people

3.6.1. Subjects

Fifty-two individuals (37 females) between the ages of 19 and 51 were recruited through a campus advertisement. Subjects were excluded if they reported a history of major disease, neurological or psychiatric diseases, or chronic pain. Informed consent was obtained from all subjects in accordance with the Declaration of Helsinki. The study was approved by the Research Ethics Committee of the University of Liverpool. All subjects were compensated for time and travel expenses.

3.6.2. MRI data acquisition

Subjects attended the Magnetic Resonance and Image Analysis Research Centre (MARIARC) at the University of Liverpool. Before their MR scan, all subjects underwent a safety screening, interviewed by a senior radiologist to confirm their suitability for the session. They were also required to complete several questionnaires: Pain Catastrophizing Scale (PCS (Sullivan et al., 1995)), Fear of Pain Questionnaire – III (FPQ-III (McNeil and Rainwater, 1998)), and State-Trait Anxiety Inventory (STAI (Spielberger et al., 1983)).

Magnetic resonance imaging was performed with a 3-Tesla Trio whole body scanner (Siemens, Magnetom, Erlangern Germany) and an 8-channel head coil. A high-resolution three-dimensional structural T1-weighted image was acquired for each subject using a modified driven equilibrium Fourier transform (MDEFT) sequence with the following parameters: TR = 7.92 ms, TE = 2.48 ms, flip angle =

16 °, 176 sagittal slices, slice thickness = 1mm, matrix = 256 × 256, in-plane voxel size = 1 mm × 1 mm, total acquisition time = 12:51 mins. The same scanner and the same scanning protocol were used for all subjects.

3.6.3. Pre-processing and voxel based morphometry analysis

Voxel-based morphometry (VBM) analysis was used to investigate the correlations between pain catastrophising and grey matter (GM) and white matter (WM) volumes, using the Statistical Parametric Mapping 8 package (SPM8, Welcome Trust Centre for Neuroimaging, University College London, UK; http://www.fil.ion.ucl.ac.uk/spm/) implemented in Matlab R2011a (The Mathworks Inc, USA). The pre-processing was based on the Diffeomorphic Anatomical Registration using Exponentiated Lie algebra (DARTEL (Ashburner, 2007)) for diffeomorphic image registration. DARTEL has been formulated to include an option for estimating inverse consistent deformations. Nonlinear registration is considered as a local optimisation problem, which is solved using the Levenberg-Marquardt strategy. A constant Eulerian velocity framework is used, which allows a rapid scaling and squaring method to be used in the computers. Such a technique improves the inter-subject registration. As DARTEL produces more accurate registration (Klein et al., 2009), it allows improved sensitivity such as that needed to evaluate the relationship between the regional GM volume and pain catastrophising.

DARTEL processing included several steps, as follows. (1) Setting the T1-weighted MR image origin to the anterior commissure. (2) Segmenting the adjusted images using the New Segmentation algorithm in SPM8 toolbox (Ashburner and Friston, 2005). The resulting GM and WM images were rigidly registered onto their common mean image. (3) Estimating the deformations from each subject's data to a

common, average template using an iterative procedure. (4) Matching the custom template created in the previous step to Montreal Neurological Institute (MNI) space, using an affine registration to map the custom coordinate space to the more standard MNI space. (5) Applying the modulation with the Jacobian determinants to preserve the amount volume of grey or white matter in the images, so that they were the same as those in the original images. (6) Finally, Smoothing the images using an isotropic Gaussian kernel of 10 mm full width at half maximum.

Correlations between pain catastrophising scores and GM, WM, cerebrospinal fluid (CSF) volumes, and the total intracranial volume (TIV), obtained in the brain segmentation step of the image pre-processing, were evaluated, using Pearson's correlation analysis. TIV was calculated as the sum of the GM, WM, and CSF volumes. The distributions of age, PCS, FPQ-III, and STAI scores were tested using the normality test. All statistical comparisons were performed in SPSS v.20 (SPSS Inc, Chicago, USA), with a Bonferroni correction of $p < 0.05$.

A multiple regression analysis was performed to investigate the correlations between grey matter alterations and pain catastrophising after adjusting for age, gender, fear of pain and anxiety. Pain catastrophising scores were used as the independent variable, regional GM volume was used as the dependent variable, and age, gender, scores of FPQ-III and STAI were used as the covaiates. Clinical VBM studies have reported that it is too conservative to obtain results with the rigorous statistical family-wise error (FWE) correction thresholds used in the statistical parametric mapping voxel-wise analysis of the whole brain, since pain-related grey matter alterations may be small (Schmidt-Wilcke et al., 2005, Rocca et al., 2006, Schmidt-Wilcke et al., 2006, Valfrèet al., 2008, Schmidt-Wilcke et al., 2010).

Alternatively, as in a previous paper (Schmidt-Wilcke et al., 2006), an uncorrected threshold of $p < 0.001$ (with a cluster extent of 50 contiguous voxels) for multiple comparisons at a voxel level throughout the whole brain was employed in the conventional VBM analysis. A brain mask was employed on both the GM and WM to avoid possible edge effects around the border between the two.

3.6.4. Subcortical shape analysis

All high-resolution T1-weighted images were processed and analysed with FSL version 4.1.9 (FMRIB Software Library, Oxford, UK, http://www.fmrib.ox.ac.uk/fsl). After extracting the brain of the T1-weighted MR images (to exclude the skull and other tissues) using brain extraction tool (BET), FMRIB's integrated registration and segmentation tool (FIRST) was applied for the evaluation of deep subcortical structures (Patenaude, 2007). FIRST performs both registration and segmentation of 15 subcortical structures (brainstem, left and right of nucleus accumbens, amygdala, caudate, hippocampus, palladium, putamen and thalamus). This method is based on multivariate Gaussian shape/appearance models, using a large, manually labelled data set as a training template wherein the subcortical structures are parameterised as surface meshes with established vertices (Patenaude et al., 2011). During registration, T1-weighted MR images were transformed to the MNI 152 standard space, by means of 12 degrees of freedom affine registration (i.e. three translations, three rotations, three scaling and three skews). Subsequently, a subcortical mask template was applied, followed by segmentation based on shape and voxel intensities. In an automated process, the extracted images are affine registered (12 degrees of freedom) to the training template and subsequently to the MNI 152 standard space subcortical mask template.

Finally, shape and intensity models in the images are used to automatically segment the structures. This method of shape analysis was recently validated and shown to be consistent over a variety of magnetic field strengths and acquisition systems (Goodro et al., 2012).

Correlations between shape alternations and PCS scores were assessed on a per-vertex basis. FIRST generates a surface mesh for each structure in each subject with a deformable mesh model. The vertex number and its correspondence are fixed so that corresponding vertices can be compared across subjects in standard MNI space, using a multivariate GLM with Pillai's trace as the test statistic. Regional changes in the vertices across all subjects were examined with F-statistics using PCS scores as a continual regressor and gender as a covariate (Patenaude et al., 2011). The results were corrected for multiple comparisons using the false discovery rate method (FDR, $p < 0.05$) (Benjamini and Hochberg, 1995). The statistic was rendered on the shape surface, providing a map of the regions where the structure changed significantly with the changing of PCS scores.

The subcortical surfaces generated for each subject are transformed back to the original space and boundary correction before the volume of each structure is measured in cubic millimetres (mm3). For each subcortical structure, a linear regression model was designed, in which the PCS scores were included as the dependent variables and the volume of each structure as independent variables in SPSS v. 20 (SPSS Inc, Chicago, USA), with the Bonferroni correction of $p < 0.05$.

Chapter Four

Results

4.1. Experiment 1: Effects of pain catastrophising on the classification of ambiguous pain

Hypothesis:

High-, compared to low, pain catastrophisers will identify pain scenes in scrambled pictures at a higher scrambling level (i.e., high level of background noise).

4.1.1. Demographic characteristics

Age and scores (mean ± SD) of the Pain Catastrophizing Scales, Fear of Pain Questionnaire – III, and State-Trait Anxiety Inventory in high and low pain catastrophising groups are shown in Table 4.1. Pain catastrophising scores showed statistically significant differences between subjects with high and low pain catastrophising traits, before ($t(83) = 23.6$, $P < 0.0001$) and after ($t(83) = 21.6$, $P < 0.0001$) the experiment. Paired t-tests illustrated that there was no significant difference within groups between the PCS scores before and after the experiment ($t(84) = -1.6$, $P > 0.05$), suggesting the recruited participants were fit to their pain catastrophising traits. The High-Cat group compared to the Low-Cat group scored significantly higher in FPQ-III ($t(83) = 4.6$, $P < 0.0001$). No further significant group differences were found in STAI.

4.1.2. Picture ratings

Table 4.2 shows the mean values of valence, arousal and complexity for the three types of pictures in High-Cat and Low-Cat groups. A significant main effect of

picture type appeared differently in terms of valence ($F(2,166) = 695.0$, $P < 0.0001$), arousal ($F(2,166) = 420.6$, $P < 0.0001$), and complexity ($F(2,166) = 195.7$, $P < 0.0001$) which was due to the fact that, Negative pictures compared to Pain and Neutral pictures were considered as the most negatively affective, the strongest arousal, and the most complex to recognise. In addition, high pain catastrophisers attributed stronger negative emotion ($F(1,83) = 7.8$, $P = 0.007$) and arousal ($F(1,83) = 6.4$, $P = 0.013$) to all three picture types, relative to low pain catastrophisers. There were also significant interactions between pain catastrophising and picture type for valence ($F(2,166) = 5.5$, $P = 0.005$) and arousal ($F(2,166) = 6.2$, $P = 0.007$). Pairwise comparisons revealed that High-Cat subjects reported statistically significant stronger negative affect ($F(1,83) = 10.4$, $P = 0.002$) and arousal ($F(1,83) = 10.1$, $P = 0.002$) to Pain pictures, compared with Low-Cat participants, but not to Negative and Neutral pictures ($P > 0.05$). No further significant main effect of pain catastrophising, or interaction, were found for complexity ($P > 0.05$).

Table 4.1 Participant characteristics during the observation of scrambled pictures. Values are mean ± standard deviation (SD).

	High pain catastrophisers	Low pain catastrophisers
Age	20.0 ± 2.3	21.3 ± 3.1
Pain Catastrophizing Scale (Before)	31.0 ± 5.3	8.1 ± 3.5
Pain Catastrophizing Scale (After)	31.8 ± 6.2	8.8 ± 3.2
Fear of Pain Questionnaire-III	94.1 ± 14.2	78.4 ± 17.4
State-Trait Anxiety Inventory (State)	44.5 ± 5.4	44.7 ± 4.2
State-Trait Anxiety Inventory (Trait)	46.1 ± 5.4	45.4 ± 4.3

Table 4.2 Subjective ratings of valence, arousal and complexity for observed pictures. Mean ± standard errors of picture valence, arousal and complexity attributed to Negative, Neutral and Pain pictures in high and low pain catastrophising groups.

	High pain catastrophisers			Low pain catastrophisers		
	Negative	Neutral	Pain	Negative	Neutral	Pain
Valence	6.7 ± 0.2	1.0 ± 0.0	5.4 ± 0.2	6.3 ± 0.2	1.0 ± 0.0	4.4 ±0.2
Arousal	6.1 ± 0.2	1.0 ± 0.0	4.5 ± 0.2	5.7 ± 0.2	1.0 ± 0.0	3.4 ± 0.2
Complexity	4.4 ± 0.3	1.3 ± 0.1	2.5 ± 0.2	4.6 ± 0.3	1.6 ± 0.1	2.7 ± 0.2

4.1.3. Error rate

Error rate was defined as the percentage of incorrect responses. Incorrect responses were considered as the target stimulus being reported as one of the other two categories. For example, if a subject reported a Negative picture (Target stimulus) as belonging to the Pain category, it was defined as an incorrect response. The mean percentages of total error rate were 4.2 ± 4.7 (%, mean ± SD) in High-Cat and 3.6 ± 3.6 (%) in Low-Cat groups ($t(83) = 0.7$, $P > 0.05$). A 2 × 3 ANOVA for repeated measures demonstrated that Negative pictures had the highest error rates in comparison with Neutral and Pain pictures ($F(2,166) = 26.8$, $P < 0.0001$). No significant group differences and interactions between pain catastrophising and picture type were found ($P > 0.05$). Table 4.3 shows mean values of the error rate for these three picture types in high and low pain catastrophising groups.

Table 4.3 Error rates of observed pictures. Mean ± standard errors of the error rate (%) for Negative, Neutral, and Pain pictures in high and low pain catastrophisers

Target	Negative		Neutral		Pain	
Response	Neutral	Pain	Negative	Pain	Negative	Neutral
High-Cat	0.1 ± 0.0	3.2 ± 0.6	0.1 ± 0.1	0.2 ± 0.1	0.1 ± 0.1	0.1 ± 0.2
Low-Cat	0.1 ± 0.0	2.1 ± 0.5	0.3 ± 0.1	0.2 ± 0.1	0.3 ± 0.1	0.1 ± 0.2

Notes: High-Cat = high pain catastrophisers, Low-Cat = low pain catastrophisers.

4.1.4. Target detection

Of particular interest was whether the high, compared to the low, pain catastrophising group would detect pictures with pain content at a higher scrambling level and with stronger confidence. Fig. 4.1 shows the detection threshold and confidence ratings for high and low pain catastrophisers for Negative, Neutral, and Pain pictures. A 2 × 3 ANOVA for repeated measures revealed a statistically significant main effect of picture types with a large effect size ($F(2,166) = 68.9$, $P < 0.0001$, $\eta_p^2 = 0.45$). Paired-sample t-tests showed that Pain pictures were detected at a higher level of detection threshold compared to Negative pictures ($t(84) = 8.0$, $P < 0.0001$), but at a lower level of detection threshold relative to Neutral pictures ($t(84) = -2.8$, $P = 0.007$). The main effect of pain catastrophising was statistically non-significant ($F(1,83) = 1.5$, $P = 0.225$, $\eta_p^2 = 0.018$), although mean thresholds indicated that High-Cat subjects (44.5% ± 1.3%) detected all pictures at a higher scrambling percentage than Low-Cat subjects (42.3% ± 1.2%). There was no statistically significant interaction of pain catastrophising group by picture type ($F(2,166) = 1.8$, $P = 0.176$, $\eta_p^2 = 0.021$).

As far as decision confidence is concerned, a statistically significant main effect of picture types ($F(2,166) = 17.5$, $P < 0.0001$, $\eta_p^2 = 0.174$) was found. Subjects

had less confidence in their decision when detecting Negative compared to Pain ($t(84) = -3.3$, $P = 0.001$) or Neutral ($t(84) = -5.3$, $P < 0.0001$) pictures. However, neither the main effect of group ($F(1,83) = 2.0$, $P = 0.162$, $\eta_p^2 = 0.02$) nor the interaction between group and picture types ($F(2,166) = 0.3$, $P = 0.759$, $\eta_p^2 = 0.003$) was statistically significant.

In addition, Student's independent t-test confirmed that subjects with high pain catastrophising (5.0 ± 0.9, mean $\pm$ SD) attributed significantly stronger pain to Pain pictures ($t(83) = 2.4$, $P = 0.02$) during detecting the scrambled pictures, compared to low pain catastrophising group (4.4 ± 1.3). A 2×2 repeated measures ANOVA of valence with the two groups and two picture types (Negative vs. Neutral pictures) showed a significant effect of picture type ($F(1,83) = 848.7$, $P < 0.0001$, $\eta_p^2 = 0.911$). Results indicated Negative, relative to Neutral pictures, were considered as more negatively affective while subjects were detecting the scrambled pictures. No further significant group main effect or interaction was found ($P > 0.05$).

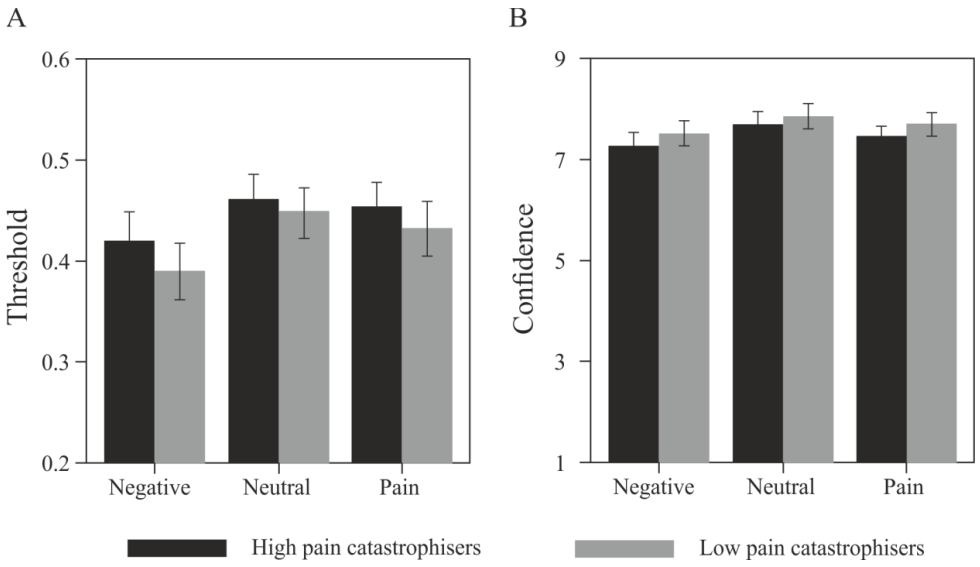

Fig. 4.1 Detection threshold and confidence for the scrambled pictures. Detection threshold and confidence ratings on Negative, Neutral, and Pain pictures, are shown separately for high and low pain catastrophisers. A. Detection threshold. B. Confidence ratings. Error bars: 95% confidence intervals.

4.2. Experiment 2: Effects of pain catastrophising on attention to pain in others: an eye movement study

Hypothesis:

High-, compared to low, pain catastrophisers will attribute stronger pain to pain scenes, will allocate attention more quickly, and dwell on visual pain stimuli longer.

4.2.1. Participant characteristics

Age and scores of the Pain Catastrophizing Scales, Fear of Pain Questionnaire-III, State-Trait Anxiety Inventory and Interpersonal Reactivity Index and its subscales are shown in Table 4.4. A significant difference in pain catastrophising scores between High-Cat and Low-Cat groups was shown ($t(26) = 13.5$, $p < 0.0001$). The pain catastrophising scores in both groups were comparable with previous studies involving grouping of subjects into high- and low pain catastrophising groups based on Pain Catastrophizing Scales (Sullivan et al., 1995, Sullivan and Neish, 1999, Crombez et al., 2004, Van Damme et al., 2004). The High-Cat group, compared with the Low-Cat group, scored significantly higher in FPQ-III ($t(26) = 2.6$, $p = 0.017$) and STAI Y-1 (right now feeling) ($t(26) = 2.5$, $p = 0.018$), but not in STAI Y-2 (general feeling), IRI and its subscales ($p > 0.05$). A positive significant correlation between Fear of Pain and STAI Y-1 was found ($r(28) = 0.467$, $p = 0.012$). These results suggest that High-Cat subjects displayed stronger characteristics of pain catastrophising (i.e. fear of pain and emotional distress), relative to Low-Cat subjects.

Table 4.5 shows the mean values and standard error of affective valence, arousal and pain for both types of photographs in High-Cat and Low-Cat groups. The 2 × 3 ANOVAs for repeated measures revealed that the two types of pictures were perceived differently in term of valence ($F(1,26) = 246.6$, $p < 0.0001$), arousal ($F(1,26) = 94.9$, $P < 0.0001$), and pain ($F(1,26) = 403.8$, $p < 0.0001$). Subjects considered Pain, compared to Non-Pain, pictures as more negative affective, eliciting stronger arousal, and containing greater pain. A main effect of group was found in valence ($F(1,26) = 9.1$, $p = 0.006$) and pain ($F(1,26) = 7.9$, $p = 0.009$). The effect was due to stronger negative emotion and stronger pain attributed by High-Cat people to both types of pictures compared to Low-Cat group. There were also significant group × picture type interactions for valence ($F(1,26) = 4.2$, $p = 0.05$) and pain ($F(1,26) = 7.6$, $p = 0.011$). Pairwise comparisons implicated that high pain catastrophisers, relative to low pain catastrophisers, reported statistically significant stronger negative emotion to both Pain ($F(1,26) = 7.8$, $p = 0.01$) and Non-Pain pictures ($F(1,26) = 5.6$, $p = 0.025$). High pain catastrophisers reported much more pain to Pain pictures ($F(1,26) = 8.1$, $p = 0.008$), relative to low pain catastrophisers, but not Non-Pain pictures ($p > 0.05$).

Table 4.4 Participant characteristics in the eye movement study. Mean ± standard deviation of participant characteristics in all and both high- and low pain catastrophisers.

	All	High-Cat	Low-Cat
Age	18.9 ± 2.0	19.3 ± 2.8	18.6 ± 0.7
PCS	18.5 ± 12.0	30.3 ± 4.0	8.2 ± 4.6
Fear of Pain	80.2 ± 20.0	89.7 ± 18.5	72.0 ± 17.9
STAI Y-1	44.8 ± 5.2	47.2 ± 5.0	42.7 ± 5.7
STAI Y-2	45.4 ± 6.9	45.1 ± 8.2	45.6 ± 5.7
IRI	68.8 ± 13.1	70.3 ± 17.2	67.5 ± 8.5
Perspective Taking	17.1 ± 4.9	16.3 ± 5.5	17.7 ± 4.4
Fantasy	16.8 ± 6.1	18.7 ± 4.5	15.1 ± 6.9
Empathic Concern	20.3 ± 4.4	18.9 ± 5.8	21.4 ± 2.3
Personal Distress	14.6 ± 6.0	16.4 ± 6.0	13.1 ± 5.6

Note: PCS = Pain Catastrophizing Scale, STAI Y-1 = State-Trait Anxiety Inventory (right now feeling), STAI Y-2 = State-Trait Anxiety Inventory (general feeling), IRI = Interpersonal Reactivity Index, High-Cat = high pain catastrophisers, Low-Cat = low pain catastrophisers.

Table 4.5 Subjective ratings to the observed pictures in the eye movement study. Mean ± standard error of valence, arousal and pain attributed to visual scenes implying or not implying pain in groups of high- and low pain catastrophisers.

	High pain catastrophisers		Low pain catastrophisers	
	Pain scenes	Non-pain Scenes	Pain scenes	Non-pain Scenes
Valence	5.8 ± 0.4	1.8 ± 0.2	4.3 ± 0.3	1.3 ± 0.1
Arousal	5.0 ± 0.5	1.7 ± 0.1	4.0 ± 0.5	1.3 ± 0.1
Pain	6.1 ± 0.4	1.4 ± 0.1	4.7 ± 0.3	1.2 ± 0.1

4.2.2. Direction of initial fixation

Eye movement (EM) direction bias scores were obtained for each participant by calculating the number of trials when first gaze was directed at the Pain picture as a percentage of total trials in which a fixation was made on either the Pain or Non-

Pain picture. Scores greater than 50% reflect a bias in initial orienting towards Pain pictures, relative to Non-Pain pictures (50% indicates no bias). High and low pain catastrophisers directed their first fixations at Pain pictures on 49.3% (SD = 3.8) and 50.3% (SD = 5.9) trials, respectively, and there was no significant different between groups ($t(24) = -0.5$, $p > 0.05$). To examine whether participants preferentially oriented their first fixation towards Pain, rather than Non-Pain, pictures, their bias scores were compared with 50%. The percentage of first fixation directed at Pain pictures was not statistically significant in High-Cat ($t(10) = -0.6$, $p > 0.05$) and Low-Cat ($t(14) = 0.2$, $p > 0.05$) groups. Results indicate that groups directed their attention towards Pain or Non-Pain pictures without differences.

4.2.3. First fixation latency

The mean first fixation latency of Pain and Non-Pain pictures is shown in Fig. 4.2A and Table 4.6. A repeated measures ANOVA with group (High- vs. Low-Cat participants) as a between-subject variable and picture type (Pain vs. Non-Pain) as a within-subject variable reported that neither main effects of group ($F(1,26) = 0.029$, $p > 0.05$, $\eta_p^2 = 0.001$) and picture type ($F(1,26) = 1.02$, $p > 0.05$, $\eta_p^2 = 0.038$), nor group × picture type interaction ($F(1,26) = 0.899$, $p > 0.05$, $\eta_p^2 = 0.033$) were of significance. Bias in first fixation latencies for Pain and Non-Pain picture pairs was evaluated by subtracting the first fixation latency of the Non-Pain picture from the first fixation latency of the Pain picture in each trial. An independent-samples t-test revealed that high pain catastrophisers did not differ with the low pain catastrophising group in the bias of their initial fixation latency towards Pain pictures ($t(26) = -1.0$, $p > 0.05$).

Table 4.6 Eye movement data in the eye movement study. Mean ± standard error of eye movement data (in milliseconds) in high and low pain catastrophisers for Pain and Non-Pain pictures.

		High-Cat	Low-Cat
First fixation latency (ms)			
	Pain	539.0 ± 39.6	540.5 ± 34.4
	Non-Pain	560.0 ± 43.1	541.2 ± 30.7
First fixation duration (ms)			
	Pain	283.7 ± 31.5	271.5 ± 20.7
	Non-Pain	257.7 ± 20.8	248.7 ± 16.2
Average fixation duration (ms)			
	Pain	715.6 ± 82.5	691.5 ± 73.8
	Non-Pain	492.4 ± 50.0	490.8 ± 49.8

4.2.4. First fixation duration

Initial fixation duration bias scores for Pain vs. Non-Pain picture pair was obtained by subtracting the first fixation duration of each Non-Pain picture from the fixation duration of the corresponding Pain picture in each trial. Pain catastrophising group differences in first fixation duration towards Pain pictures ($t(26) = 0.2$, $p > 0.05$) were not significant. The ANOVAs of first fixation duration showed a statistically significant main effect of picture type ($F(1,26) = 7.5$, $p = 0.011$, $\eta_p^2 = 0.225$), indicating that subjects spent more time of their initial gaze on Pain, compared to Non-Pain, pictures (Fig. 5.2B, Table 5.6). No further group main effect ($F(1,26) = 0.12$, $p > 0.05$, $\eta_p^2 = 0.005$) or interaction ($F(1,26) = 0.031$, $p > 0.05$, $\eta_p^2 = 0.001$) was found.

4.2.5. Average fixation duration

Average fixation duration bias scores were calculating by subtracting the gaze duration of Non-Pain picture from the gaze duration of Pain picture per trial. The comparison between groups did not yeild the significance ($t(26) = 0.3$, $p > 0.05$). The ANOVA for repeated measures found that Pain, compared to Non-Pain, pictures obtained significantly more attention over the course of each trial ($F(1,26) = 39.1$, $p < 0.0001$, $\eta_p^2 = 0.601$) (Fig. 4.2C, Table 4.6). Pain catastrophising group differences in gaze duration were not significant ($F(1,26) = 0.022$, $p > 0.05$, $\eta_p^2 = 0.001$), nor was the group × picture type interaction ($F(1,26) = 0.1$, $p > 0.05$, $\eta_p^2 = 0.004$).

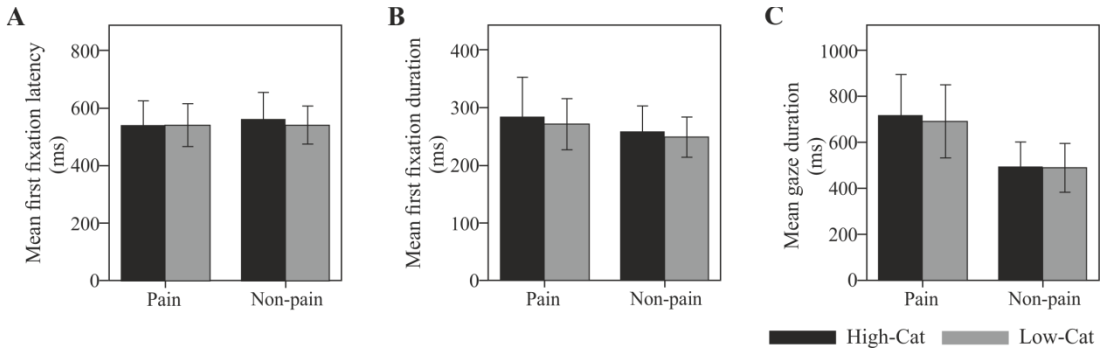

Fig. 4.2 Fixation time (in milliseconds) to Pain and Non-Pain pictures. Mean first fixation latency (A), mean first fixation duration (B), and mean gaze duration (C) on Pain and Non-Pain pictures for high and low pain catastrophisers. Pain = Pain pictures, Non-pain = Non-Pain pictures. High-Cat = high pain catastrophisers, dark rectangle bars. Low-Cat = low pain catastrophisers, grey rectangle bars. Error bars: 95% confidence intervals.

4.2.6. Correlations between EM data and subjective ratings

Pearson's correlations were performed between EM data (i.e. first fixation latency, first fixation duration, and gaze duration) and subjective ratings of valence, arousal and pain in High-Cat and Low-Cat groups for Pain and Non-Pain pictures. In order to reduce the risk of type one error in multiple correlations, Bonferroni's adjustments of P values were applied. A 95% confidence level was employed throughout. Two statistically significant corrections were found. First fixation

latencies of Pain pictures were significantly positively correlated with arousal (r(13) = 0.6, p = 0.017) in people with high pain catastrophising. In addition, a statistically significant negative correlation between gaze duration of Non-Pain pictures and the corresponding subjective pain ratings was found in High-Cat group (r(13) = -0.6, p = 0.026). Fig. 4.3 illustrates the scatter plots and linear regression lines for the valence, arousal and pain ratings and first fixation latency for Pain pictures and gaze duration for Non-Pain pictures in High-Cat and Low-Cat groups, respectively. Results indicate that high pain catastrophisers initially engaged with Pain pictures later if considered as stronger subjective arousal, and maintained attention on Non-Pain pictures when considered as containing less pain.

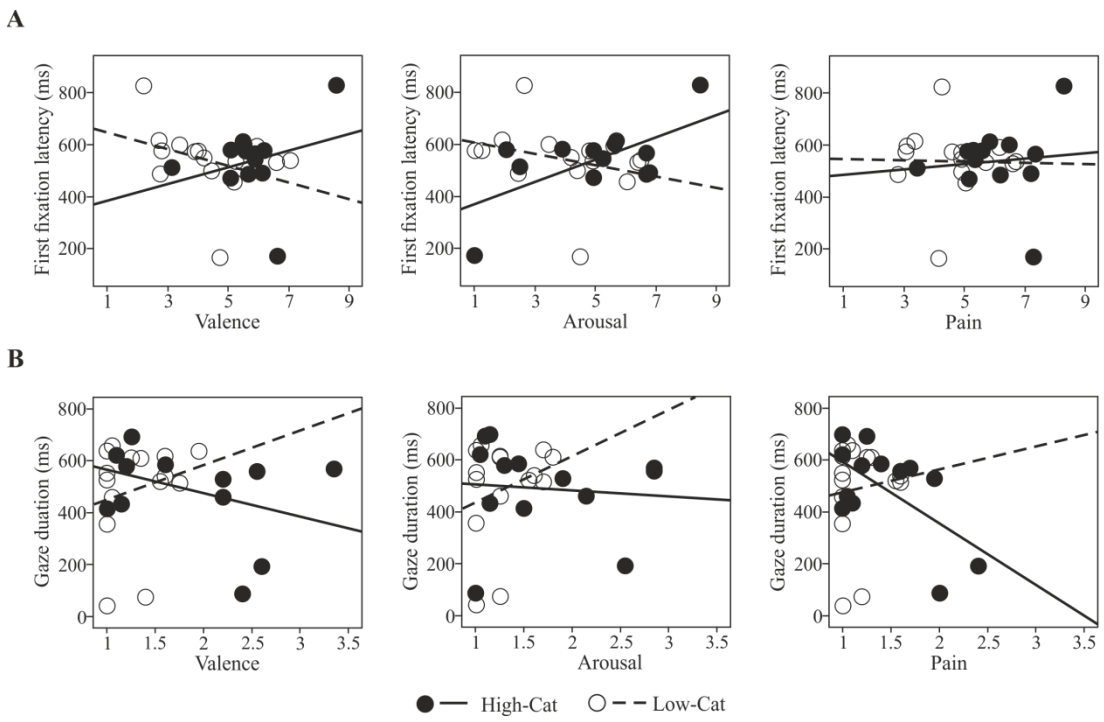

Fig. 4.3 Correlations between fixation time of pictures and subjective ratings. Scatter plots and the linear regression lines illustrating the associations between subjective ratings of valence, arousal, and pain during viewing Pain (A) and Non-Pain (B) pictures, and the corresponding fixation time (in milliseconds) between high and low pain catastrophisers. A. Relationships between first fixation latency to Pain pictures and subjective ratings. B. Correlations between gaze duration to Non-Pain pictures and subjective ratings. High-Cat = high pain catastrophisers, dark circles, solid lines. Low-Cat = low pain catastrophisers, white circles, dashed lines.

4.2.7. Reaction time (RT) to probes

Mean and standard deviation (mean ± SD) of RTs to probes replacing Pain and Non-Pain pictures were 1401 ± 321 ms and 1458 ± 297 ms in the High-Cat group, and 1393 ± 367 ms and 1386 ± 352 ms in the Low-Cat group. A 2 × 2 repeated measures ANOVA with group and RT to probe (Pain vs. Non-Pain pictures) did not show any significant main effects (picture type: $F(1,26) = 0.671$, $p > 0.05$, $\eta_p^2 = 0.025$; group: $F(1,26) = 0.107$, $p > 0.05$, $\eta_p^2 = 0.004$) or interaction effect ($F(1,26) = 1.07$, $p > 0.05$, $\eta_p^2 = 0.04$). Results suggest that subjects did not perform differently when detecting Pain and Non-Pain pictures.

To evaluate the degree of correct discrimination between Pain and Non-Pain pictures, a two-way ANOVA for repeated measures with groups and correct responses to the pictures was employed. No significant main effects or interactions were found ($p > 0.05$), indicating subjects were capable to respond correctly to Pain and Non-Pain pictures behaviourally, and both groups performed similarly in discrimination of both picture types.

4.3. Experiment 3: Effects of pain catastrophising on attention to pain in others: a second eye movement study

Hypothesis:

High-, compared to low, pain catastrophisers will show attentional bias towards pain scenes and not towards negative emotional stimuli.

4.3.1. Participant characteristics

Table 4.7 summarises subjects' characteristics, including age and scores (mean ± SD) of the Pain Catastrophizing Scales, Fear of Pain Questionnaire – III, State-Trait Anxiety Inventory, and Interpersonal Reactivity Index and its subscales. Statistically significant pain catastrophising group differences were found in PCS ($t(30) = 14.9$, $p < 0.001$), FPQ-III ($t(30) = 3.6$, $p = 0.001$), IRI ($t(30) = 2.4$, $p = 0.023$), and Fantasy scale ($t(30) = 2.1$, $p = 0.05$). Results implicate that high pain catastrophisers displayed stronger characteristics of pain catastrophising, such as fear of pain and dispositional empathy, compared with low pain catastrophisers. No further significant group differences were observed in STAI.

Table 4.8 shows the mean values and standard error of affective valence, arousal and pain for Negative, Pain, and Non-Pain pictures in the groups with high and low pain catastrophising traits. A significant main effect of picture type showed differently in terms of valence and arousal which was due to the fact that, Negative pictures compared to Pain and Non-Pain pictures were considered as the most negative affective ($F(2,60) = 211.4$, $p < 0.0001$) and the strongest arousal ($F(2,60) = 176.0$, $p < 0.0001$). In addition, High-Cat, compared with Low-Cat, groups attributed greater negative emotion ($F(1,30) = 5.3$, $p = 0.028$) to all three types of pictures. The

interaction of group by picture type for valence ($F(2,60) = 2.0$, $p = 0.145$) was not significant. However, pairwise comparisons revealed that high, relative to low, pain catastrophisers reported statistically significant stronger negative emotion to Pain pictures ($F(1,30) = 6.6$, $p = 0.016$), but not the other two types of pictures ($p > 0.05$). Subjects with high, compared with low, pain catastrophising scored Pain and Non-Pain pictures containing more pain with marginal significance ($F(1,30) = 3.6$, $p = 0.068$). A significant main effect of picture type (Pain vs. Non-Pain) was also found indicating that subjects attributed more pain to Pain than Non-Pain pictures ($F(1,30) = 401.6$, $p < 0.0001$). The interaction between group and picture type (Pain vs. Non-Pain) was not significant ($F(1,30) = 0.7$, $p > 0.05$).

Table 4.7 Participant characteristics in the second eye movement study. Mean ± standard deviation of participant characteristics in all and both high- and low pain catastrophisers.

	High pain catastrophisers (N = 17)	Low pain catastrophisers (N = 15)
Age	19.9 ± 2.8	22.3 ± 3.8
PCS	32.3 ± 5.1	9.0 ± 3.8
Fear of Pain	93.5 ± 16.9	69.9 ± 20.2
STAI Y-1	44.1 ± 6.8	44.5 ± 4.0
STAI Y-2	46.6 ± 4.6	44.9 ± 3.2
IRI	69.7 ± 8.1	60.6 ± 12.4
Perspective Taking	17.1 ± 3.6	15.9 ± 5.2
Fantasy	19.9 ± 4.5	15.7 ± 6.7
Empathic Concern	19.6 ± 3.0	17.6 ± 3.0
Personal Distress	13.2 ± 4.6	11.4 ± 4.2

Note: PCS = Pain Catastrophizing Scale, STAI Y-1 = State-Trait Anxiety Inventory (right now feeling), STAI Y-2 = State-Trait Anxiety Inventory (general feeling), IRI = Interpersonal Reactivity Index, High-Cat = high pain catastrophisers, Low-Cat = low pain catastrophisers.

Table 4.8 Subjective ratings to observed pictures in the second eye movement study. Mean ± standard error of valence, arousal and pain attributed to Negative, Pain, and Non-Pain pictures in groups of high- and low pain catastrophisers.

	High pain catastrophisers			Low pain catastrophisers		
	Negative	Pain	Non-Pain	Negative	Pain	Non-Pain
Valence	6.0 ± 0.3	5.1 ± 0.2	1.5 ± 0.2	5.6 ± 0.3	4.0 ± 0.4	1.3 ± 0.1
Arousal	5.7 ± 0.3	4.8 ± 0.2	1.6 ± 0.1	5.4 ± 0.3	4.0 ± 0.4	1.3 ± 0.1
Pain	_	5.1 ± 0.2	1.4 ± 0.1	_	4.6 ± 0.3	1.2 ± 0.1

4.3.2. EM bias in attentional orientation

Eye movement (EM) direction bias scores were obtained for each subject by calculating the number of trials when first gaze was directed at the target picture as a percentage of total trials in which a fixation was made on the paired-match picture. Target pictures were Pain pictures in Pain– Non-Pain pair, Negative pictures in Negative– Non-Pain pair, and Pain pictures in Pain– Negative pair. The ANOVAs reported null effects of group ($F(1,30) = 0.5$, $p > 0.05$), picture pair ($F(2,60) = 1.1$, $p > 0.05$), and group × picture pair ($F(2,60) = 0.1$, $p > 0.05$). On average, the proportions of first fixations to Pain (High-Cat: 49.7% ± 5.7%, M ± SD, Low-Cat: 49.5% ± 4.1%) and Negative (High-Cat: 51.6% ± 7.6%, Low-Cat: 51.1% ± 10.9%) pictures that were paired with Non-Pain pictures were not significantly larger than 50% that reflects a bias in initial orienting towards Pain pictures in high (Pain: $t(15) = -0.2$, $p > 0.05$, Negative: $t(14) = 0.8$, $p > 0.05$) and low (Pain: $t(14) = -0.4$, $p > 0.05$, Negative: $t(14) = 0.4$, $p > 0.05$) pain catastrophisers. Thus, subjects with high and low pain catastrophising scores did not show preferential patterns of first fixation orientation on Pain, Non-Pain, and Negative pictures.

Bias in initial gaze latencies for three picture pairs were evaluated by subtracting the first fixation latency of the control picture from the first fixation latency of the target picture in each trial. Neither significant main effects of group ($F(1,30) = 0.3$, $p > 0.05$, $\eta_p^2 = 0.009$) or picture pair ($F(2,60) = 0.7$, $p > 0.05$, $\eta_p^2 = 0.01$), nor interaction of group by picture pair ($F(2,60) = 0.2$, $p > 0.05$, $\eta_p^2 = 0.006$) emerged (Fig. 4.4A, Table 4.9). Repeated measures ANOVAs for each picture pair were also performed. Only Pain– Non-Pain pair showed a significant main effect of picture type ($F(1,30) = 5.2$, $p = 0.029$, $\eta_p^2 = 0.148$), suggesting that subjects showed shorter initial fixation latencies toward Non-Pain pictures than those of Pain pictures. No further main effects or interactions were found ($p > 0.05$).

4.3.3. EM bias in attentional maintenance

First fixation duration bias scores for three picture pairs were obtained by subtracting the first fixation duration of the paired-match picture from the first fixation duration of the target picture in each trial. The repeated measures ANOVAs did not yeild any significant main effects of group ($F(1,30) = 0.1$, $p > 0.05$, $\eta_p^2 = 0.003$) or picture pair ($F(2,60) = 2.5$, $p > 0.05$, $\eta_p^2 = 0.078$), or group × picture pair interaction ($F(2,60) = 0.7$, $p > 0.05$, $\eta_p^2 = 0.025$) (Fig. 4.4B, Table 4.9).

Average fixation duration bias scores were calculated by subtracting the gaze duration of control picture from the gaze duration of target picture per trial. Null effects of group ($F(1,30) = 0.006$, $p > 0.05$, $\eta_p^2 < 0.0001$), picture pair ($F(2,60) = 0.9$, $p > 0.05$, $\eta_p^2 = 0.028$), and interaction by group × picture pair ($F(2,60) = 0.1$, $p > 0.05$, $\eta_p^2 = 0.003$) were found (Fig. 4.4C, Table 4.9). Another repeated measures ANOVA with a between-subject variable (group) and two with-subject variables (bias scores for Pain– Non-Pain pair vs. Negative– Non-Pain pair) was performed.

Although neither the main effect for pain catastrophising ($F(1,30) < 0.0001$, $p > 0.05$, $\eta_p^2 < 0.0001$), nor interaction ($F(1,30) = 0.6$, $p > 0.05$, $\eta_p^2 = 0.019$) was significant, a main effect emerged for picture pair ($F(1,30) = 5.5$, $p = 0.026$, $\eta_p^2 = 0.155$). ANOVAs for these two picture pairs revealed that the significant main effect of picture type emerged in the Pain– Non-Pain pair ($F(1,30) = 15.0$, $p = 0.001$, $\eta_p^2 = 0.333$), but not the Negative– Non-Pain pair ($F(1,30) = 0.1$, $p > 0.05$, $\eta_p^2 = 0.002$). Interestingly, according to the figure, longer gaze durations for Pain pictures and shorter gaze durations for Negative pictures when competing with Non-Pain pictures were observed in High-Cat subjects. No further significant effects were found ($p > 0.05$). Results indicated that participants spent significantly longer time gazing at Pain pictures than Negative pictures.

4.3.4. EM bias in attentional re-engagement

The index of fixation frequencies was employed to evaluate the pattern of disengagement from particular stimulus types followed by re-engagement toward these stimuli. Fixation frequency bias score was calculated by subtracting the total number of gazes on each paired match picture from the corresponding target picture in each trial. Neither differences of pain catastrophising groups or picture types, nor interaction were significant. However, ANOVAs for repeated measures showed significant main effects of picture type in Pain– Non-Pain ($F(2,60) = 6.6$, $p = 0.016$) and Negative– Non-Pain ($F(2,60) = 7.6$, $p = 0.01$) picture pairs. Results suggest participants made more frequent fixations on Pain and Negative pictures than Non-Pain pictures.

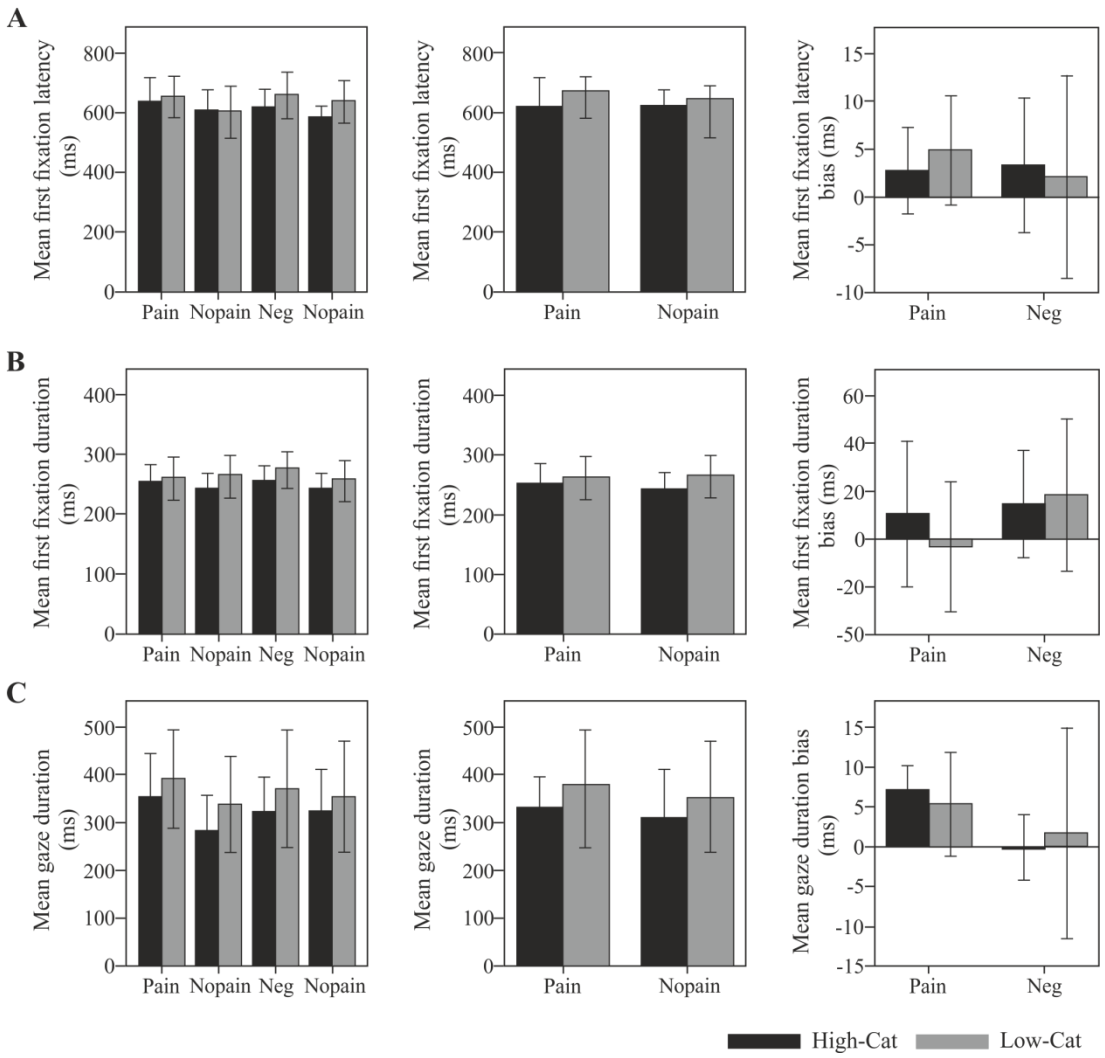

Fig. 4.4 Fixation time (in milliseconds) to Pain and Negative pictures paired with Non-Pain pictures in high and low pain catastrophising groups.

(1) The first column shows fixation time for Pain– Non-Pain and Negative– Non-Pain picture pairs in both groups. First four rectangle bars represent the fixation time to Pain and Non-Pain pictures, while, the rest four represent those of Negative and Non-Pain pictures, respectively. (2) The second column illustrates fixation time for Pain– Non-Pain pair in two groups, respectively. (3) The last column indicates fixation bias scores toward Pain and Negative pictures for high and low pain catastrophisers. Fixation bias scores were calculated by subtracting fixation time for Non-Pain pictures from fixation time for Pain or Negative pictures in each trial. A. First fixation latency. B. First fixation duration. C. Gaze duration. Pain = Pain pictures, Nopain = Non-Pain pictures, Neg = Negative pictures. High-Cat = high pain catastrophisers, dark rectangle bars. Low-Cat = low pain catastrophisers, grey rectangle bars. Error bars: 95% confidence intervals.

Table 4.9 Eye movement data in the second eye movement study. Mean ± standard error of eye movement data in high and low pain catastrophisers for Pain, Non-Pain, and Negative pictures.

		High-Cat	Low-Cat
First fixation latency (ms)			
Pain– Non-Pain	Pain	637.1 ± 39.9	654.8 ± 32.7
	Non-Pain	609.3 ± 32.2	605.7 ± 40.4
Negative– Non-Pain	Negative	619.9 ± 28.8	661.0 ± 36.0
	Non-Pain	586.5 ± 18.5	639.7 ± 32.8
Pain– Negative	Pain	621.6 ± 30.5	673.2 ± 35.2
	Negative	624.0 ± 34.7	647.3 ± 31.0
First fixation duration (ms)			
Pain– Non-Pain	Pain	254.0 ± 15.8	263.0 ± 16.8
	Non-Pain	243.4 ± 13.7	266.2 ± 16.6
Negative– Non-Pain	Negative	257.5 ± 12.7	277.5 ± 14.2
	Non-Pain	242.8 ± 14.0	259.2 ± 16.0
Pain– Negative	Pain	245.1 ± 12.7	273.8 ± 20.3
	Negative	268.4 ± 12.9	277.7 ± 17.1
Average fixation duration (ms)			
Pain– Non-Pain	Pain	354.4 ± 43.3	391.3 ± 48.3
	Non-Pain	283.1 ± 35.2	338.0 ± 47.1
Negative– Non-Pain	Negative	322.6 ± 34.4	371.0 ± 57.4
	Non-Pain	323.8 ± 41.3	354.5 ± 54.1
Pain– Negative	Pain	333.1 ± 45.0	380.3 ± 52.5
	Negative	311.9 ± 36.4	353.8 ± 54.5
Total fixation counts (N)			
Pain– Non-Pain	Pain	11.4 ± 0.5	11.0 ± 0.3
	Non-Pain	10.8 ± 0.4	10.6 ± 0.5
Negative– Non-Pain	Negative	11.2 ± 0.5	11.5 ± 0.5
	Non-Pain	10.6 ± 0.6	10.6 ± 0.3
Pain– Negative	Pain	11.1 ± 0.6	10.9 ± 0.4
	Negative	11.1 ± 0.6	10.6 ± 0.4

4.3.5. Correlations between EM data and subjective ratings

Pearson's correlations between EM data (i.e. first fixation latency, first fixation duration, and fixation duration) and subjective ratings of valence and arousal for three picture types, and pain for Pain and Non-Pain pictures in groups of high and low pain catastrophising were carried out. Three statistically significant correlations were found. For Negative– Non-Pain pair, first fixation latencies of Non-Pain pictures significantly negatively correlated with subjective ratings of valence ($r(15) = -0.6$, $p = 0.02$), arousal ($r(15) = -0.7$, $p = 0.006$), and pain ($r(15) = -0.6$, $p = 0.02$) in the Low-Cat group only. In addition, the correlations between initial gaze duration of Pain pictures and valence were statistically significant for Pain– Non-Pain ($r(17) = -0.6$, $p = 0.011$) and Pain– Negative ($r(17) = -0.5$, $p = 0.033$) pairs in high pain catastrophisers. Fig. 4.5 demonstrates the scatter plots and linear regression lines for the valence, arousal and pain ratings and first fixation latency in Negative– Non-Pain pair, first fixation duration in Pain– Non-Pain and Pain– Negative pairs for groups of high and low pain catastrophising, respectively. Results implicate that greater negative emotion, stronger arousal, and more subjective pain to Non-Pain pictures for Negative– Non-Pain pair was related to faster initial attention in the Low-Cat group, and High-Cat subjects spent less time initially gazing at Pain pictures if considered as containing greater negative affect.

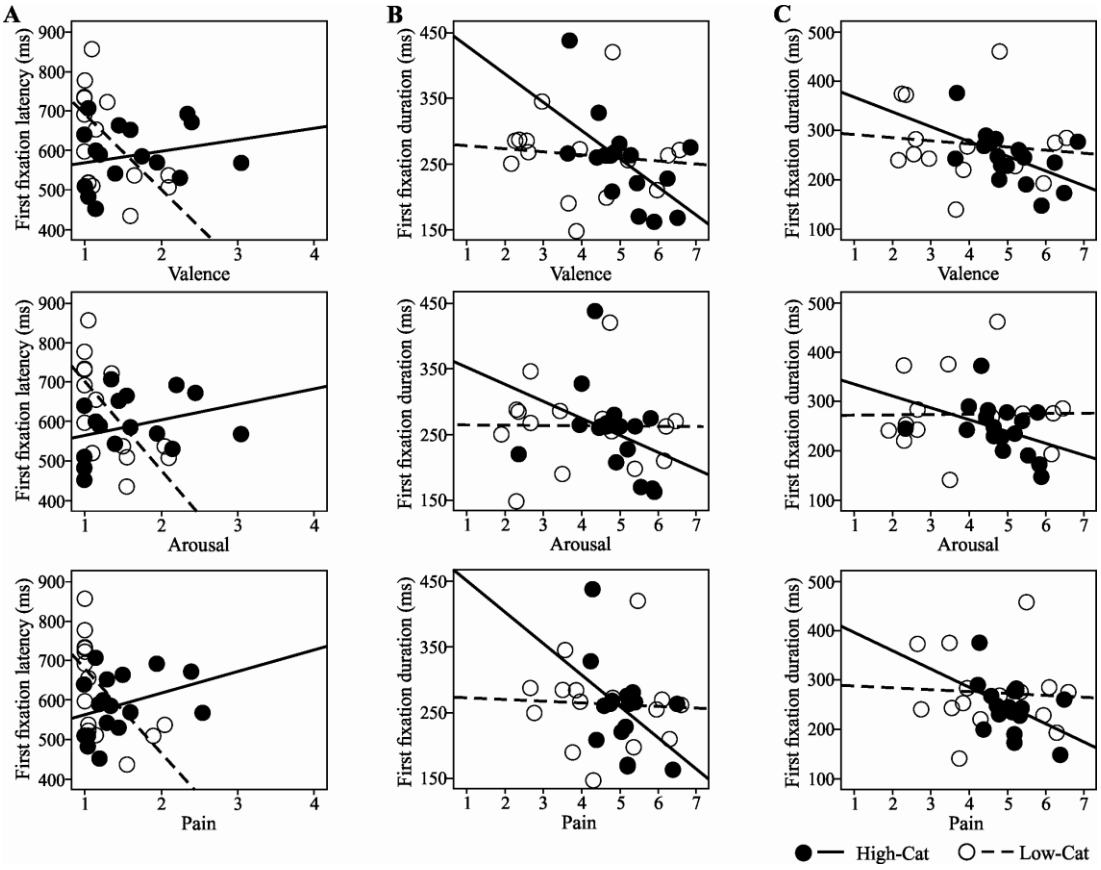

Fig. 4.5 Correlations between first fixation time to Pain and Non-Pain pictures. Scatter plots and the linear regression lines demonstrating relationships between subjective ratings of valence, arousal, and pain during view Non-Pain (A) and Pain (B and C) pictures, and the corresponding first fixation time (in milliseconds) between participants with high and low pain catastrophising scores. A. Relationships between first fixation latency to Non-Pain pictures in Negative– Non-Pain picture pair and subjective ratings. B. Correlations between first fixation duration to Pain pictures in Pain– Non-Pain picture pair and subjective ratings. C. Associations between firs fixation duration to Pain pictures in Pain– Negative pair and subjective ratings. High-Cat = high pain catastrophisers, dark circles, solid lines. Low-Cat = low pain catastrophisers, white circles, dashed lines.

4.3.6. Reaction time (RT) to probes

Attentional bias scores in RT were calculated with the formula [(PlDr – PrDr) + (PlDl – PrDl)]/2 (Macleod and Mathew, 1988), where P = Pain or Negative pictures, D = dot probe, l = left, and r = right. Positive values were indicative of vigilance (i.e. faster RT to probes after Pain pictures than probes after Non-Pain pictures), zero scores reflected no attentional bias, and negative scores suggested avoidance (e.g. slower RT to probes following Pain pictures) than probes after Non-

Pain pictures). Results indicated that Low-Cat subjects reacted more quickly to probes after target pictures in all three picture pairs. However, High-Cat people showed slower RT to probes after Pain/Negative pictures in Pain– Non-Pain and Negative– Non-Pain pairs, but had almost the same RT in Pain– Negative pair. For RT data, a 2 × 3 repeated measures ANOVA with a between subject factor (groups) and three within-subject factors (attention bias scores: Pain– Non-Pain, Negative– Non-Pain, and Pain– Negative) revealed a statistically significant main effect of pain catastrophising ($F(1,30) = 9.2$, $p = 0.005$, $\eta_p^2 = 0.234$), but null effects for picture pair ($F(2,60) = 1.2$, $p > 0.05$, $\eta_p^2 = 0.039$) and interaction of group × picture pair ($F(2,60) = 0.008$, $p > 0.05$, $\eta_p^2 < 0.0001$). Another three ANOVAs for repeated measures were conducted between picture pairs. The significant effect of pain catastrophising was only found in Pain– Non-Pain vs. Pain– Negative picture pairs ($F(1,30) = 8.5$, $p = 0.007$, $\eta_p^2 = 0.221$), indicating that High-Cat subjects responded slower to Pain scenes (target pictures) than Low-Cat people did. Results suggest that high pain catastrophisers are motivated to avoid the threatening content, especially the content containing physical pain.

Subsequently, a 2 (group) × 2 (congruence) × 3 (picture pair) ANOVA with repeated measures was performed, in order to investigate the impact of congruence of target-probe location combinations on reaction time (Table 4.10). Null effects appeared for group ($F(1,30) = 0.2$, $p > 0.05$), congruence ($F(1,30) = 0.5$, $p > 0.05$), picture pair ($F(2,60) = 0.1$, $p > 0.05$), group × picture pair ($F(2,60) = 0.2$, $p > 0.05$), congruence × picture pair ($F(2,60) = 1.2$, $p > 0.05$), and group × congruence × picture pair ($F(2,60) = 0.08$, $p > 0.05$). However, the interaction of group × congruence ($F(1,30) = 9.2$, $p = 0.005$) was statistically significant. Pairwise comparisons implicated that Low-Cat subjects responded to congruent target-probe

location significantly faster than incongruent combinations ($F(1,30) = 6.5$, $p = 0.016$).

Table 4.10 Reaction time to probes in the second eye movement study.
Mean ± standard error of reaction time to probes (ms) in high and low pain catastrophising groups.

Target picture position	Probe position	High-Cat	Low-Cat
Pain– Non-Pain			
Left	Left	474.4 ± 18.0	477.4 ± 18.3
Left	Right	464.2 ± 17.0	488.1 ± 16.0
Right	Left	460.2 ± 19.6	476.4 ± 18.0
Right	Right	470.5 ± 18.3	471.4 ± 22.0
Negative– Non-Pain			
Left	Left	472.2 ± 19.5	474.0 ± 15.8
Left	Right	459.1 ± 17.2	484.9 ± 15.8
Right	Left	467.1 ± 17.8	472.3 ± 62.4
Right	Right	473.2 ± 17.2	469.9 ± 21.2
Pain– Negative			
Left	Left	471.6 ± 21.2	470.0 ± 15.9
Left	Right	468.5 ± 18.9	481.6 ± 16.3
Right	Left	465.0 ± 19.1	490.7 ± 19.2
Right	Right	461.9 ± 19.2	467.0 ± 17.4

4.4. Experiment 4: Pain catastrophising effects on the cortical responses to viewing pain in others

Hypothesis:

High-, compared to low, pain catastrophisers will attribute stronger pain to pain scenes, and manifest stronger activation in cortical regions mediating emotional processing and attention.

4.4.1. Behavioural data

The mean pain catastrophising scores were 20.6 ± 12.3 (mean ± SD) in all subjects, 31.8 ± 5.7 in High-Cat and 9.4 ± 3.8 in Low-Cat groups ($t(28) = 12.8$, $P < 0.0001$). These mean pain catastrophising scores are comparable with those reported in previous studies that grouped subjects into high and low- pain catastrophising groups based on the Pain Catastrophizing Scale (Sullivan et al., 1995, Sullivan and Neish, 1999, Sullivan et al., 2002b, Sullivan et al., 2004, Van Damme et al., 2004, Wideman et al., 2009). The High-Cat and Low-Cat groups did not differ in total IRI scores (41.0 ± 12.1, mean ± SD; High-Cat: 47.0 ± 11.7; Low-Cat: 41.0 ± 12.0) or in any of the four IRI subscales ($P > 0.05$).

Table 4.11 shows the mean values of affective valence, arousal and pain for both types of pictures in High-Cat and Low-Cat groups. For valence, a two-way ANOVA for repeated measures revealed statistically significant main effects of pain catastrophising ($F(1,28) = 4.8$, $P = 0.038$) and picture type ($F(1,28) = 196.6$, $P < 0.0001$). The interaction between group and picture type was not statistically significant ($F(1,28) = 0.7$, $P > 0.05$). These effects pointed to a stronger negative affective evaluation of both pain and non-pain pictures in High-Cat than Low-Cat

group, and to a stronger negative affect during viewing pain than non-pain pictures in both groups. The arousal associated with viewing pictures was stronger when viewing pain than non-pain scenes ($F(1,28) = 206.5$, $P < 0.001$) but similar across High-Cat and Low-Cat groups ($P > 0.05$). The interaction of group × picture type was not statistically significant ($F(1,28) = 0.03$, $P > 0.05$).

Subjects attributed stronger pain to pain than non-pain pictures ($F(1,28) = 378.6$, $P < 0.0001$). High-Cat group compared to Low-Cat group rated both the pain- and non-pain scenes as containing greater pain ($F(1,28) = 4.9$, $P = 0.036$) (Table 1). The interaction between groups and picture types was not statistically significant ($F(1,28) = 1.8$, $P = 0.187$).

To evaluate the degree of discrimination between pain and non-pain pictures in High-Cat and Low-Cat groups, the sensitivity index (*d'*) and response bias were computed. These measures are derived from the signal detection theory (DeCarlo, 1998), and allowed for evaluation of whether pain and non-pain visual scenes are discriminated correctly and equally in both catastrophising groups. The mean scores ± SD of *d'* were 2.9 ± 0.6 in High-Cat and 2.8 ± 0.7 in Low-Cat group, respectively ($P > 0.05$). There were no statistical differences in *d'* or response bias between the two groups ($P > 0.05$). Thus, subjects were able to discriminate pain and non-pain scenes behaviourally, and the High-Cat and Low-Cat groups performed similarly in discrimination of pain and non-pain scenes.

Table 4.11 Subjective ratings to pictures during observation of pictures. Means ± standard errors of the mean of picture valence and arousal, and pain attributed to pain and non-pain pictures in high and low pain catastrophisers.

	High pain catastrophisers		Low pain catastrophisers	
	Pain	Non-pain	Pain	Non-pain
Valence	5.6 ± 0.4	1.6 ± 0.1	4.7 ± 0.3	1.2 ± 0.1
Arousal	5.0 ± 0.4	1.5 ± 0.2	4.8 ± 0.4	1.4 ± 0.2
Pain	5.7 ± 0.3	1.3 ± 0.1	4.9 ± 0.3	1.1 ± 0.1

5.4.2. Source dipole model

Fig. 4.6A shows the source dipole waveforms and isopotential scalp maps of the four source dipoles across subjects and conditions. Fig. 4.6B shows the cluster maxima and CLARA maps for each of four source dipoles. Source dipoles are numbered from 1 to 4 in Fig. 4.6 (A-C).

Source 1 showed a maximum at 496 ms following the onset of visual stimuli. The isopotential lines, mapped at the peak of 496 ms in Fig. 5.6A, suggested a positive maximum at the lower forehead and a negative maximum in the medial frontal region. CLARA indicated the presence of a source in the rostral anterior cingulate cortex (rACC; Brodmann area 24/32; approximate Talairach coordinates: x = 2 mm, y = 43 mm, z = 2 mm) (Fig. 4.6B). Source dipole 2 peaked at 544 ms, and was accounted for the negative potential maximum in the left lower face and a positive potential maximum in the left posterior parietal region. This source was fitted in the left medial temporal cortex involving the parahippocampal gyrus (PHG_L; Brodmann area 36; approximate Talairach coordinates: x = -34 mm, y = -37 mm, z = -13 mm). Source 3 peaked approximately 8 ms later than source 1, and was accounted for a maximal negativity in the lower right face and a positive potential

maximum in the right posterior parietal region suggesting a dipole operating in the right medial temporal cortex. Source 3 was denoted as the right parahippocampal gyrus (PHG_R; Brodmann area 35; approximate Talairach coordinates: x = 30 mm, y = -26 mm, z = 13 mm). Finally, source dipole 4 explained the positive vertex potential maximum at 580 ms and 760 ms. This source showed a negativity around the chin and the neck, and the isopotential lines pointed to the presence of a dipole located deep in the medial parietal cortex. The approximate Talairach coordinates of source 4 (x = 0 mm, y = -27 mm, z = 34 mm) were consistent with a source dipole located in the posterior cingulate cortex (PCC; Brodmann area 23/31).

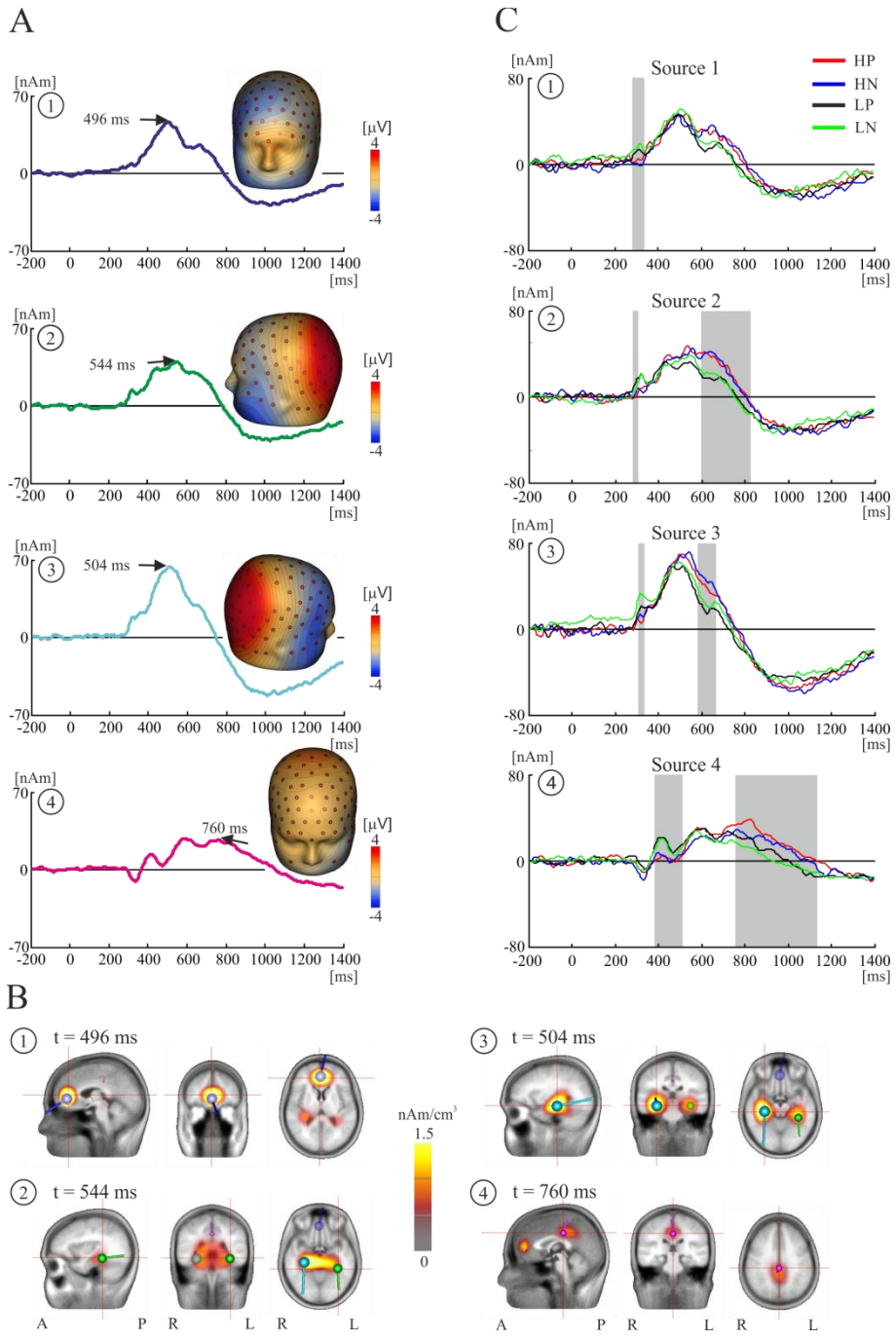

Fig. 4.6 Source dipole model and source waveforms during observation of pictures.
A. The grand average waveforms of four equivalent source dipoles and their isopotential line maps. The isopotential maps were plotted at the temporal maxima, highlighted with an arrow and labelled with the latency value. The source dipoles are numbered from 1 to 4.
B. CLARA source activation maps and source dipole locations of four cortical sources. The peak latency of each source corresponds to that in panel A. A = anterior, P = posterior, L = left, R = right. The numbering of dipoles corresponds to that in A. 1 = blue dipole, 2 = green dipole, 3 = ice blue dipole, 4 = magenta dipole.
C. The grand average waveforms of four equivalent source dipoles, numbered from 1 to 4, in high and low pain catastrophising groups during viewing pain and non-pain scenes. Red line = pain photographs in High-Cat group (HP), blue line = non-pain photographs in High-Cat group (HN), black line = pain photographs in Low-Cat group (LP), green line = non-pain photographs in Low-Cat group (LN). The grey-filled rectangles indicate epochs used in statistical analyses.

4.4.3. Effects of pain catastrophising on source dipole waveforms

Fig. 4.6C shows the average source waveforms in each of four source dipoles for pain and non-pain pictures in High-Cat and Low-Cat groups. Intervals manifesting statistically significant effects of group or type of pictures or their interaction, according to the permutation analysis involving all four sources and all time points, are indicated with grey rectangles in Fig. 4.6C. Table 4.12 gives the intervals used in the statistical analysis, and the mean and standard error of source dipole components in pain and non-pain pictures in each group of subjects.

In source 1, located in the rACC, the source activity was stronger in the Low-Cat than the High-Cat groups for both types of pictures ($F(1,28) = 7.2$, $P = 0.012$) during the time epoch of 280–336 ms (Fig. 4.6C and Table 4.12).

In source 2, located in PHG_L, two intervals showed statistically significant ANOVA effects. In the epoch of 284–308 ms, the ANOVA disclosed a significant interaction of group × picture type ($F(1,28) = 9.7$, $P = 0.004$). The interaction effect was due to greater source activity during viewing pain than non-pain pictures in the Low-Cat group ($F(1,28) = 5.85$, $P = 0.022$), whilst the difference between pain and non-pain pictures in High-Cat group was not statistically significant ($F(1,28) = 3.94$, $P = 0.066$). In the late latency of 596–828 ms, a statistically significant main effect of group ($F(1,28) = 6.4$, $P = 0.017$) was observed. The effect was due to stronger source activity in the High-Cat, compared to Low-Cat, group.

In the interval 308–336 ms of the right medial temporal source waveform (source 3), there was a statistically significant main effect of group ($F(1,28) = 4.3$, $P = 0.046$) with low pain catastrophisers displaying stronger source activity than high pain catastrophisers during viewing both types of pictures. In addition, a main effect

of picture type was statistically significant ($F(1,28) = 5.6$, $P = 0.025$) in this epoch, with non-pain pictures inducing stronger cortical activity than pain pictures. In the late interval (580–664 ms), amplitude of source 3 was stronger during viewing non-pain than pain pictures ($F(1,28) = 5.7$, $P = 0.024$).

In source 4, fitted in the PCC, a statistically significant effect of pain catastrophising ($F(1,28) = 6.4$, $P = 0.017$) was shown in the latency epoch of 384 ms to 452 ms, which was caused by a larger source amplitude in Low-Cat than High-Cat group. In contrast, source activation in the late interval (756–1144 ms) was stronger in High-Cat than Low-Cat group ($F(1,28) = 5.8$, $P = 0.022$). The main effect of picture type was significant in this time interval with pain pictures eliciting stronger source activity relative to non-pain pictures ($F(1,28) = 15.6$, $P < 0.001$).

Table 4.12 Source activation showing significant intervals of interest during observation of pictures. Mean ± standard error of the mean of source dipole moments (in nAm) in select time epochs in high and low pain catastrophisers during viewing pain or non-pain pictures. Source 1 = rostral anterior cingulated cortex; Source 2 = left paraphippocampal gyrus; Source 3 = right parahippocampal gyrus; Source 4 = posterior cingulate cortex.

	Epoch	High pain catastrophisers		Low pain catastrophisers	
Source	(ms)	Pain	Non-pain	Pain	Non-pain
Source 1	280–336	3.8 ± 4.0	-0.5 ± 3.7	11.7 ± 4.0	16.0 ± 3.7
Source 2	284–308	1.1 ± 4.6	6.6 ± 4.3	15.9 ± 4.6	9.2 ± 4.3
Source 2	596–828	36.6 ± 5.0	37.9 ± 5.5	16.9 ± 5.0	20.6 ± 5.0
Source 3	308–336	6.8 ± 5.8	11.5 ± 5.9	18.8 ± 5.8	30.8 ± 5.9
Source 3	580–664	44.0 ± 7.3	50.4 ± 7.6	23.4 ± 7.3	30.7 ± 7.6
Source 4	384–452	3.6 ± 4.5	6.0 ± 4.7	21.3 ± 4.5	18.9 ± 4.7
Source 4	756–1144	36.0 ± 4.6	24.8 ± 3.6	21.0 ± 4.6	13.8 ± 3.6

4.4.4. Correlations between source components and subjective responses to photographs

Pearson's correlation coefficients were calculated between the source activation differences [Pain – Non-Pain pictures] in sources and intervals manifesting statistically significant effects of group (Table 4.12) and the [Pain – Non-Pain pictures] differences in subjective ratings of valence, arousal and pain. It found two statistically significant correlation coefficients surpassing Bonferroni-Šidák corrected P values. There were statistically significant correlations between the amplitude of the long latency (756–1144 ms) PCC source (source 4) and arousal ($r(15) = 0.7$, $P = 0.002$), and pain ($r(15) = 0.7$, $P = 0.002$) in the Low-Cat group only. Fig. 4.7 illustrates the scatter plots and linear regression lines for the valence, arousal and pain rating scales and the source amplitude differences of the late PCC activation in High-Cat and Low-Cat groups. Results suggest that the activation of the PCC in the late epoch was related to stronger subjective arousal and observed pain elicited by visual stimuli in the Low-Cat group but not in the High-Cat group.

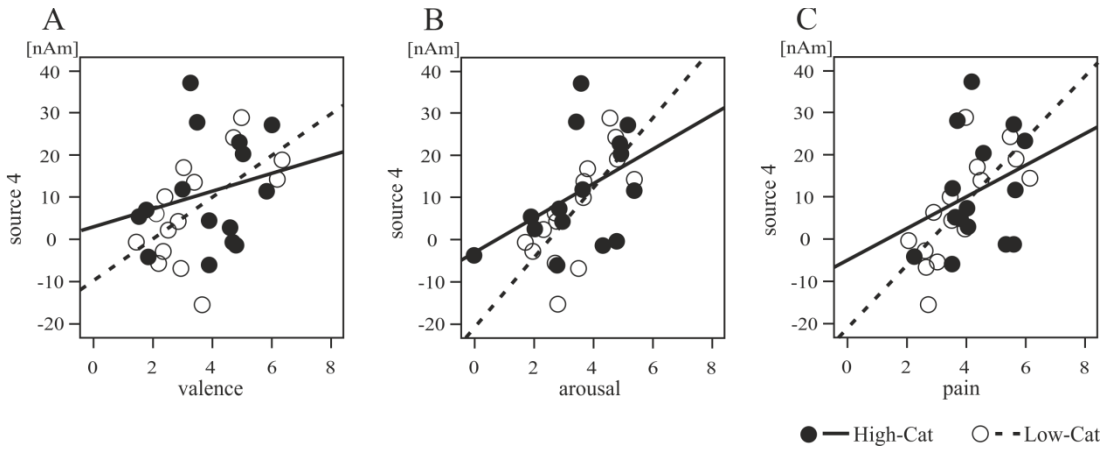

Fig. 4.7 Correlations between the posterior cingulate source dipole and subjective ratings to pictures. Scatter plots and the linear regression lines illustrating relationships between subjective ratings of valence, arousal and pain attributed to visual stimuli and the source amplitude differences between two conditions of the posterior cingulate source dipole in the interval of from 756 to 1144 ms. A. Valence. B. Arousal. C. Pain. High-Cat = high pain catastrophisers, dark circles, solid line. Low-Cat = low pain catastrophisers, white circles, dashed line.

4.5. Experiment 5: Pain catastrophising effects on the cortical responses to laser stimulation during viewing of comforting hand postures

Hypothesis:

High-, compared to low, pain catastrophisers will report smaller pain and manifest diminished cortical activation during viewing of comfort-giving hand postures.

4.5.1. Behavioural data

The mean pain catastrophising scores were 29.8 ± 4.4 (mean ± SD) in High-Cat and 6.8 ± 4.1 in Low-Cat groups ($t(22) = 13.2$, $P < 0.0001$). These mean pain catastrophising scores are comparable with previous studies that grouped subjects into high- and low pain catastrophising groups according to the Pain Catastrophizing Scale (Sullivan et al., 1995, Sullivan and Neish, 1999, Crombez et al., 2004, Van Damme et al., 2004, Wideman et al., 2009). Independent t-tests also revealed that High-Cat, compared to Low-Cat, subjects scored higher in STAI-State (right now feeling) scale ($t(22) = -3.5$, $P = 0.006$). No further significant differences in the STAI-Trait, IRI scales, or its subscales between two groups ($P > 0.05$) were found.

The average laser intensity provoking pain was 1.5 ± 0.2 J for all subjects, 1.5 ± 0.2 J for High-Cat group and 1.5 ± 0.1 J for Low-Cat group ($t(22) = -0.2$, $P > 0.05$).

The mean value and standard deviation (SD) of pain, comforting, empathy and pleasantness in each experimental condition are listed in Table 4.13. Subjects reported a moderate pain sensation similar to a pricking pain during laser stimulation. Fig. 4.8 shows the subjective pain rating for each condition in the High-

and Low-Cat groups. A 2 × 3 ANOVA for repeated measures revealed subjective pain, evaluated after each laser stimulus, was statistically significantly affected by picture types ($F(2,44) = 10.5$, $P < 0.0001$). Paired-sample t-tests showed that laser stimuli were perceived as less painful during viewing Comfort pictures than Touch or Non-Touch pictures. This indicated that viewing Comfort pictures significantly attenuated the pain intensity. Results also showed a significant interaction between group and pictures ($F(2,44) = 3.8$, $P = 0.041$). Pairwise comparisons showed that high pain catastrophisers rated the pain as less intense while viewing Comfort pictures than while viewing Touch ($P = 0.002$) or Non-Touch ($P = 0.001$) pictures. However, the main effect of pain catastrophising group did not show significance ($F(1,22) = 1.2$, $P > 0.05$).

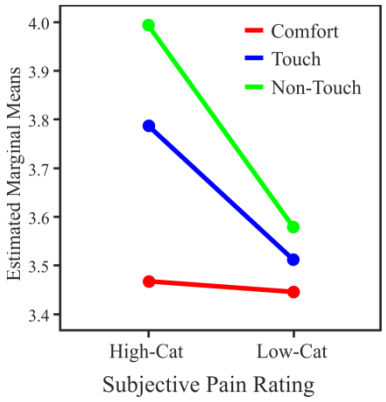

Fig. 4.8 Mean subjective pain ratings to hand postures pictures. Mean subjective pain ratings for Comfort, Touch, and Non-Touch pictures in high and low pain catastrophisers. High-Cat = high pain catastrophisers, Low-Cat = low pain catastrophisers.

Table 4.13 Effects of emotional pictures on subjective measures.

A. Mean ± standard error of mean of subjective pain and picture comforting, empathy and pleasantness attributed to Comfort, Touch and Non-Touch pictures in high and low pain catastrophisers.

	High pain catastrophisers			Low pain catastrophisers		
	Comfort	Touch	Non-Touch	Comfort	Touch	Non-Touch
Pain	3.5 ±0.2	3.8 ±0.2	4.0 ±0.2	3.4 ±0.2	3.5 ±0.2	3.6 ±0.2
Comforting	7.2 ±0.3	4.0 ±0.5	2.9 ±0.4	6.1 ±0.3	3.9 ±0.5	2.4 ±0.4
Empathy	7.5 ±0.3	3.6 ±0.5	2.6 ±0.4	6.3 ±0.3	3.8 ±0.5	2.6 ±0.4
Pleasantness	7.2 ±0.4	3.9 ±0.5	2.7 ±0.4	5.6 ±0.4	3.4 ±0.5	2.4 ±0.4

B. Paired-sample t-tests of pain, comforting, empathy and pleasantness associated with Comfort, Touch and Non-Touch pictures.

	Comfort – Touch	Comfort – Non-Touch	Touch – Non-Touch
Pain	$t(23) = -3.2$, $P = 0.004$	$t(23) = -3.5$, $P = 0.002$	$t(23) = -2.0$, $P = 0.062$
Comforting	$t(23) = 7.0$, $P < 0.0001$	$t(23) = 9.0$, $P < 0.0001$	$t(23) = 3.3$, $P = 0.003$
Empathy	$t(23) = 8.0$, $P < 0.0001$	$t(23) = 9.6$, $P < 0.0001$	$t(23) = 3.0$, $P = 0.006$
Pleasantness	$t(23) = 6.1$, $P < 0.0001$	$t(23) = 8.6$, $P < 0.0001$	$t(23) = 3.1$, $P = 0.005$

The 2 × 3 ANOVAs for repeated measures revealed that the three types of pictures were perceived differently in term of comforting ($F(2,44) = 50.4$, $P < 0.0001$), empathy ($F(2,44) = 61.3$, $P < 0.0001$), and pleasantness ($F(2,44) = 45.3$, $P < 0.0001$). Comfort pictures were perceived as more comforting, empathetic, and pleasant, compared with the other two picture types. The main effects of pain catastrophising and the interactions between group and picture types for these three subjective ratings were not statistically significant ($P > 0.05$). High-Cat people, though, attributed more pleasantness to all three pictures than Low-Cat people did ($F(1,22) = 4.4$, $P = 0.047$). The effects suggested that the three types of pictures differed from each other in term of comforting, empathy and pleasantness.

4.5.2. Source dipole model for visual-evoked potentials

Fig. 4.9 shows the source dipole waveforms and isopotential scalp maps of the six source dipoles across subjects and conditions. Source dipoles are numbered from 1 to 6 in Fig. 4.9 and Fig. 4.10 (A-D).

Source 1 shows a maximum at 133 ms following the onset of visual stimuli. The scalp maps, mapped at the peak of 133 ms in Fig. 4.9, demonstrated a positive potential at the midline of parietal-occipital region. LAURA indicated that the location of a source was in the medial surface of the occipital lobe, involving calcarine gyrus and cuneus (Brodmann area 17/31; approximate Talairach coordinates: x = 0 mm, y = -62 mm, z = 10 mm). Source dipole 2 showed one maximum at 311 ms and another smaller maximum at 193 ms around the vertex. The isopotential lines mapped at the peak of 193 ms pointed to the presence of a dipole located in the medial parietal region, suggesting a source operating in the mid-cingulate cortex (MCC; Brodmann area 31; approximate Talairach coordinates: x = 1 mm, y = -33 mm, z = 35 mm). Source 3 was fitted to the left medial temporal region, with the most likely origin in the parahippocampal gryus (PHG_L; Brodmann area 35; approximate Talairach coordinates: x = -18 mm, y = -18 mm, z = -13 mm). Source 3 accounted for the maximal negativity in the lower left face, peaking at 376 ms, and a positive maximum in the left posterior parietal region. Source dipole 4 located almost symmetrically to source 3 in the right medial temporal gyrus, peaking at 132 ms and 305 ms, and corresponded to the parahippocampal gyrus (PHG_R; Brodmann area 35; approximate Talairach coordinates: x = 23 mm, y = -26 mm, z = -23 mm). This source explained a strong maximal negativity that was detected by the right suborbital electrodes, and pointed to a positive potential maximum in the right posterior parietal region. Source 5 peaked at 126 ms and 317 ms, and accounted for

the negative potential in the medial frontal region and a maximal positivity at the lower forehead. This source was fitted in rostral anterior cingulate cortex (rACC; Brodmann area 32; approximate Talairach coordinates: x = -2 mm, y = 43 mm, z = 5 mm). Finally, source 6 peaked approximately 14 ms later than source 2. A relatively weak negative potential was seem around the vertex at 207 ms. This source was located in the medial part of superior frontal gryus, purportedly involving left paracentral lobule (Brodmann area 5/6; approximate Talairach coordinates: x = -3 mm, y = -32 mm, z = 63 mm).

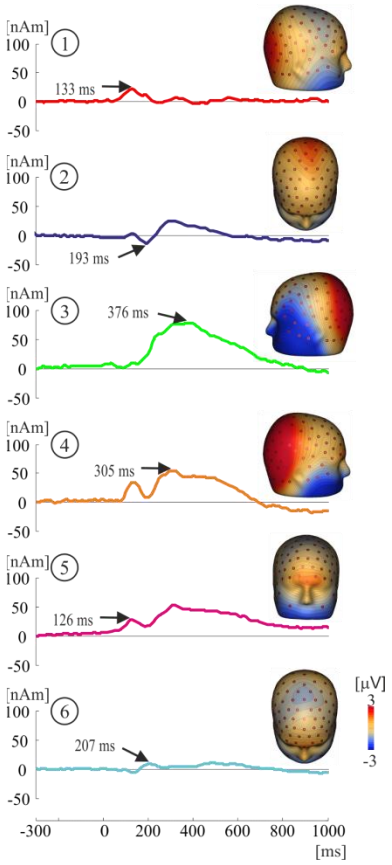

Fig. 4.9 The grand averaged waveforms of six equivalent source dipoles and their isopotential line maps for visual-evoked potentials. The isopotential maps were plotted at the selected time point, highlighted with an arrow and labelled with the latency value. The source dipoles are numbered from 1 to 6.

4.5.3. Effects of pain catastrophising on source dipole waveforms of picture viewing with a filter of 0.1-30 Hz

Fig. 4.10A shows the average source waveforms in each of six source dipoles in High-Cat and Low-Cat subjects with the bandpass filter of 0.1-30 Hz. Intervals illustrating statistically significant effects of group, according to the permutation analysis involving all six sources and all time points, are displayed with grey-filled rectangles.

In source 1, corresponding to the primary visual cortex, a repeated measure ANOVA of mean amplitudes found a significant main effect of group at 101–216 ms ($F(1,22) = 5.8$, $P = 0.025$), with the High-Cat group showing stronger source activation to the pictures than the Low-Cat group (Fig. 4.10A).

In source 2 (MCC), a statistically significant main effect of group was found (822–865 ms), with Low-Cat subjects showing stronger source activity than High-Cat people during picture viewing ($F(1,22) = 4.4$, $P = 0.048$).

In the interval 83–146 ms of the PHG_L source waveform (source 3), a main effect of group was significant ($F(1,22) = 9.8$, $P = 0.005$). Results indicated attenuated amplitude in High-Cat people compared with Low-Cat people, during picture viewing.

In source 4 (PHG_R), the ANOVA revealed a significant group effect ($F(1,22) = 6.4$, $P = 0.019$), with low pain catastrophisers exhibiting stronger source activation to the pictures than High-Cat people, during the period between 78 to 97 ms.

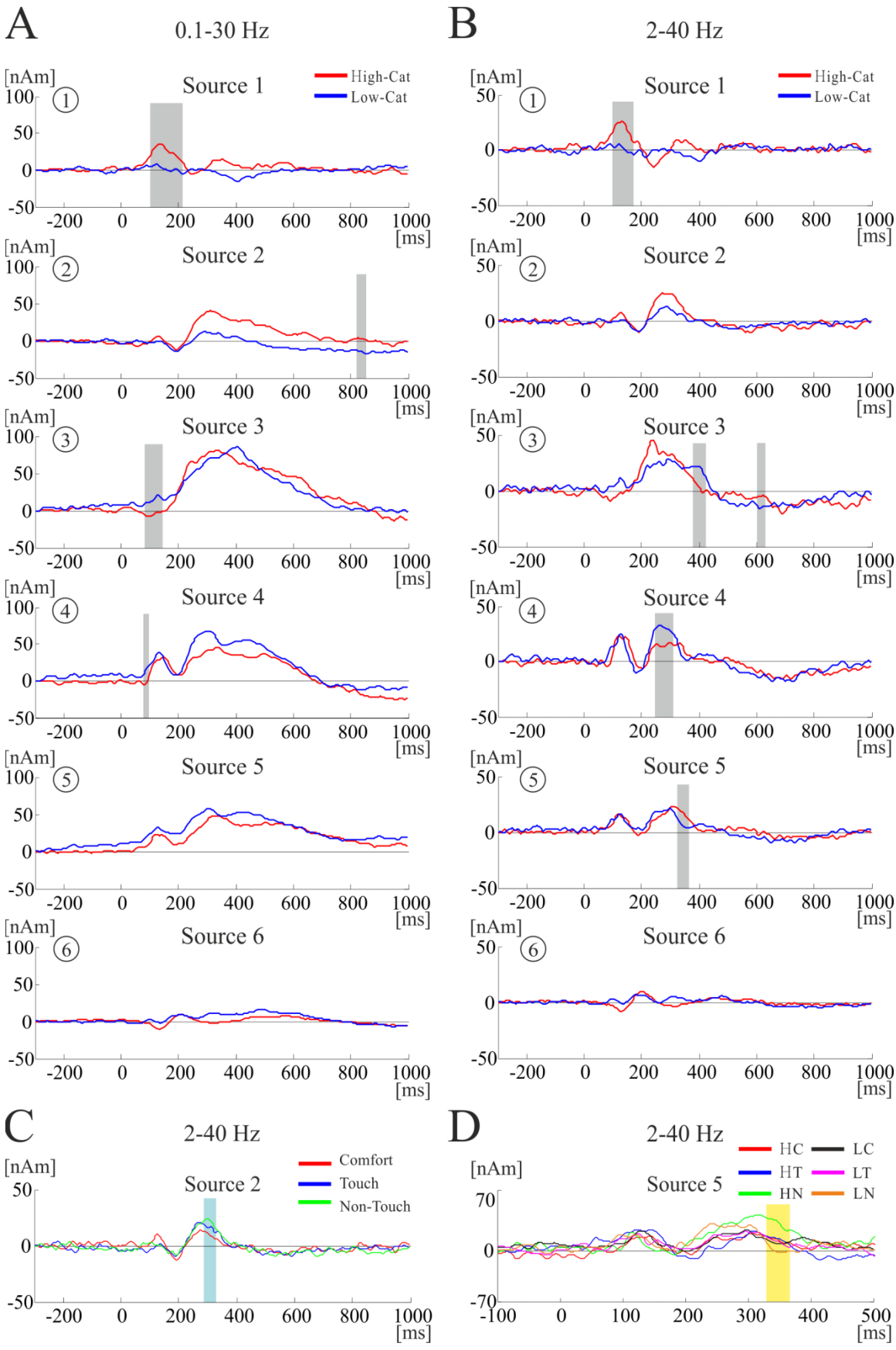
A
0.1-30 Hz
Source 1
High-Cat
Low-Cat
Source 2
Source 3
Source 4
Source 5
Source 6
[nAm]
[ms]
B
2-40 Hz
C
2-40 Hz
Source 2
Comfort
Touch
Non-Touch
D
2-40 Hz
Source 5
HC
HT
HN
LC
LT
LN

Fig. 4.10 Source waveforms for visual-evoked potentials with different bandpass filters.
A. The average waveforms of six equivalent source dipoles in high and low pain catastrophisers with the bandpass filter of 0.1-30 Hz, numbered from 1 to 6, during viewing of pictures in high and low pain catastrophisers. Red line = High-Cat group, blue line = Low-Cat group. The grey-filled rectangles show epochs with significant group effects.
B. The average waveforms of six equivalent source dipoles in high and low pain catastrophisers with the bandpass filter of 2-40 Hz.
C. The average waveforms of Source 2 (MCC) for Comfort, Touch, and Non-Touch pictures, using the 2-40 Hz filter. Red line = Comfort pictures, Blue line = Touch pictures, Green line = Non-Touch pictures. The blue-filled rectangle indicates epoch with significant picture effect.
D. The average waveforms of Source 5 (rACC), with a filter of 2-40 Hz, during viewing of Comfort, Touch, and Non-Touch pictures in high and low pain catastrophisers. Red line = Comfort pictures in High-Cat group (HC), blue line = Touch pictures in High-Cat group (HT), green line = Non-Touch in High-Cat group (HN), black line = Comfort pictures in Low-Cat group (LC), magenta line = Touch pictures in Low-Cat group (LT), orange line = Non-Touch pictures in Low-Cat group (LN). The yellow-filled rectangle shows the epoch with significant interaction between group and picture type.

4.5.4. Effects of pain catastrophising on source dipole waveforms of picture viewing with a filter of 2-40 Hz

For the ERP analysis with the filter of 2-40 Hz, intervals illustrating statistically significant effects of group (Fig. 4.10B), or picture type (Fig. 4.10C) or their interaction (Fig. 4.10D), according to the permutation analysis involving all six sources and all time points, are displayed with colour filled rectangles.

In source 1, the interval of 99–173 ms displayed a statistically significant ANOVA effect of group (Fig. 4.10B). Results found that in this latency stronger source activation in High-Cat, compared to Low-Cat, subjects ($F(1,22) = 4.6$, $P = 0.043$).

In the interval 289–332 ms of source 2 (MCC), a statistically significant main effect of picture type was found ($F(1,22) = 4.7$, $P = 0.015$). A paired sample t-test suggested that Non-Touch elicited stronger source amplitude across subjects ($t(1,23) = -3.1$, $P = 0.005$) in comparison to Comfort pictures (Fig. 4.10C).

In the interval of 381–426 ms ($F(1,22) = 5.0$, $P = 0.026$) and 605–634 ms ($F(1,22) = 7.8$, $P = 0.011$) of the left temporal region (source 3), statistically significant group effects were found. Low-Cat people showed larger source amplitude than the High-Cat group during viewing pictures.

In source 4 (PHG_R), High-Cat participants showed significantly stronger cortical activation to pictures than low pain catastrophisers during the epoch of 248–312 ms ($F(1,22) = 4.4$, $P = 0.047$).

In source 5 (rACC), a significant main effect of group ($F(1,22) = 5.1$, $P = 0.033$) and a significant interaction of group by picture type ($F(2,44) = 5.9$, $P = 0.013$) were found during the epoch from 326 to 366 ms. In this period, people with high pain catastrophising exhibited larger amplitude to picture stimuli, compared to Low-Cat people (Fig. 4.10B). High-Cat people also displayed stronger cortical responses to Non-Touch pictures than Low-Cat people did ($P = 0.005$) (Fig. 4.10D).

4.5.5. Source dipole model for LEPs

Fig. 4.11A shows the source dipole waveforms and isopotential scalp maps of the six source dipoles across subjects and conditions. Fig. 4.11B shows the cluster and CLARA maps for each of six source dipoles at selected time point. Source dipoles are numbered from 1 to 6 in Fig. 4.11 (A-C) and Fig. 4.12 (A-C).

Source 1 shows a maximum at 170 ms following the onset of laser stimuli. The scalp maps, mapped at 150 ms in Fig. 4.11A, illustrated a negative potential at the temporal region contralateral to the stimulated side, consistent with previous studies suggesting the location of laser-evoked N1 component (Treede et al., 1988, Garcia-Larrea et al., 1997, Hu et al., 2010). CLARA indicated that the location of a

source was in the left operculo-insular region, involving posterior insula and parietal operculum (approximate Talairach coordinates: x = -35 mm, y = -15 mm, z = -6 mm) (Fig. 4.11B). Source dipole 2 peaked approximately 30 ms later than source 1. A relatively weak negative potential was seen in the right temporal region at 160 ms. This source was located almost symmetrically to source 1 in the right operculo-insula region, purportedly involving posterior insula and parietal operculum (approximate Talairach coordinates: x = 38 mm, y = -10 mm, z = -3 mm). Source 3 explained a negative potential maximum at 185 ms and a maximal positivity at 280 ms around the vertex electrodes. The isopotential lines, peaking at 185 ms, pointed to the presence of a dipole located deep in the medial parietal cortex. This is indicative of a source operating in the mid-cingulate cortex (MCC; Brodmann area 24/31; approximate Talairach coordinates: x = 0 mm, y = -22 mm, z = 43 mm). Collaborating with previous studies (Bromm and Treede, 1987, Garcia-Larrea et al., 2003, Mouraux and Iannetti, 2009), this source suggested a classical LEP component – a negative-positive biphasic deflection (N2-P2). Source dipole 4 peaked at 227 ms and 316 ms, and accounted for the negative potential in the medial frontal region and a maximal positivity at the lower forehead. This source was fitted in the rostral anterior cingulate cortex (rACC; Brodmann area 24/32; approximate Talairach coordinates: x = 4 mm, y = 46 mm, z = 10 mm). Source 5 was located in the left medial temporal cortex, peaking at 221 ms and 325 ms, and corresponding to the parahippocampal gyrus (PHG_L; Brodmann area 34/28; approximate Talairach coordinates: x = -20 mm, y = -8 mm, z = -19 mm). This source explained a strong maximal negativity that was detected by the left suborbital electrodes, and pointed to a positive potential maximum in the left posterior parietal region. Finally, source 6 was almost symmetrically located to source 5 in the right medial temporal gyrus,

with the most likely origin in the parahippocampal gyrus (PHG_R; Brodmann area 36/28; approximate Talairach coordinates: x = 32 mm, y = -6 mm, z = -18 mm). Source 6 accounted for the maximal negativity in the lower right face, peaking at 312 ms, and a positive maximum in the right posterior parietal region.

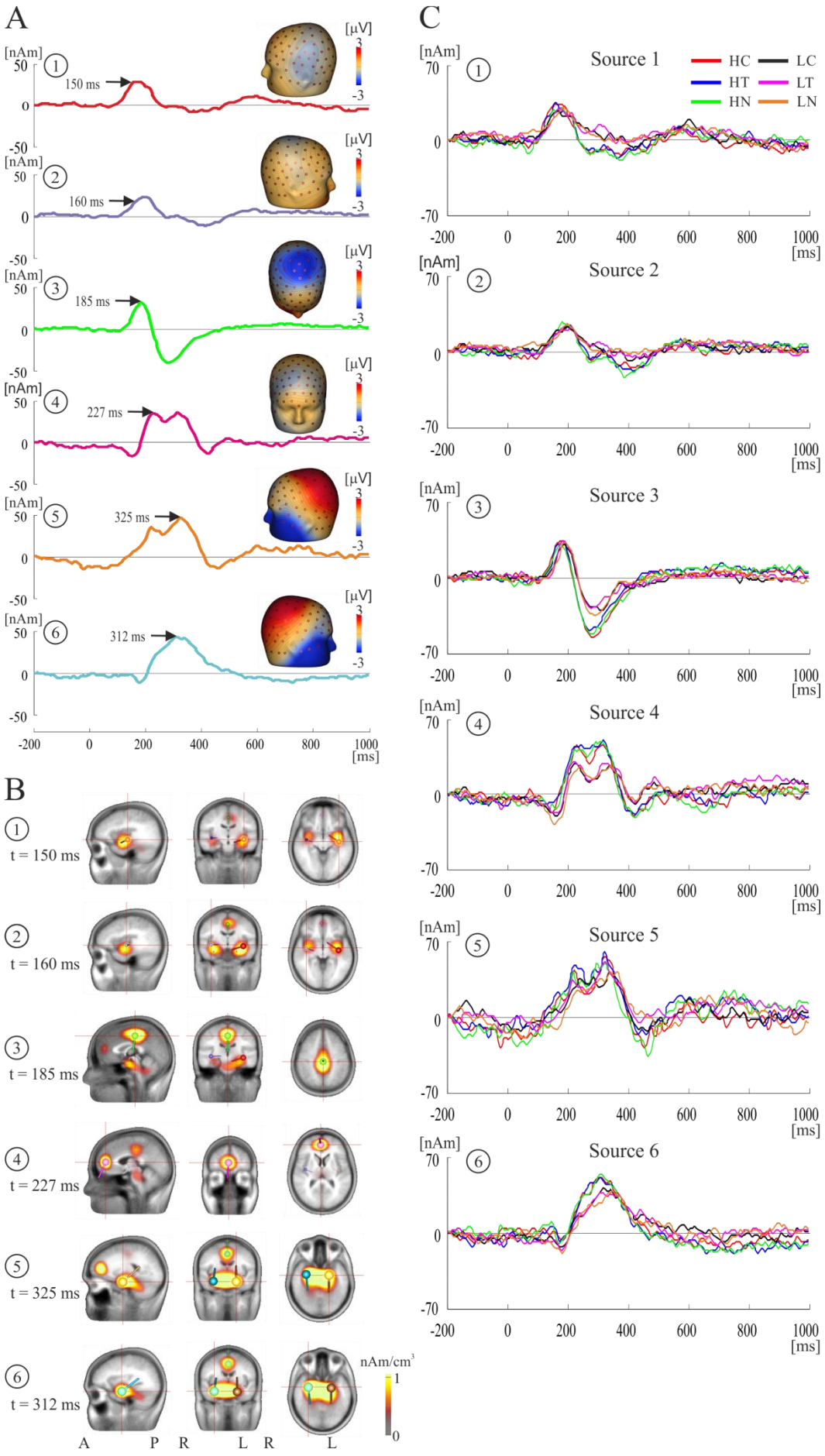
A
[nAm]
[μV]
150 ms
160 ms
185 ms
227 ms
325 ms
312 ms
[ms]
B
t = 150 ms
t = 160 ms
t = 185 ms
t = 227 ms
t = 325 ms
t = 312 ms
nAm/cm³
A P R L R L
C
Source 1
Source 2
Source 3
Source 4
Source 5
Source 6
HC LC
HT LT
HN LN

Fig. 4.11 Source dipoles and source waveforms for laser evoked potentials.
A. The grand averaged waveforms of six equivalent source dipoles and their isopotential line maps. The isopotential maps were plotted at the selected time point, highlighted with an arrow and labelled with the latency value. The source dipoles are numbered from 1 to 6.
B. CLARA source activation maps and locations of six source dipoles. The selected time point of each source corresponds to that in panel A. A = anterior, P = posterior, L = left, R = right. The numbering of dipoles corresponds to that in A. 1 = red dipole, 2 = blue dipole, 3 = green dipole, 4 = magenta dipole, 5 = orange dipole, 6 = ice blue dipole.
C. The grand averaged waveforms of six equivalent source dipoles, numbered from 1 to 6, during viewing Comfort, Touch, and Non-Touch pictures in high and low pain catastrophisers. Red line = Comfort pictures in High-Cat group (HC), blue line = Touch pictures in High-Cat group (HT), green line = Non-Touch in High-Cat group (HN), black line = Comfort pictures in Low-Cat group (LC), magenta line = Touch pictures in Low-Cat group (LT), orange line = Non-Touch pictures in Low-Cat group (LN).

4.5.6. Effects of pain catastrophising on source dipole waveforms

Fig. 4.11C shows the averaged source waveforms in each of six source dipoles for Comfort, Touch, and Non-Touch pictures in High-Cat and Low-Cat subjects. Intervals illustrating statistically significant effects of group (Fig. 4.12A), or pictures type (Fig. 4.12B), or their interaction (Fig. 4.12C), according to the permutation analysis involving all six sources and all time points, are displayed with colour filled rectangles in Fig. 4.12. Table 4.14 shows the intervals employed in the statistical analysis, and the mean and standard error of source dipoles in the three types of pictures for each group of subjects.

In source 1, located in the left operculo-insular cortex, the source activity was stronger in the High-Cat group than the Low-Cat group in all types of pictures in the time epochs of 223–404 ms ($F(1,22) = 9.1$, $P = 0.006$) and 414–492 ms ($F(1,22) = 6.1$, $P = 0.021$) (Fig. 4.12A and Table 4.14).

In source 2, located in the right operculo-insular cortex, three intervals showed statistically significant effects. In the latency of 353–472 ms, a statistically significant main effect of group was observed ($F(1,22) = 4.8$, $P = 0.04$), indicating a

larger amplitude in the High-Cat, compared to the Low-Cat, groups. In particular, in the epoch of 459–472 ms, the ANOVA revealed a significant main effect of group ($F(1,22) = 4.7$, $P = 0.042$) (Fig. 4.12A) and a significant interaction of group × picture type ($F(2,44) = 3.8$, $P = 0.035$) (Fig. 4.12C). Pairwise comparison tests suggested that the High-Cat, compared to Low-Cat, subjects under noxious laser stimulation displayed greater source activity during viewing of Non-Touch pictures ($F(1,22) = 11.5$, $P = 0.003$), whilst the group differences for viewing Comfort ($F(1,22) = 0.1$, $P > 0.05$) and Touch ($F(1,22) = 1.2$, $P > 0.05$) pictures were not statistically significant. In the late interval of 705–738 ms, there was a significant main effect of picture type ($F(2,44) = 6.3$, $P = 0.005$). Paired-sample t-tests suggested a statistically significant decrease in source strength during viewing Comfort pictures, compared to Touch ($t(23) = -3.4$, $P = 0.002$) or Non-Touch ($t(23) = -3.2$, $P = 0.004$) pictures among all subjects (Fig. 4.12B).

In the interval 210–392 ms of the MCC source waveform (source 3), there was a statistically significant main effect of group ($F(1,22) = 5.8$, $P = 0.025$) with high pain catastrophisers displaying stronger source activity to the laser stimuli than the low pain catastrophisers during viewing three types of pictures.

In source 4, fitted in the rACC, repeated measure ANOVAs of mean amplitudes showed a significant main effect of group at 169–192 ms ($F(1,22) = 4.7$, $P = 0.042$) and 363–517 ms ($F(1,22) = 16.9$, $P < 0.0001$). In both latency windows, relative to the Low-Cat group, the High-Cat group displayed larger source amplitudes to the pictorial stimuli.

In source 5, located in the PHG_L, only a main effect of picture type was significant ($F(2,44) = 10.8$, $P < 0.0001$) in the window of 714–735 ms. Paired-

sample t-tests illustrated that Comfort pictures elicited less source activity in this time window, relative to Touch ($t(23) = -4.3$, $P < 0.0001$) and Non-Touch ($t(23) = -3.9$, $P = 0.001$) pictures (Fig. 4.12B).

In the epoch 438–506 ms of the right medial temporal source waveform (source 6), there was a significant main effect of group ($F(1,22) = 4.6$, $P = 0.043$), suggesting a stronger source activation in the Low-Cat, compared with High-Cat, subjects.

4.5.7. Correlations between source components and subjective pain ratings

Pearson's correlation coefficients were calculated between source dipole components and intervals manifesting statistically significant effects of group (Table 4.14), and the subjective pain ratings in High-Cat and Low-Cat groups for the three picture types. Only one statistically significant correlation with Bonferroni corrected P values was found. The amplitude of the early epoch (169–192 ms) of the anterior cingulate cortex (source 4) for Comfort pictures was significantly correlated with subjective pain ratings ($r(12) = 0.6$, $P = 0.027$) in the Low-Cat group only. Fig. 4.13 shows the scatter plots and linear regression lines for the subjective pain rating scales and the source amplitudes of the early rACC component in High-Cat and Low-Cat groups for Comfort, Touch, and Non-Touch pictures. Results suggest that stronger subjective perceived pain elicited by the noxious laser stimuli was related to greater cortical activity of the rACC in the early time window in the Low-Cat group but not in the High-Cat group, when viewing Comfort pictures.

Table 4.14 Source activation showing significant intervals of interest during laser stimulation. Mean ± standard error of mean of source dipole moments (in nAm) in selected time epochs in high and low pain catastrophisers during viewing of Comfort, Touch, and Non-Touch pictures. Source 1 = left operculo-insular cortex, Source 2 = right operculo-insular cortex, Source 3 = mid-cingulate cortex, Source 4 = rostral anterior cingulate cortex, Source 5 = left parahippocampal gyrus, Source 6 = right parahippocampal gyrus.

	Epoch	High pain catastrophisers			Low pain catastrophisers		
Source	(ms)	Comfort	Touch	Non-Touch	Comfort	Touch	Non-Touch
Source 1	223–404	-8.5 ± 3.6	-8.6 ± 3.8	-10.8 ± 3.9	5.9 ± 3.6	6.5 ± 3.8	3.8 ± 3.9
	414–492	-8.0 ± 3.7	-4.9 ± 2.5	-10.1 ± 3.2	-1.9 ± 3.7	3.2 ± 2.5	1.9 ± 3.2
Source 2	353–472	-12.2 ± 3.7	-14.4 ± 4.1	-16.5 ± 4.4	-4.8 ± 3.7	-3.6 ± 4.1	0.1 ± 4.4
	459–472	-7.1 ± 3.0	-9.3 ± 3.1	-12.9 ± 3.0	-5.6 ± 3.0	-4.4 ± 3.1	1.7 ± 3.0
	705–738	-1.7 ± 1.7	4.9 ± 2.7	7.8 ± 3.0	1.5 ± 1.7	8.6 ± 2.7	7.3 ± 3.0
Source 3	210–392	-33.9 ± 5.1	-28.8 ± 4.7	-32.2 ± 5.6	-14.7 ± 5.1	-13.9 ± 4.7	-15.6 ± 5.6
Source 4	169–192	9.2 ± 8.0	10.4 ± 6.1	6.4 ± 6.4	-8.3 ± 8.0	-6.1 ± 6.1	-15.9 ± 6.4
	363–517	-8.1 ± 2.6	-6.7 ± 2.9	-9.7 ± 3.0	3.9 ± 2.6	6.3 ± 2.9	4.2 ± 3.0
Source 5	714–735	-6.5 ± 6.3	14.5 ± 6.2	20.6 ± 8.7	-0.1 ± 6.3	13.3 ± 6.2	17.1 ± 8.7
Source 6	438–506	1.9 ± 3.8	-1.7 ± 4.8	-1.6 ± 4.7	11.4 ± 3.8	12.0 ± 4.8	8.9 ± 4.7

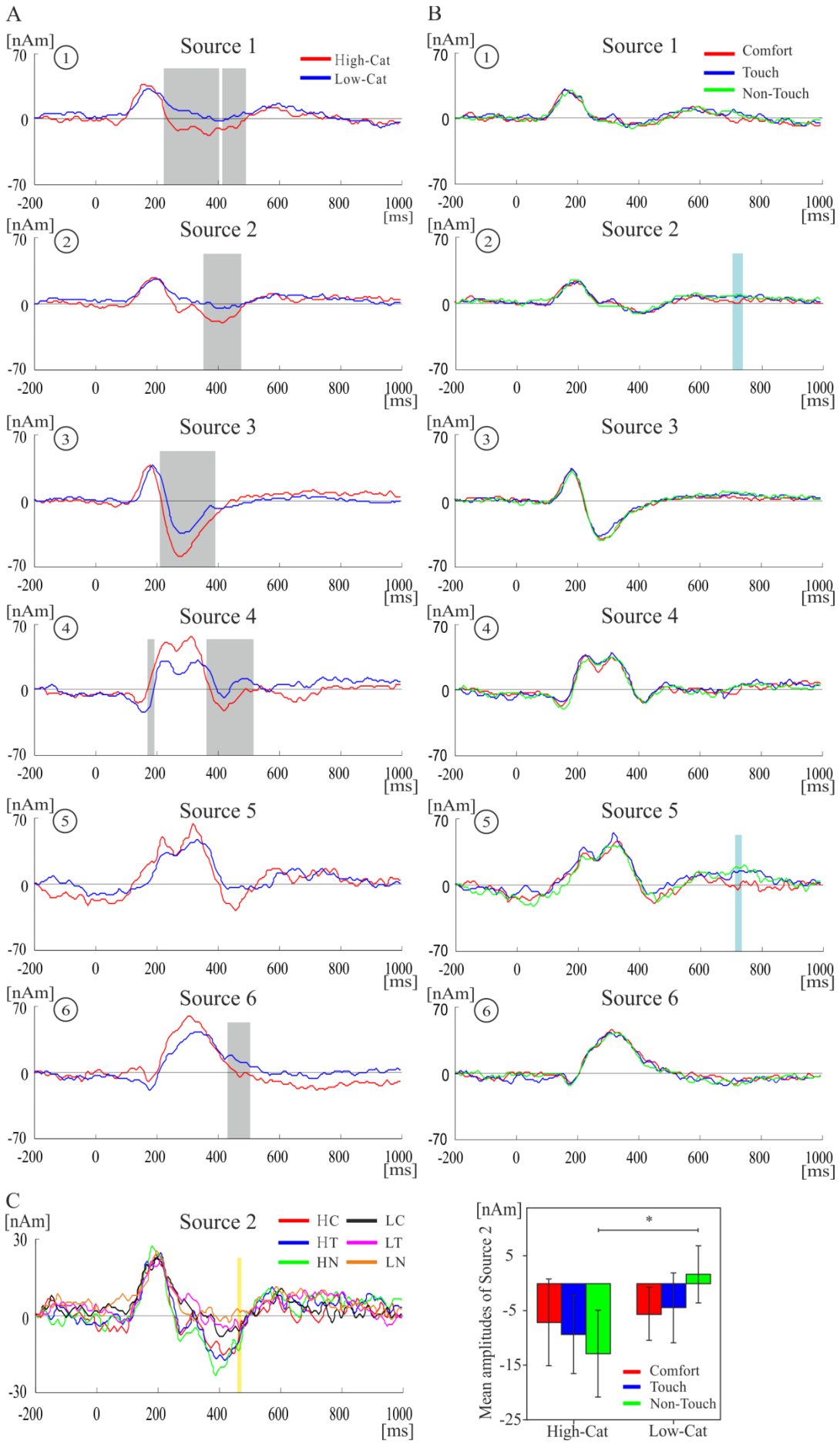
A
B
Source 1
Source 2
Source 3
Source 4
Source 5
Source 6
High-Cat
Low-Cat
Comfort
Touch
Non-Touch
[nAm]
[ms]
C
HC
HT
HN
LC
LT
LN
Mean amplitudes of Source 2
*
High-Cat
Low-Cat

Fig. 4.12 Source waveforms for laser evoked potentials with significant intervals of interest.
A. The averaged waveforms of six equivalent source dipoles in high and low pain catastrophisers, numbered from 1 to 6, during viewing pictures in high and low pain catastrophisers. Red line = High-Cat group, blue line = Low-Cat group. The grey-filled rectangles suggest epochs with significant group effects.
B. The averaged waveforms of six equivalent source dipoles for Comfort, Touch, and Non-Touch pictures. Red line = Comfort pictures, Blue line = Touch pictures, Green line = Non-Touch pictures. The blue-filled rectangles indicate epochs with a significant effect of picture type.
C. Left: The averaged waveforms of Source 2, the right operculo-insular cortex, during viewing of Comfort, Touch, and Non-Touch pictures in high and low pain catastrophisers. Red line = Comfort pictures in High-Cat group (HC), blue line = Touch pictures in High-Cat group (HT), green line = Non-Touch in High-Cat group (HN), black line = Comfort pictures in Low-Cat group (LC), magenta line = Touch pictures in Low-Cat group (LT), orange line = Non-Touch pictures in Low-Cat group (LN). The yellow-filled rectangle shows the epoch with a significant interaction between group and picture type. Right: The bar chart of Source 2 amplitudes for the three conditions between the two groups. Red line = Comfort pictures, Blue line = Touch pictures, Green line = Non-Touch pictures, High-Cat = high pain catastrophisers, Low-Cat = low pain catastrophisers. * $P < 0.05$. Error bars: 95% confidence intervals.

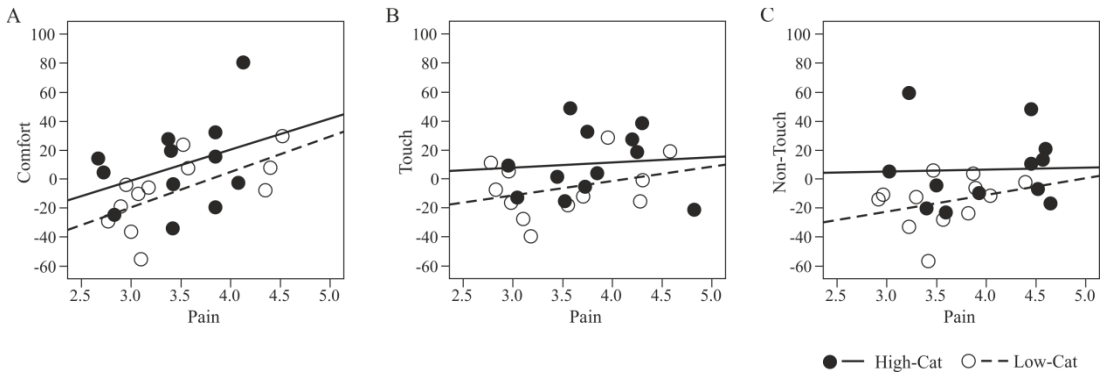

Fig. 4.13 Correlations between rostral anterior cingulate source dipole and subjective pain ratings to laser stimulation. Scatter plots and the linear regression lines illustrating relationships between subjective pain ratings attributed to laser stimuli during viewing Comfort, Touch and Non-Touch pictures, and the corresponding source amplitude of rostral anterior cingulate cortex (source 4) between high and low pain catastrophisers in the time epoch of 169–192 ms. A. Comfort. B. Touch. C. Non-Touch. High-Cat = high pain catastrophising group, dark circles, solid line. Low-Cat = low pain catastrophising group, white circles, dashed line.

4.6. Experiment 6: Pain catastrophising and structural features of cortical and subcortical brain regions in healthy people

Hypothesis:

Pain catastrophising scores in healthy people will correlate with volume and shape changes in pain processing region.

4.6.1. Demographic characteristics

The demographic data are presented in Table 4.15. The mean age was 29.6 years (SD = 8.8), with a range of 19 – 51 years. PCS scores had an average of 12.9 (SD = 9.1, Median = 11.0), with a range of 0 – 34. PCS scores were negatively correlated with age ($r(52) = -0.5$, $P < 0.0001$), indicating that younger subjects were more affected by pain catastrophising. Age, PCS scores, fear of pain, anxiety trait for both genders and anxiety state for males distributed normally according to the Kolmogorov-Smirnov test ($p > 0.05$). Anxiety state for female ($Z = 0.2$, $p = 0.014$) was not. The distributions of subjects' demographic characteristics are illustrated in Fig. 4.14. PCS scores were also positively correlated with STAI-State ($r(52) = 0.3$, $P = 0.025$), suggesting that subjects with high pain catastrophising trait may feel more emotional distress before their MR scan.

4.6.2. Correlations between total intracranial volumes and psychometrical variables

There were no statistically significant Peason's coefficient correlations between psychometrical variables (i.e. PCS, FPQ-III, STAI) and global GM, WM, CSF and total intracranial volumes ($P > 0.05$).

Table 4.15 Mean ± standard deviation (SD) of demographic characteristics and brain volumes.

	Mean	SD
Age	29.6	8.8
Pain Catastrophizing Scale	12.9	9.1
Fear of Pain Questionnaire - III	77.3	15.8
State-Trait Anxiety Inventory – State	34.3	10.2
State-Trait Anxiety Inventory – Trait	38.0	9.5
Grey matter volumes (ml)	69505	61.5
Whit matter volumes (ml)	491.1	43.6
Cerebrospinal fluid volumes (ml)	291.7	29.0
Total intra-cranial volumes (ml)	1478.3	129.2

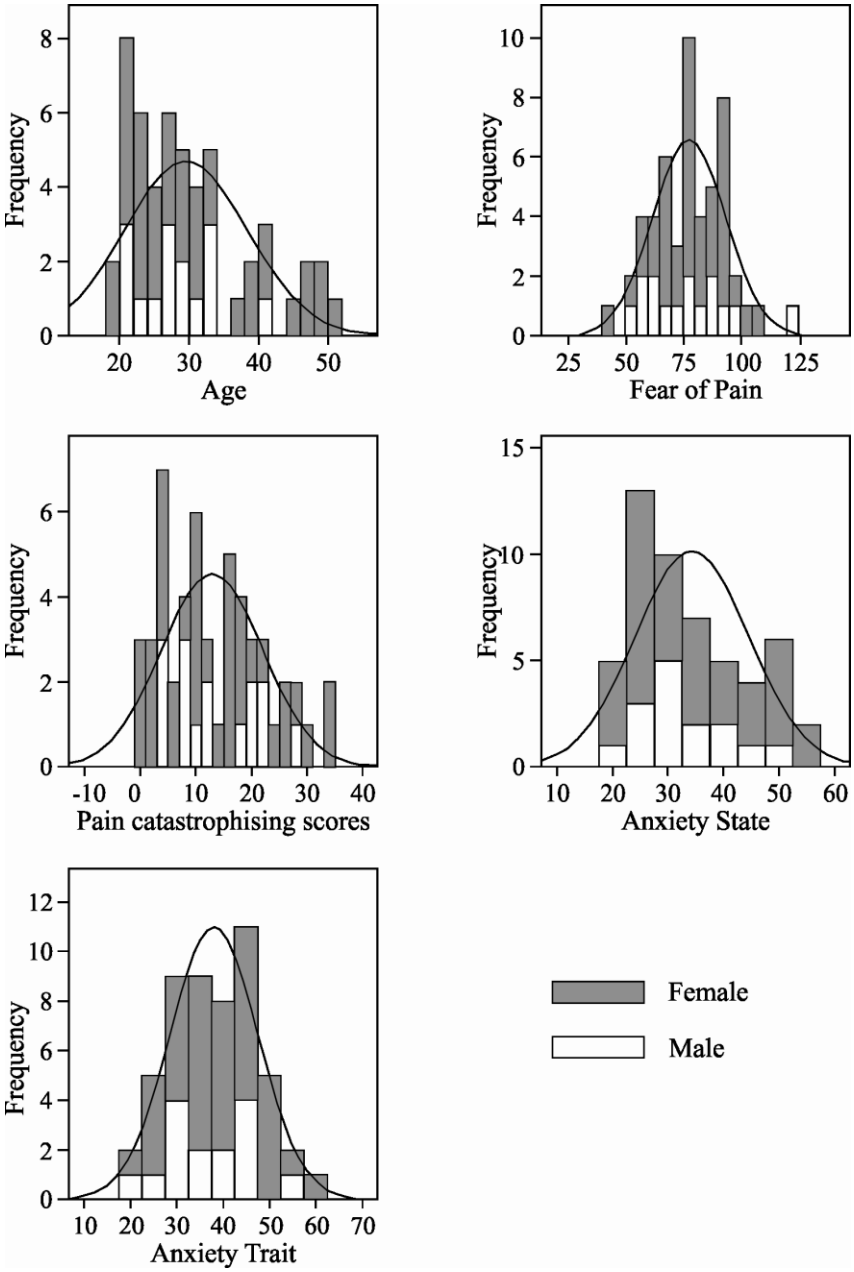

Fig. 4.14 Demographic characteristics of participants. Histogram of age, fear of pain, pain catastrophising scores, anxiety state and trait distribution of the subjects in the study. The normal distribution curves are also shown. Female = grey rectangle bars. Male = white rectangle bars.

4.6.3. Voxel-based morphometry (VBM)

After controlling for age, gender, fear of pain, and anxiety, the VBM correlation analyses (uncorrected $P < 0.001$, $k = 50$ voxels) were performed with the PCS scores as the predictor (Fig. 4.15). Results revealed positive correlations between regional GM volumes and PCS scores in right parahippocampal gyrus

(PHG), right angular gyrus, right paracentral lobule, posterior cingulate cortex (PCC), and left middle temporal gyrus, suggesting an increase in grey matter with increasing PCS scores (Table 4.16, Fig. 4.16). The reversed correlation analysis demonstrated GM volume reductions with increasing PCS scores in the left superior frontal gyrus (Table 4.16, Fig. 4.16). Pearson's correlation analyses showed that GM volumes of ROIs were significantly correlated with PCS scores ($P < 0.05$), but not with FPQ-III scores ($P > 0.05$). The significant correlations between GM volumes of the six regions and PCS scores are shown in Fig. 4.16 and Table 4.16.

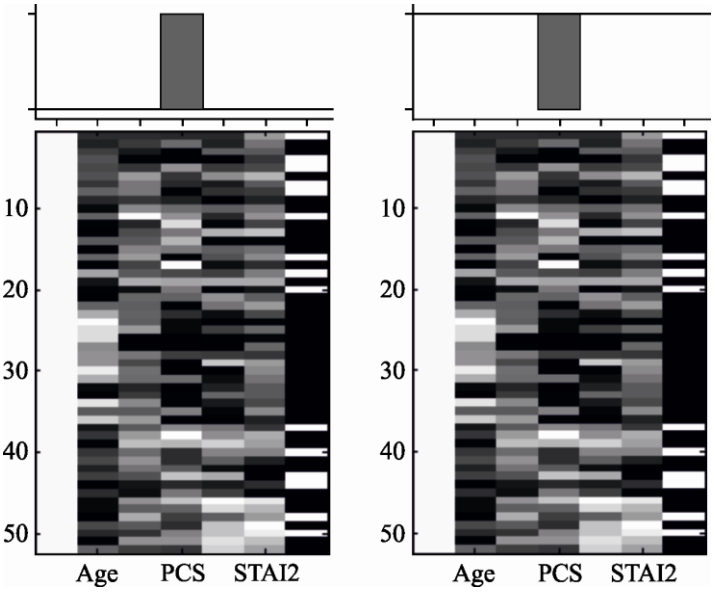

Fig. 4.15 Design matrix: Contrasts between pain catastrophising scores and regional grey matter volumes among 52 subjects. Top left panel represents the positive correlations. Top right panel indicates the negative relationships. Bottom panels demonstrates the default contrasts between the scans (first column) and six covaritates of age, fear of pain, PCS, anxiety state and trait (from the second to sixth columns, respectively). PCS = pain catastrophising scores, STAI2 = State-Trait Anxiety Inventory – Trait.

Table 4.16 Local grey matter volume in healthy people. Coordinates of grey matter volume regions controlled for multiple comparisons with uncorrected P < 0.001, and a cluster extent of 50 voxels.

Location	Brodmann Area	Coordinate MNI	k	T	Z	P
Grey matter: positive correlation						
Right parahippocampal gyrus	36	39 -31 -19	255	4.6	4.2	< 0.0001
Right angular gyrus	39	46 -65 32	505	4.3	3.9	< 0.0001
Right paracentral lobule	5	1 -44 54	346	3.9	3.6	< 0.0001
Posterior cingulate cortex	31	3 -35 46	346	3.6	3.3	< 0.0001
Left middle temporal gyrus	39	-41 -51 7	76	3.6	3.4	< 0.0001
Grey matter: negative correlation						
Left superior frontal gyrus	8	-14 41 40	1065	4.0	3.7	< 0.0001
Left superior frontal gyrus	8	-14 48 28	1065	3.4	3.2	0.001

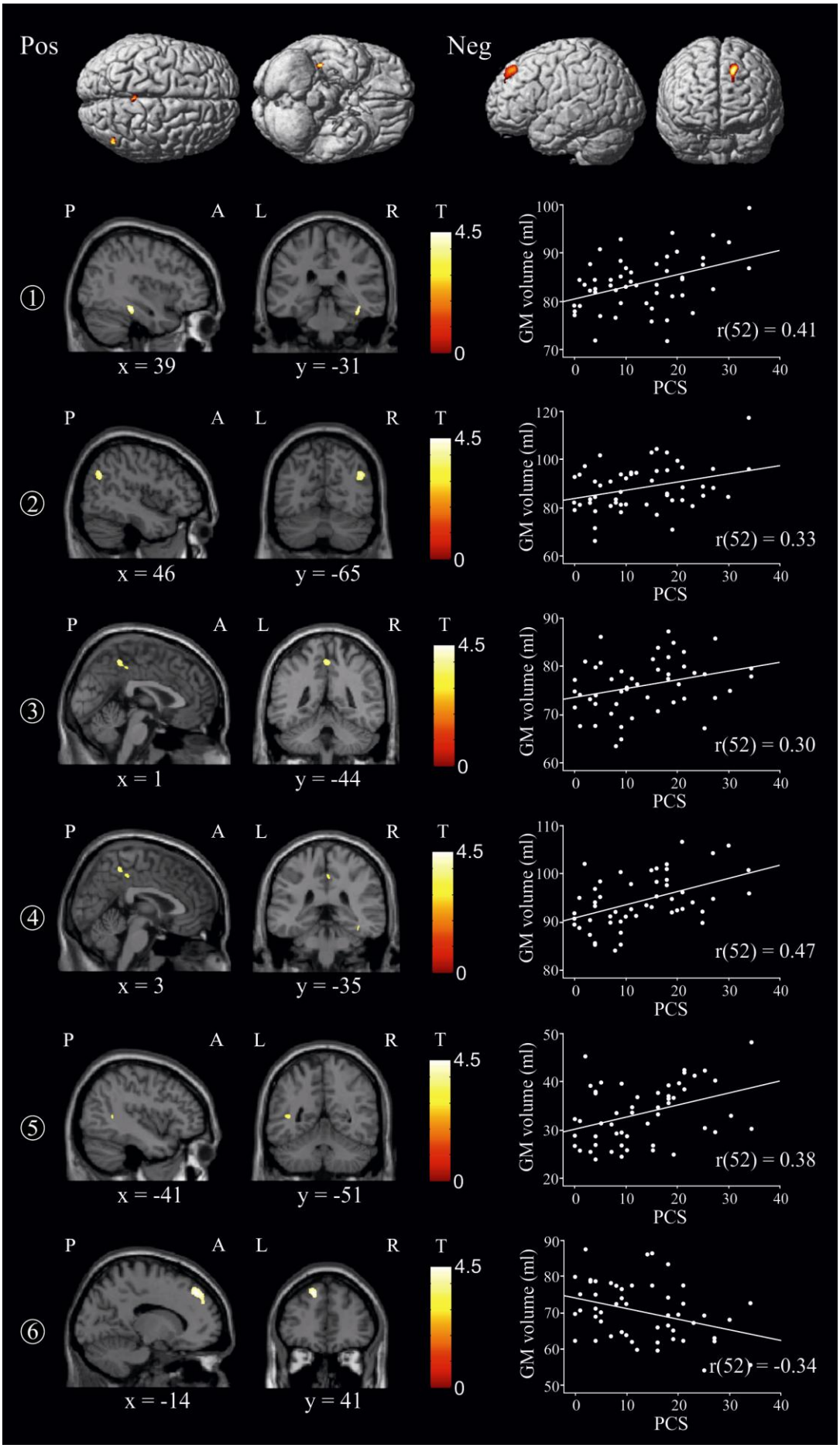
Pos
Neg
P
A
L
R
T
4.5
0
①
x = 39
y = -31
GM volume (ml)
PCS
r(52) = 0.41
②
x = 46
y = -65
r(52) = 0.33
③
x = 1
y = -44
r(52) = 0.30
④
x = 3
y = -35
r(52) = 0.47
⑤
x = -41
y = -51
r(52) = 0.38
⑥
x = -14
y = 41
r(52) = -0.34

Fig. 4.16 Correlations between grey matter (GM) volume and PCS scores. Upper: The rendering of the cortical regions in which PCS scores were positively (top left panel) and negatively (top right panel) correlated with GM volume (uncorrected $P < 0.001$ with a cluster extent of 50 voxels, for all shown effects), while controlling for age, gender, fear of pain, and anxiety. Lower: Saggittal and horizontal views and the corresponding scatter-plot and regression line of the relationship between PCS scores and GM volume alternations in each region of significant results on the averaged T1-weighted MR image of 52 subjects. Yellow clusters show the locations of the significant clusters in the rendering and anatomical views. The colour bars represent voxel-level T statistical values. The mean cluster GM volumes are extracted from the spherical ROI with a 5 mm radius at the peak voxel. The regression lines and Pearson's correlation coefficient ($P < 0.05$) are shown in the graphs. The ROIs are numbered from 1 to 6. 1 = right parahippocampal gyrus (sphere at [39 -31 -19], 220 voxels), 2 = right angular gyrus (sphere at [46 -65 32], 353 voxels), 3 = right paracentral lobule (sphere at [1 -44 54], 241 voxels), 4 = posterior cingulate cortex (sphere at [3 -35 46], 83 voxels), 5 = left middle temporal gyrus (sphere at [-41 -51 7], 76 voxels), 6 = left superior frontal gyrus (sphere at [-14 41 40], 417 voxels). Pos = positive correlations, Neg = negative correlations, A = anterior, P = posterior, L = left, R = right.

4.6.4. Shape analysis

Vertex analysis was performed to investigate the correlations between the vertex locations of 15 subcortical structures and PCS scores, adjusted for gender. The left caudate and bilateral putamen showed significant positive correlations with PCS scores following FDR correction ($p < 0.05$, corrected, Fig. 4.17). The left caudate demonstrated an outward movement of the vectors on the ventral medial surfaces ($P < 0.001$). The caudal dorsal and ventral medial surfaces of left putamen showed outward movements of the vectors ($P = 0.02$). Also, the vectors showed outward movements on the ventral medial and dorsal lateral aspects of right putamen ($P = 0.01$). Results suggested volume expansions in these regions, indicating that subjects with higher pain catastrophising trait may have a larger size of these three sub-cortical structures. Fig. 4.17 shows the significant locations and F-statistics of

the shape change of the left caudate and bilateral putamen positively correlated with PCS scores.

Linear regression analysis was performed to evaluate the relationships between the volumes of left caudate and bilateral putamen and PCS scores. No significant correlations between PCS scores and left caudate ($B = -0.1$, $p > 0.05$), between PCS scores and left putamen ($B = 0.2$, $p > 0.05$), or between PCS scores right putamen ($B = 0.2$, $p > 0.05$) were found.

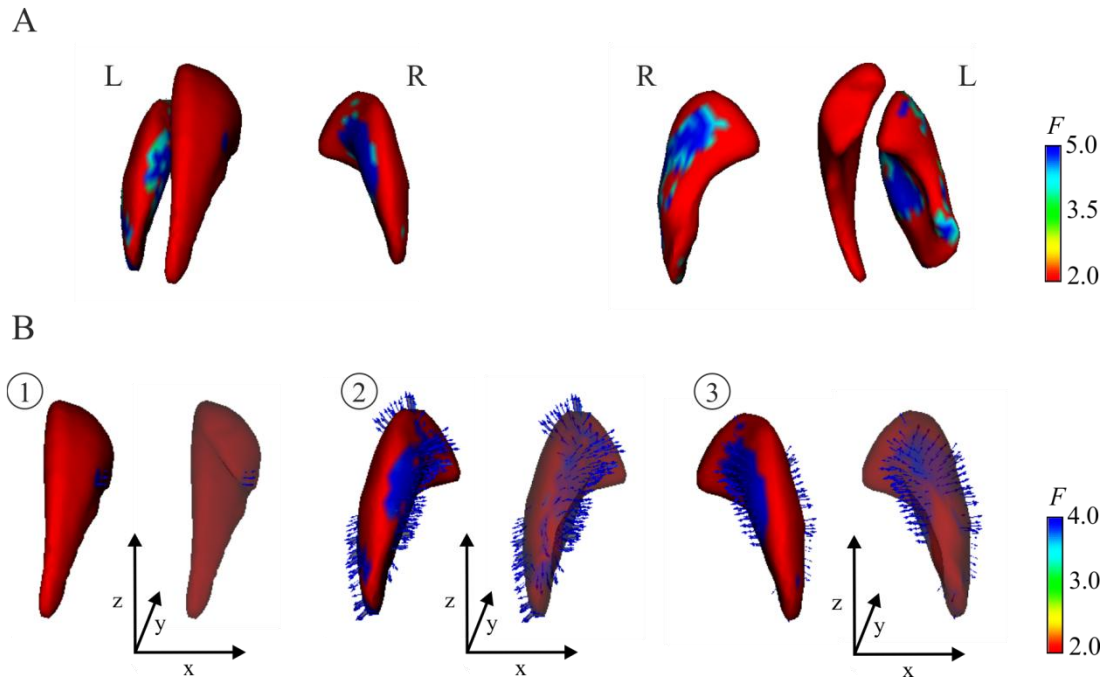

Fig. 4.17 Shape alterations positively correlated with PCS scores in the left caudate and bilateral putamen. A. The local regions exhibit shape changes in the left caudate and bilateral putamen following FDR correction. B. The locations of shape alterations and the corresponding semi-transparent images following FDR correction. Outward directions of vectors represent the outward position of vertices indicative of shape expansion. Arrow colour and surface colour indicate the *F*-statistic of the change in the specific vertices (see colour bar). Red colour indicates areas which did not differ significantly following FDR correction. 1 = left caudate, 2 = left putamen, 3 = right putamen, L = left, R = right.

Chapter Five

Study Discussions

5.1. Experiment 1: Effects of pain catastrophising on the classification of ambiguous pain

Since high pain catastrophisers are continuously ready to respond to pain cues, they become experts at recognising pain in others. Experiment 1 was the first behavioural study using visual scrambled stimuli to investigate attentional sensitivity to pain cues in high and low pain catastrophisers. The main findings of this study were as follows.

- High- compared to low pain catastrophising individuals attributed greater pain, stronger negative emotion, and more arousal to pictures depicting pain in others.
- All participants identified pain pictures with a higher level of background noise than negative emotional pictures, and with a lower level than neutral pictures.
- High- and low pain catastrophisers did not differ in detection threshold or confidence during viewing of scrambled pain, neutral, and negative emotional pictures.

The present data confirms that individuals with high pain catastrophising report stronger pain to pain scenes compared to low pain catastrophisers, even though the information was buried in an ambiguous background. The present findings accorded with previous studies (Sullivan et al., 2006b, Martel et al., 2008), showing that high pain catastrophisers predict greater pain in others compared with low pain catastrophisers. An increased sensitivity to pain in others may explain the different pain rating patterns between groups when processing ambiguous visual pain stimuli. This hypothesis fits the features of pain catastrophising, in that pain catastrophising is associated with excessive attention to pain and with greater pain intensity (Sullivan et al., 2001b, Quartana et al., 2009).

In this study, all participants identified pain scenes at a medium scrambling level, compared with negative emotional and neutral pictures. However, pain catastrophising has not modulated the detection of pain cues. Interestingly, high pain catastrophisers demonstrated a slightly better capability to identify all stimulus types, compared to low pain catastrophising group. Especially, high pain catastrophisers identified pain scenes (45.4%) from the noisy background slightly faster than low pain catastrophising group (43.2%). Previous studies of pain catastrophising support this view (Crombez et al., 1998a, Goubert et al., 2004b), showing that pain catastrophising is associated with excessive attention to a pain threat. Although

current data showed a slightly increased sensitivity to pain cues in high pain catastrophisers, the hypothesis that high, compared to low, pain catastrophisers would identify pain cues at a higher scrambling level was not confirmed.

Furthermore, the present study found that high- compared to low pain catastrophisers mistakenly classified negative emotional scenes as pain scenes with a slightly higher frequency, even though the error rate did not reach significance. The results extend the findings by van Damme et al. (2004) who demonstrated that high pain catastrophisers had difficulty in using uncertain information about the occurrence of pain. The present findings suggest that high pain catastrophisers may overestimate the occurrence probability of pain-related information, although the impending stimuli contained only negative affect. This conclusion is supported by the study of Crombez et al. (1998b), which reported that disruption of a primary task by low-intensity pain stimuli was more pronounced in pain-free students with a high level of catastrophic thinking about pain.

The non-significant findings in the detection task may be attributed to methodological issues. A similar scrambling technique was also employed in previous studies using EEG or fMRI (Cano et al., 2009b, Esterman and Yantis, 2010, Hindi Attar et al., 2010). Compared with previous studies, the total number of stimuli in this experiment was relatively small, with a total of 45 trials. Therefore,

the current data was not sufficiently powered to detect moderate / small effects. In addition, the image coherence rate may be too slow in current study (1% per 750 ms), compared to the study by Eserman and Yantis (2010) with a rate of 1% per 75 ms. Such a slow coherence rate may lead to two consequences. One is increasing the detection accuracy. The slower the coherence rate employed, the longer the display time; therefore the lower error rates may occur. The other is subject fatigue, which may lower their attentional sensitivity and divert attention to elsewhere, due to the long experiment duration. Therefore, future research needs to be careful with the experimental design.

In summary, the current study demonstrated that high pain catastrophisers attributed greater pain to others, in comparison to low pain catastrophisers. No reliable group differences or any interactions between group and the type of scrambled stimuli were found. Therefore, this study suggested that high pain catastrophisers did not show greater sensitivity to pain cues in a noisy background.

5.2. Experiment 2 & 3: Effects of pain catastrophising on attention to pain in others: two eye movement studies

The two eye tracking studies in this thesis explored the role of observer's pain catastrophising modulating attention towards pain in others. It has been hypothesised that high levels of pain catastrophising would be associated with stronger pain estimation and greater attention towards pain scenes. In addition, the present two studies investigated whether high pain catastrophisers' attention towards others' pain was characterised by initial orienting or maintained attention to pain scenes.

The first eye tracking study (Experiment 2) employed pain and graphically matched non-pain pictures, and reported the main findings as follows.

- People with high pain catastrophising scores reported greater pain to pain scenes than low pain catastrophisers.
- Both catastrophising groups maintained longer attention to pain scenes than non-pain scenes.
- The present eye movement data failed to prove that people reporting high, compared to low, pain catastrophising paid more attention particularly to pain scenes, regardless of initial orientation or maintenance of attention indices.

- In high pain catastrophisers, but not in low pain catastrophisers, first fixation latencies to pain scenes were positively correlated with arousal, whereas gaze durations to non-pain scenes were negatively associated with subjective pain ratings.

In Experiment 2, the non-significant group differences in eye movement data during viewing of scenes depicting pain and non-pain could be attributed to several causes. First, due to the small sample size (13 High-Cat vs. 15 Low-Cat participants) in this study, statistical power was limited to detect only large effects (.80). Second, eye movement is not the sole index of attention measurements, even though the eye tracking technique allows for more precisely measuring temporal attentional dynamics. For instance, it has been shown that pain-related information was covertly processed, while neutral stimuli obtained overt gaze attention (Weierich et al., 2008). The dot-probe tasks are often used to measure attentional processing. A meta-analysis of visual-probe task study indicated that the chronic pain population showed significant attentional bias towards pain-related information during the early stage of attention orientation (Schoth et al., 2012). Therefore, the utilisation of a dot-probe task has been recommended to complement eye movement measurement in future studies (Yang et al., 2012). Last but not least, it has been addressed that emotional information can capture attention (Browning et al., 2010, Lautenbacher et al., 2010).

Attentional bias towards pain can be driven not only by pain information itself, but also by negative emotional value (Asmundson, 2012, Crombez et al., 2013). Thus, to clarify whether attentional processes differ specifically to pain stimuli or also to general negative emotional information in high and low pain catastrophisers, negative emotional stimuli those not containing pain should be employed in future studies involving pain catastrophising.

The second eye tracking study (Experiment 3) in this thesis modified the design of Experiment 2 by adding negative emotional pictures and by employing a dot-probe task. The main findings of Experiment 3 were as follows.

- High- compared to low pain catastrophisers reported greater negative affect to all picture types, including negative emotional pictures.
- Both pain catastrophising groups showed shorter first fixation latencies, and maintained longer gaze durations, to pain scenes during viewing a pair of Pain and Non-Pain pictures.
- All participants showed a cycle of disengagement followed by re-engagement towards pain and negative affective scenes, relative to non-pain scenes.
- High-Cat, but not Low-Cat, individuals showed statistically significant negative correlations between initial fixation durations to pain pictures and valence ratings.

- In the dot-probe task, a significant interaction between group and congruency was found, with Low-Cat subjects responding to congruent target-probe location significantly faster than to incongruent combinations. In addition, high pain catastrophisers were slower to respond to probes after pain scenes than low pain catastrophisers.

In these two studies, high- compared to low pain catastrophisers reported stronger pain to pain and non-pain scenes. The main effect of pain catastrophising in Experiment 3 approached significance (P = 0.068). Data from the two eye tracking studies has confirmed the results in Experiment 1 of viewing pictorial stimuli, showing greater sensitivity to pain in others in high pain catastrophisers. These findings were consistent with the previous finding that high pain catastrophisers reported more intense pain during viewing of others in a cold pressor test (Sullivan et al., 2006b). Collaborating with previous studies, the results of Experiment 1, 2, and 3 support the communal coping model of pain catastrophising (Keefe et al., 1989, Sullivan et al., 2001b, Turner et al., 2002), suggesting that high pain catastrophisers can share other's pain during the observation of pain in others.

Although eye movement data failed to provide significant results, these two studies revealed several statistically significant correlations between eye movement data and subjective picture ratings in the high pain catastrophising group.

With respect to initial attentional allocation, High-Cat individuals directed their initial attention more slowly towards pain scenes, which contained stronger arousal (Experiment 2). Data partially confirmed previous findings by (Vervoort et al., 2013a) who found that high pain catastrophising people showed decreased tendency to initially orient to pain faces. The present studies and previous data indicated that high pain catastrophisers displayed attentional avoidance to pain scenes. It has been suggested that the initial orientation pattern in high pain catastrophisers may be associated with pre-attentive processing accompanied by different emotional or behavioural consequences, which has been addressed extensively in the emotion literature (Robinson, 1998, Yao et al., 2011, Spreckelmeyer et al., 2013). Pre-attentive processing is known to facilitate stimuli detection and emotional reaction when stimuli are relevant to one's existing cognitive-affective state. In High-Cat participants, pain-related information may facilitate pre-attentive processing of Pain pictures, and trigger negative emotional responses and avoidance behaviour. In support of this view, previous studies have demonstrated that high levels of pain catastrophising may elicit personal emotional distress and associated avoidance behaviour during the viewing of pain in others (Robinson et al., 2001, Goubert et al., 2009b, Yamada and Decety, 2009, Caes et al., 2011, Caes et al., 2012a, Caes et al., 2012c).

With regards to the attentional maintenance, High-Cat participants maintained shorter initial attention towards pain scenes when stimuli were considered as more negative affective (Experiment 3), and demonstrated longer gaze durations toward non-pain stimuli with less perceived pain (Experiment 2). A previous eye movement study found that chronic pain patients reporting high fear of pain showed shorter initial fixation durations to health catastrophe words, compared with those with low fear of pain. This study indicated that explore of threat can manifest attentional avoidance to negative information (Yang et al., 2013). Therefore, the shorter first fixation durations to pain scenes in high pain catastrophisers may reflect a strategic escape tendency to minimise emotional discomfort. This tendency may last for the entire attentional processing.

In the dot-probe task, the present study found a significant interaction effect between group and congruency, indicating that selective attention to target stimuli (i.e. Pain pictures) was dependent upon the levels of pain catastrophising. The trend of attentional bias towards pain/ negative emotional stimuli was observed in Low-Cat subjects only. In addition, high- compared to low pain catastrophising individuals showed prolonged responses to probes after pain scenes. Results contribute to the view that pain catastrophising is associated with increased avoidance behaviour. Similar findings were found in a recent dot-probe study

involving pain catastrophising (Vervoort et al., 2013b). Vervoort et al. (2013b) revealed that children increasingly shifted attention away from pain faces with increasing levels of children's magnification and greater parental rumination and helplessness. People with high pain catastrophising alleviate emotional distress through attentional avoidance. The emotional regulatory function of attentional avoidance towards pain-threat information has been demonstrated in high pain catastrophisers (Caes et al., 2011, Vervoort et al., 2011a, Caes et al., 2012b, Vervoort et al., 2012). In the present study, attentional avoidance may serve a similar emotional regulatory function in High-Cat participants during viewing of pain scenes, although this strategy has been considered as maladaptive in pain catastrophisers (Vlaeyen and Linton, 2000).

The small sample size in both eye tracking studies may be one of the explanations for the non-significance of group differences. Despite limitations, the current findings concluded that high pain catastrophising individuals attributed greater pain to pain scenes, compared to low pain catastrophisers. High pain catastrophisers showed a tendency of attentional avoidance to pain scenes in the early and late stages of attention processing during viewing pain in others. The present studies supported the cognitive-affective model (Eccleston and Crombez, 1999), and proposed that pain imposed an overriding attentional priority that

motivated avoidance behaviour, particularly in the context of pain catastrophising (Sullivan et al., 2001b, Quartana et al., 2009).

5.3. Experiment 4: Pain catastrophising effects on the cortical responses to viewing pain in others

Experiment 4 utilised ERP analyses to investigate the neural basis of viewing pain in others in high and low pain catastrophisers during viewing of pain and non-pain scenes. The main findings were as follows.

- High-Cat individuals reported stronger pain and unpleasantness to pain scenes than Low-Cat people. They also attributed stronger pain to non-pain scenes.
- Low-Cat compared to High-Cat subjects manifested stronger cortical responses in the early latency window (280–450 ms) in the rACC, PHG_R, and PCC, whereas High-Cat participants showed greater activations in the late latency period (600–1100 ms) in PHG_L and PCC.
- In Low-Cat subjects, only the activation in PHG_L in the early latency period (284–308 ms) differentiated between pain and non-pain pictures, with pain pictures showing greater source activity than non-pain pictures.
- Only the Low-Cat group showed statistically significant correlations between cortical activity in PCC in the late latency epoch and pain and arousal ratings.

Participants with high pain catastrophising scores attributed stronger pain and unpleasantness to visual scenes depicting potential somatic pain in others than participants with low pain catastrophising scores. Interestingly, the high pain catastrophising group also attributed pain to pictures depicting low risk of pain, suggesting that high pain catastrophising subjects would likely interpret scenes and stimuli as painful based on a remote, indirect and small possibility of pain being inflicted. Such generalisation in processing visual pain stimuli may be one of the cognitive distortions leading high pain catastrophisers to attribute pain to a large variety of cues with pain connotations. The present findings corroborated previous experimental data suggesting that high-pain catastrophisers attribute stronger pain to people undergoing the cold pressor test compared to low-pain catastrophisers (Sullivan et al., 2001a, Sullivan et al., 2006a).

The early latency window (280– 450 ms) corresponding to the P300 (300– 500 ms) component, displayed a spatial maxima in parietal electrodes (Hajcak et al., 2011, Fan and Han, 2008; Han and Li, 2010; Han et al., 2008). Previous studies have indicated that P300 may reflect semantic content evaluation of pictures (Schupp et al., 2003b, Schupp et al., 2004a, Hajcak et al., 2011). The current study revealed that Low-Cat, but not High-Cat, participants exhibited an augmented P300 activation to pain pictures in the early time window of PHG_L. Similar findings were

shown in a pain empathy study in which pain pictures elicited greater P300 activations in comparison to non-pain pictures in healthy individuals (Decety et al., 2010). The present findings also showed that High-Cat, compared to Low-Cat, people displayed smaller P300 amplitudes in rACC, PHG_R and PCC. It has been suggested that rACC, PHG, and PCC are involved in the pain processing (Peyron et al., 2000, Tracey, 2008). An alternative explanation is that the weaker source activations in high pain catastrophisers may reflect an implicit bias of interpreting graphically matching non-pain pictures as containing threatening pain information (Duckworth et al., 2002, Tran et al., 2011). This bias may lead to an incline of negative interpretation of innocuous stimuli (Carroll et al., 2011, Liossi et al., 2012), and weaken the differentiating ability of pain in high pain catastrophisers. This account is complemented by behavioural data with high pain catastrophisers attributing pain to non-pain stimuli. An eye tracking study also supported this explanation with high pain catastrophisers initially fixating equally on pain and non-pain faces (Vervoort et al., 2013a). Therefore, corresponding with previous data (Singer et al., 2004, Jackson et al., 2005, Jackson et al., 2006, Singer et al., 2006, Gu and Han, 2007, Lamm et al., 2007b, Fan and Han, 2008), this study proposed that the neural structures of rACC, PHG and PCC modulated the semantic decoding and

discriminative functions in the early time window of emotional picture evaluation in high pain catastrophisers.

The long latency window (600 – 1100 ms), in contrast, showed a stronger cortical activity in High-Cat, compared to Low-Cat, subjects in PHG_L and PCC. The long-latency window corresponds to the late positive potential (LPP) evoked by emotional pictures (Schupp et al., 2003a, Schupp et al., 2004a, Schupp et al., 2004b, Hajcak et al., 2011), affective faces (Werheid et al., 2007), and emotional facial expressions (Eimer and Holmes, 2007). This positive potential usually operates from 500 ms following picture onset, identified at the centro-parietal regions, and is associated with less semantic processing and more emotional processing. The present findings were consistent with a previous ERP study that found that negative pictures elicited stronger activations of PCC and PHG in the late positivity component in females (Proverbio et al., 2009). In addition, it has been postulated that the LPP is indicative of increasing influence of top-down processes (Olofsson et al., 2008, Foti et al., 2009, Weinberg and Hajcak, 2010). ERP studies suggested that phobic participants with successful cognitive-behavioural therapy engaged in less avoidance of their feared stimuli in order to regulate their emotional responses by showing enhanced LPPs (Leutgeb et al., 2009, Leutgeb et al., 2012). A recent ERP study also reported larger LPPs were elicited when people with high empathic trait

were viewing pain and non-pain pictures (Ikezawa et al., 2013). In the present study, stronger cortical activation to pain and non-pain pictures in high pain catastrophisers complemented the suggestion of retarded disengagement from pain in high pain catastrophisers (Van Damme et al., 2002b, Van Damme et al., 2004). Furthermore, the current results showed significant associations between augmented PCC activation to pain pictures in the late time window and arousal and pain ratings in Low-Cat subjects only. It indicated the overt responses to scenes implying even a remote possibility of bodily harm in high pain catastrophisers. Thus, high pain catastrophising appears to affect empathy disposition and emotion contagion during viewing of pain pictures.

Increased source activity in bilateral medial temporal cortices was reported during viewing emotional pictures. It has been suggested that the hippocampus is involved in emotional regulation of pain (Ploghaus et al., 2001, Stancak et al., 2012, Stancak et al., 2013). The parahippocampal gyrus is also well known for its involvement of the retrieval of emotional memory (Goosens, 2011). A meta-analysis review of emotion suggested that the right hippocampus was more likely to be activated by any instance of emotion in a face, body or voice, whereas the left side was more likely to link with the encoding of salient stimuli in memory (Lindquist et al., 2012). Therefore, the converse patterns of right and left parahippocampal

activations mediated by pain catastrophising in different time frames may suggest that people with high pain catastrophising performed blunted semantic analysis of pain and non-pain scenes in the beginning, then recalled their memory for emotion sharing in the late stage of empathy processing.

Taken together, observation of pain in others during passive viewing of photographs depicting high or low probability of pain being inflicted shows substantial differences in spatio-temporal patterns of cortical activation between High-Cat and Low-Cat individuals. High-Cat participants show a blunted cortical response in the latency from 280 to 450 ms corresponding to the period of semantic decoding of picture content (Schupp et al., 2003a, Schupp et al., 2003b, Schupp et al., 2004a, Schupp et al., 2004b, Schupp et al., 2007, Hajcak et al., 2011). The cortical activity in PHG_L in High-Cat subjects fails to disentangle pain and non-pain pictures suggesting a reduced capacity to evaluate the degree of threat in a visually presented scene depicting a certain risk of pain being inflicted. Further, high pain catastrophisers show stronger cortical responses in the late latency window (> 600 ms) in PHG_L and PCC. The lack of statistically significant correlations between source strength of the PCC dipole and pain and arousal ratings in High-Cat subjects suggest their undifferentiated and amplified response during this latency period, which has been shown to be associated with emotional processing of pictures. It thus

seems that attribution of comparatively high level of pain to others in high pain catastrophisers rests with their limited capacity for semantic decoding of visual stimuli involving a risk of pain being inflicted in the early latency period, and their enhanced and undifferentiated cortical activation in the later, emotional processing stage.

5.4. Experiment 5: Pain catastrophising effects on the cortical responses to laser stimulation during viewing of comforting hand postures

Experiment 5 used EEG recordings and laser stimulation to investigate the cortical responses to perceived pain during viewing of hand postures depicting a comforting touch, touch, and non-touch in high and low pain catastrophisers. The main findings were as follows.

- Subjects with high pain catastrophising scores reported less pain intensity during the observation of Comfort scenes, compared to Touch and Non-Touch conditions.
- A statistically significant interaction between group and picture type was found, with high- compared to low pain catastrophisers showing greater source activity in the right operculo-insular cortex (459–472 ms) when viewing Non-Touch pictures.
- High- compared to low pain catastrophisers manifested stronger cortical responses to noxious stimuli in the bilateral opercular-insular cortices, MCC and rACC, whereas low pain catastrophisers displayed stronger cortical activation in the PHG_R.

- Only subjects reporting low pain catastrophising scores demonstrated a significant positive correlation between source activation in the rACC in the early latency and perceived pain ratings during viewing of Comfort pictures.

High pain catastrophisers perceived less pain when observing the Comfort pictures, compared with the other two conditions. Previous studies have suggested that chronic pain patients with high pain catastrophising have a high demand for support from their spouse or partner (Keefe et al., 2003, Boothby et al., 2004, Cano, 2004, Buenaver et al., 2007). Cano (2004) also suggested pain catastrophising was associated with positive support during a short period of pain. Consistent with previous data, the present findings support the communal coping model of pain catastrophising (Sullivan et al., 2001b, Quartana et al., 2009), suggesting high pain catastrophisers can mitigate their pain through soliciting social support, such as viewing comforting hand postures.

Compared to the low pain catastrophising group, people with high pain catastrophising showed stronger cortical activation to laser evoked pain in the right operculo-insular cortex (459–472 ms) during viewing of Non-Touch pictures. Posterior insula is considered as one of the major pain processing regions (Peyron et al., 2000, Apkarian et al., 2005), and shows an early activation during noxious stimulation (Tarkka and Treede, 1993, Bromm and Chen, 1995, Iannetti et al.,

2005). This region has been universally reported as the generator of N1 LEP component (Ploner et al., 2002, Garcia-Larrea et al., 2003, Iannetti et al., 2008). Posterior insula and the adjacent secondary somatosensory cortex (SII) receive the majority of afferent fibres from the spino-thalamic tract (Dum et al., 2009), specialising in conveying emotional information, such as pain (Craig, 2002). Lesions in the region of posterior insula are associated with chronic pain and disturbances in thermoception (Garcia-Larrea et al., 2010). Moreover, activity in the posterior insula correlated with subjective reports of pain intensity (Stančák et al., 2011) suggesting its involvement in the evaluation of the sensory component of pain. Further, a placebo study implicated the role of insula in pain exacerbation, with suppressed insula activation in the pain placebo condition (Wager et al., 2004). In addition, the sensation of pleasant touch is produced by the activation of C-tactile afferents (Olausson et al., 2002, Loken et al., 2009), which project to insular cortex (Björnsdotter et al., 2010). Previous studies have showed posterior insular activation during C-tactile stimulation (McCabe et al., 2008, Liljencrantz et al., 2013). Similar activation in the posterior insula was also found in studies of observing touch (Keysers et al., 2004, Keysers et al., 2010, Morrison et al., 2011a). Therefore, the long lasting activation in the posterior insula suggested that high pain catastrophisers may prolong and amplify their cortical responses to perceived pain,

especially, when perceived support was not available. This finding is in accord with the communal coping model of pain catastrophising; catastrophisers are prone to reduce their pain perception and pain-related distress via seeking social-emotional support (Keefe et al., 1989, Sullivan et al., 2001b, Turner and Aaron, 2001, Turner et al., 2002).

Passive viewing comforting pictures also enhanced pain responses in operculo-insular cortices, MCC and rACC in high, compared to low, pain catastrophisers. All these structures have been proposed as core regions engaging in pain processing (Peyron et al., 2000, Tracey and Mantyh, 2007, Tracey, 2008). The significant group differences in these areas indicated that cortical responses to noxious pain were independent of the levels of observed comfort-giving pictures in high pain catastrophisers. Furthermore, previous studies involving pain catastrophising have reported that high pain catastrophisers exhibited augmented cortical responses to painful stimuli in the rACC in both chronic pain patients and healthy population (Gracely et al., 2004, Seminowicz and Davis, 2006). The ACC activity is associated with the affective dimension of pain (Rainville et al., 1997) and pain empathy (Singer et al., 2004), and is correlated with subjective ratings of other's pain (Jackson et al., 2005). The current study found that increased rACC activation in the early time window (169− 192 ms) was significantly correlated with

perceived pain while viewing Comfort pictures in low pain catastrophisers only. The non-significant correlation in high pain catastrophisers may indirectly support the hypothesis that viewing comforting hand postures may diminish the perceived pain in people with high pain catastrophising. This suggestion was also supported by the behavioural data that high pain catastrophisers rated less pain intensity when attending to Comfort pictures.

Finally, suppressed activation in right parahippocampal gyrus (438– 506 ms) was observed in high pain catastrophising group, during viewing of comfort-giving pictures. Activation of PHG_R corresponds to the P3 LEP component (Legrain et al., 2002, Legrain et al., 2003, Stancak et al., 2013). This component can be modulated by attending to emotional sounds (Stancak et al., 2013) and pictures (Stancak and Fallon, 2013), and rare stimuli (Kanda et al., 1996). In addition, studies of pain empathy demonstrated that the augmented P3 amplitudes were elicited by viewing pain-related pictures in the absence of physical pain (Fan and Han, 2008, Decety et al., 2010, Li and Han, 2010, Ibáñez et al., 2011, Meng et al., 2012). Parahippocampal gyrus has been shown to be activated by noxious stimuli (Valeriani et al., 1996, Valeriani et al., 2000, Ploghaus et al., 2001, Fairhurst et al., 2007, Piche et al., 2010). Moreover, as the part of the entorhinal cortex (Insausti and Amaral, 2004), the parahippocampal gyrus is proposed to be a part of the

emotion processing network (Lindquist et al., 2012). The decreased activity in the PHG_R may implicate that top-down attention was drawn away from the painful stimuli in high pain catastrophisers during the observation of social-emotional gestures, such as support. Therefore, viewing comfort-giving hand postures may attenuate the affective dimension of pain in high pain catastrophisers.

In conclusion, high-pain catastrophising people showed a reduction in pain while viewing comforting hand postures compared to non-comforting scenes. The present study also provides ERP evidence for effects of comfort-giving on the cortical responses to pain in the context of pain catastrophising. It suggests enhanced cortical activations in regions belonging to the pain network among high pain catastrophising individuals, implying that such populations over-react to pain-related stimuli. Only the long-latency activation in the ipsilateral operculo-insular cortex showed a modulation by picture type and pain catastrophising matching the pattern of perceived pain intensity. The current data suggests that pain in high-pain catastrophising individuals is modulated by the context of social-emotional cues, and that such modulation appears to be related to activation changes in the ipsilateral operculo-insular cortex.

5.5. Experiment 6: Pain catastrophising and structural features of cortical and subcortical brain regions in healthy people

Experiment 6 aimed to investigate the relationship between pain catastrophising scores and shape and volume changes of the brain in healthy people. The main findings were as follows.

- Shape analysis revealed significant positive associations between shape alterations in the left caudate and bilateral putamen and pain catastrophising, after controlling for gender.
- VBM analysis found significant positive correlations between the PCS scores and grey matter volumes in the right PHG, right angular gyrus, right paracentral lobule, PCC, and left middle temporal gyrus, and significant negative correlations in the left superior frontal volumes, after controlling for age, gender, fear of pain and anxiety.

In individuals with high PCS scores, expansions of shape were observed in the left caudate and bilateral putamen. The caudate and putamen constitute the dorsal striatum (Grahn et al., 2008). The striatum is commonly activated by noxious stimuli, including thermal (Tracey et al., 2000, Oshiro et al., 2009), pressure (Gracely et al., 2004), electrical (Downar et al., 2003, Freund et al., 2009) and laser (Bingel et al.,

2004) pain. Interestingly, Starr et al. (2011) reported that lesions in putamen caused reductions in pain perception. Chronic pain has also been shown to increase GM in the putamen (Schmidt-Wilcke et al., 2007, Younger et al., 2010) and caudate (Schweinhardt et al., 2008, DeSouza et al., 2013). These structural alterations in the dorsal striatum may be a compensatory action against nociceptive inputs. Dorsal striatum has been suggested as a key region in motor processing (Grahn et al., 2008, Knutson et al., 2009). Primate studies suggest dorsal striatum is sensitive to habit forming in the putamen (Deffains et al., 2010) and to dynamically changing reward outcomes in the caudate (Hikosaka et al., 1989). A meta-analysis study indicated that dorsal striatal lesions were more likely to compromise motor execution (Bhatia and Marsden, 1994). In addition, it should be noted that an fMRI study of fibromyalgia reported that pain activated the lentiform nuclei (i.e., the putamen and globus pallidus) bilaterally only in high pain catastrophisers (Gracely et al., 2004). The authors postulated that this unique activation may reflect that pain catastrophising is associated with dysfunctional motor control, such as greater pain behaviour and increased pain-related emotional expressions.

Dopamine release in the striatum in response to noxious stimuli leading to endogenous antinociception has been reported in healthy people (Scott et al., 2006, Wood et al., 2007). Furthermore, increased GM in the striatum may be caused by a

lack of dopamine in clinical pain conditions (Schmidt-Wilcke, 2008). Supporting this view, a dopaminergic alteration in the dorsal striatum has been previously reported in chronic pain patients (Jääskeläinen et al., 2001, Hagelberg et al., 2003, Wood et al., 2007). Therefore, expansions of the striatum shape in this study may be related to a defence mechanism in high pain catastrophisers. Catastrophisers may inhibit their pain via the dopaminergic activation of the striatum.

The functional role of hippocampus/parahippocampal gyrus has been suggested to involve pain modulation (Ploghaus et al., 2001, Bingel and Tracey, 2008, Berna et al., 2010) and regulation of negative affective (Hobin et al., 2006, Herry et al., 2008, Barkus et al., 2010, Goosens, 2011, Stancak and Fallon, 2013, Stancak et al., 2013). Augmented hippocampal activation was triggered by anxiety induced by the uncertainty of the occurrence of painful stimuli (Ploghaus et al., 2001), indicating that hippocampus reflects the activation of the pain-related anxiety (McHugh et al., 2004). Recent VBM studies have suggested that anxiety is associated with increased parahippocampal volume in patients with social anxiety disorder (Talati et al., 2013), and in the general healthy population (Wei et al., 2014). In an fMRI study using electrical stimulation on tooth pulp, hippocampal activation correlated positively with PCS scores only in the stressful context modulated by unpredictability (Lin et al., 2013). Consistent with the findings in a VBM study of

chronic vulvar pain patients (Schweinhardt et al., 2008), the present study revealed a similar positive relationship between pain catastrophising and the volume of parahippocampal gyrus. Thus, the present findings and those of previous studies suggest that a larger parahippocampal volume is associated with a vulnerability of social-psychological stress to healthy subjects with high pain catastrophising.

Previous papers have suggested the role of hippocampus in the regulation of stress hormones (such as, cortisol) secretion (Goosens, 2011). Cortisol levels in healthy people have been reported to negatively correlate with pain threshold during stress (Choi et al., 2012), and positively associate with pain severity during a cold pressor task (Goodin et al., 2012). Studies have shown that hippocampal deactivation was associated with an increase in cortisol secretion in a psychosocial stress task (Pruessner et al., 2008). In addition, Pruessner et al. (2005) reported that larger hippocampal volumes were associated with lower cortisol secretion in response to a stressor. Pain catastrophising has been associated with corticol decline in pain patients (Edwards et al., 2008, Johansson et al., 2008). Collectively, larger hippocampal/parahippocampal volumes in healthy people with high pain catastrophising may indicate a stronger control over stress hormone secretion. Pain catastrophising may be associated with abnormal hypothalamic-pituitary-adrenal axis activity in the healthy population.

In the present study, other regions showing positive correlations between GM and PCS scores were the right angular gyrus, PCC, right paracentral lobule, and left middle temporal gyrus. The brain regions of inferior parietal cortex (IPL; mainly angular gyrus) and PCC are structures of the default mode network, which may reflect the neuronal baseline activity of the human brain in the absence of external stimulation (Gusnard et al., 2001, Raichle et al., 2001, Laird et al., 2009). Deactivation of the PCC has been shown during experimental pain (Seminowicz and Davis, 2007, Kong et al., 2010). A recent neuroimaging study by Kucyi et al. (2013) found that the mind wandering away from pain enhanced cortical activation in the PCC. Increased IPL volume associated with reduced pain sensitivity in healthy people was reported in a VBM study (Emerson et al., 2014). The IPL is associated with spatial attention processing of pain (Yantis et al., 2002, Oshiro et al., 2007, Lobanov et al., 2013). Thus, high pain catastrophisers with increased GM in PCC and IPL may be more likely to maintain top-down attention to pain-related stimuli. In addition, activity in the paracentral lobule, corresponding to the supplementary motor areas, has also been associated with pain processing (Peyron et al., 2000, Oshiro et al., 2009).

Individuals with high PCS scores exhibited decreases in GM in left superior frontal gyrus, including the dorsolateral prefrontal cortex (DLPFC). The DLPFC has

been implicated in the descending modulation of pain (Lorenz, 2003). Pain catastrophising has been described as a maladaptive cognitive ability to cope with pain (Sullivan et al., 2001a, Quartana et al., 2009). Together with previous VBM findings of chronic pain patients (Blankstein et al., 2010, Seminowicz et al., 2013), the decreased volumes of DLPFC in current study may suggest a lack of control of pain processing in normal people with high pain catastrophising. Consistent with this view, healthy volunteers with high PCS scores showed a stronger negative correlation with activity in DLPFC during moderate intense pain stimulation (Seminowicz and Davis, 2006).

In summary, the present study provides evidence for a relationship between pain catastrophising and volume and shape alterations in a healthy population. Results suggest that increased volumes in regions participating in emotional processing (parahippocampal gyrus), pain (PCC), and frontal and temporal association cortices may predispose to a heighted level of pain catastrophising. Also, morphological changes in dorsal striatum contribute to the alteration of pain processing.

Chapter Six

General Discussion

Pain catastrophising, an exaggerated negative orientation towards actual and anticipated pain, is increasingly considered as an important factor in the experience of pain (Sullivan et al., 2001b). This thesis addressed behavioural, cognitive, and neural aspects of pain catastrophising in healthy people. The findings are relevant for the evaluation of three key models of pain catastrophising, the appraisal model, the attentional model, and the communal coping model (Sullivan et al., 2001b, Quartana et al., 2009).

6.1. Appraisal model

Pain catastrophising has been referred to as an appraisal problem (Jensen et al., 1991). The appraisal model of pain catastrophising suggests that individuals initially assess and evaluate the threat of pain during the primary appraisal stage , and cope with pain threat maladaptively during the secondary appraisal stage (Severeijns et al., 2004). Pain catastrophising, according to the appraisal model, is a distorted cognitive characteristic of potentially painful situation, similar to depression. In the cognitive model of depression, pain catastrophising is considered as a cognitive distortion that might contribute to the maintenance of symptoms of

depression (Beck, 1976, 1979, Beck and Emery, 1985). In this model, cognitive errors are expected to bias information associated with depression, and thus increase the likelihood of the development of depression symptoms. In the context of pain catastrophising, high pain catastrophisers may misinterpret pain-related information so that negative outcomes are expected.

Several findings of the present thesis are in support of the appraisal model. Firstly, high- compared to low pain catastrophisers attributed greater pain not only to pain scenes, but also to non-pain scenes (Experiment 2 & 4). This finding suggests over-generalisation and poor evaluation of pain-related events in high pain catastrophisers, consistent with the appraisal model.

Secondly, only low pain catastrophisers but not people with high pain catastrophising showed correlations between late posterior cingulate activation and subjective pain ratings during observation of pain pictures (Experiment 4). Along similar lines, only low pain catastrophisers showed correlations between rostral anterior cingulate activity and perceived pain ratings during viewing of comforting hand postures (Experiment 5). Moreover, low, but not high, pain catastrophisers responded faster to congruent target-probe location than to incongruent pairs (Experiment 3). This finding collaborates with neural evidence, suggesting an undifferentiated response to pain cues in high pain catastrophisers. The inaccurate

processing of pain stimuli in high pain catastrophisers may lead to the allocation of greater distorted processing of pain which would not be proportionate to the amount of pain.

6.2. Attentional model

The attentional model of pain catastrophising postulates the allocation of excessive attentional responses to pain stimuli in high pain catastrophisers (Crombez et al., 1999, Sullivan et al., 2001b, Quartana et al., 2009). Catastrophising may enhance an individual's attention to pain, resulting in difficulty disengaging from pain-related events, and increased vigilance to external stimuli (Sullivan et al., 2001b, Goubert et al., 2004b, Van Damme et al., 2004).

Event-related potential data (Experiment 4) revealed longer activation in cingulate cortex in high- compared to low pain catastrophisers while viewing pain pictures. Middle anterior cingulate cortex is involved in detecting novelty and orienting attention (Davis et al., 1997, Derbyshire et al., 1998, Peyron et al., 1999, Davidson et al., 2002, Downar et al., 2002, Legrain et al., 2009a). Anterior cingulate cortex is also activated during an attention-demanding task (Davis et al., 2000) and in studies requiring sustained attention in the absence of pain, such as the Stroop test (Peyron et al., 2000). An fMRI study of fibromyalgia patients reported that anterior

cingulate activation to the blunt pressure pain was found in high pain catastrophisers (Gracely et al., 2004). In line with these studies, the longer activation of cingulate cortex in high pain catastrophisers may provide a neurophysiological underpinning for the attentional model of pain catastrophising, and particularly to the findings of a longer duration to pain cues in high pain catastrophisers (Van Damme et al., 2002b, Van Damme et al., 2004).

In the dot-probe task (Experiment 3), high pain catastrophisers responded to probes after pain scenes slower than low pain catastrophisers did. Although high and low pain catastrophisers did not differ in their fixation time to pain scenes, significant correlations between fixation time and subjective ratings of pain pictures were found. This finding may suggest attentional avoidance of pain scenes in high pain catastrophisers.

The absence of effects of pain catastrophising on sensitivity to pain cues in a noisy background (Experiment 1) is inconsistent with the attentional model of pain catastrophising (Crombez et al., 1998a, Goubert et al., 2004b). One possible explanation might be that high sensitivity may reflect a tendency to be receptive of sensations, independently of a catastrophising mode of attention. A recent study revealed that low anxiety people reported high sensitivity to bodily signals and low levels of monitoring and pain catastrophising, whereas high anxiety people reported

low sensitivity and high levels of monitoring and pain catastrophising (Ginzburg et al., 2013). Future research should focus on effects of pain catastrophising on sensitivity to pain cues.

6.3. Communal coping model

Sullivan et al. (2000b) and Keefe et al. (1989) proposed a communal coping model of pain catastrophising. In this model, high pain catastrophisers are likely to diminish their pain and emotional discomfort by soliciting social support (Keefe et al., 1989, Sullivan et al., 2001b, Turner et al., 2002). Therefore, in order to attract the attention of others, high pain catastrophisers may show a high frequency of pain behaviours, stronger emotional distress, and heightened pain perception.

The thesis provides strong support for the communal coping model. Firstly, subjective pain ratings of pain in others correlated with pain catastrophising scores (Experiment 1- 4) high pain catastrophisers attributing stronger pain to pain in others, confirming the communal coping model (Keefe et al., 1989, Sullivan et al., 2001b, Turner et al., 2002). This finding accords with previous studies (Sullivan et al., 2006b, Martel et al., 2008) suggesting a systematic tendency in high pain catastrophisers to overestimate others' pain.

Secondly, event-related potential analysis of EEG data recorded during viewing of pain and non-pain pictures (Experiment 4) revealed different patterns of cortical activation in high- and low pain catastrophisers, with high pain catastrophisers showing a blunted cortical response in the early stage and enhanced cortical activation in the later stage of processing. Specific regions of rostral anterior cingulate cortex, posterior cingulate cortex, and parahippocampal gyrus were involved in pain processing in high pain catastrophisers. In line with the communal coping model (Keefe et al., 1989, Sullivan et al., 2001b, Turner et al., 2002), enhanced cortical activity in high pain catastrophisers may suggest that pain catastrophising is associated with stronger dispositional empathy for pain.

Thirdly, laser-evoked potential data (Experiment 5) during viewing of comforting hand postures showed that high, compared to low, pain catastrophisers reported less pain while viewing of comforting hand postures but not while viewing hands of those not providing positive support. Previous studies have suggested that pain catastrophising is strongly associated with greater solicitation of support by pain patients during short period of pain (Cano, 2004, Buenaver et al., 2007). Therefore, high pain catastrophisers are likely to seek support to minimise their pain. Greater source activations to pictures not showing comforting gestures were observed in the right operculo-insular cortex in high- compared to low pain catastrophisers. Posterior

insula is involved in pain processing (Peyron et al., 2000, Apkarian et al., 2005) and the activation of C-tactile afferents (Olausson et al., 2002, Loken et al., 2009). The matching patterns of perceived pain intensity and source activation in posterior insula suggested that high pain catastrophisers may attenuate their pain intensity during viewing of comforting hand postures. These findings are consistent with the communal coping model (Keefe et al., 1989, Sullivan et al., 2001b, Quartana et al., 2009), showing that high pain catastrophisers could benefit from social support.

6.4. Brain structure and pain catastrophising

This thesis identified morphological changes in the cortical grey matter and subcortical structures of healthy people that were correlated with pain catastrophising scores (Experiment 6). The shape alterations seen in the dorsal striatum, identified using a novel shape analysis technique, is of particular interest. Moreover, significant correlations were found between pain catastrophising scores and the grey matter volume in parahippocampal gyrus, angular gyrus, paracentral lobule, posterior cingulate cortex, and temporal and frontal associated cortices.

The associations between pain catastrophising and structural brain features may be explained by either plasticity or by genetic predisposition. As far as plasticity is concerned, it is likely that high pain catastrophisers activate pain centre more than

low pain catastrophisers, providing the grounds for plasticity effects to occur. The frequent employment of a relevant cognitive function may lead to the structural brain alterations allowing adjustments to environmental demands. For example, the posterior hippocampus volumes of London taxi drivers are larger than those of age-matched controls (Maguire et al., 2000), and the enlargement of posterior hippocampus correlated with the amount of time spent in this job. Male symphony orchestra musicians manifest increased grey matter volume in Broca's area than those of gender and IQ-matched non-musicians (Sluming et al., 2002). In addition, a study of fibromyalgia patients reported that beta-band event related desynchronisation in the ipsilateral central-parietal region during mechanic-tactile stimulation correlated with the clinical manual tender point scale (Fallon et al., 2013) , suggesting abnormal processing of somatosensory input which may contribute to clinical symptom severity. Therefore, a high frequency exposure to pain-related events may contribute to plastic changes of brain structure in healthy people with high pain catastrophising. Moreover, maternal pain behaviour impacts directly on children's pain experiences (Chambers et al., 2002), suggesting that parental influences can influence the formation of their children's pain behaviour and possibly pain catastrophising. Parent symptom-related talk is strongly associated with pain symptom complains in high pain catastrophising children (Williams et al.,

2011). Parent catastrophising about their children's pain is also positively correlated with children's fear of pain (Vervoort et al., 2011b) and children's pain intensity (Vervoort et al., 2013b). A longitudinal study revealed that parental pain catastrophising after the surgery can predict children's postsurgical pain (Pagéet al., 2013).

The association between pain catastrophising and brain structural features may be related to genetic predisposition. A twin study has revealed that genetic factors determine individual brain structure and function. For example, cognitive performance is linked with the frontal regions where the structures were under greater genetic control (Thompson et al., 2001). A number of genes have been identified for prefrontal and hippocampal grey matter densities (Peper et al., 2007). Recent studies found that a few candidate genes are associated with pain catastrophising. For example, pain catastrophising scores are negatively correlated with the serotonin receptor 3B gene, which is involved in pain modulation (Horjales-Araujo et al., 2013). The catechol-O-methyltransferase gene interacts with individual differences in pain catastrophising to predict long-term pain-related outcomes (George et al., 2008b, George et al., 2014). In addition, fear conditioned stimuli evoked greater cortical activation in rostral anterior cingulate cortex/ dorsomedial prefrontal cortex in the individuals with the NPSR1 (neuropeptide S receptor gene) T

allele (Raczka et al., 2010), suggesting a gene for catastrophising over-interpreted fear reactions.

The present findings did not provide any data to conclusively prove whether the brain structural features associated with individual pain catastrophising were influenced by plasticity or genetic predisposition. Therefore, future research should look for whether environmental factors, or genetic predisposition, or the interaction of these two factors, may influence the brain structure in pain catastrophisers.

6.5 Clinical applications of the findings

The finding of high pain catastrophisers benefiting from viewing of comfort-giving postures during noxious laser stimulation highlights the potential of social-emotional contexts to be utilised as a therapy tool to alter pain catastrophising in chronic pain patients. Previously, it was proposed that treatment-associated reductions in pain catastrophising (such as cognitive-behavioural therapy or behavioural intervention), perhaps helpless dimension in particular, were associated with improvement in pain intensity in patients with chronic pain (Turner et al., 2005, Smeets et al., 2006, Turner et al., 2006, George et al., 2008a, Quartana et al., 2009). This thesis demonstrated that cortical activations to painful stimuli associated with the observation of comforting postures are altered in healthy people with high pain

catastrophising. This finding suggests that the context of social-emotional cues is a psychological method that could assist to improve pain intensity in high pain catastrophisers, to better target psychological therapeutic interventions. Such application is not only applied in chronic pain patients, but also applied in population with other forms of catastrophising, such as, social phobia and panic disorder.

The morphological findings in the current thesis revealed morphological alterations of cortical and subcortical structures in healthy people associated with pain catastrophising. This result accords with previous data which suggests a potential relationship between pain catastrophising and dysfunctional motor control, such as the ACC and putamen alterations only in fibromyalgia patients with high pain catastrophising (Gracely et al., 2004). This could be important for future diagnosis and treatment methods. If it was possible to identify high pain catastrophisers with potential structural brain alterations among chronic pain patients, they would likely require an individual targeted treatment plan. For example, recently, it was shown that patients with chronic pain exhibit reduced pain catastrophising associated with increased grey matter volume in pain processing regions following cognitive-behavioural therapy (Seminowicz et al., 2013). The structural brain alterations may be affected by specific current therapeutic interventions. A longitudinal investigation of cortical and subcortical morphology

could improve understanding of the neural basis of pain catastrophising, or the mechanisms of suitable interventions.

6.6. Limitations

There are a number of limitations of this thesis. Firstly, the age range of the subjects was limited. All subjects were young adults in their early-twenties. However, pain catastrophising is an important factor in pain outcomes not only in young adults (Sullivan et al., 1995, Sullivan and Neish, 1999) but also in children (Crombez et al., 2003, Vervoort et al., 2006) and older people (Wood et al., 2013). Children's pain catastrophising has been found to be strongly associated with parental responses (Goubert et al., 2009a, Vervoort et al., 2009, Esteve et al., 2014). The relationship between pain catastrophising and pain could be mediated by depressed mood in older adults with persistent pain (Wood et al., 2013). However, these studies also only focused on specific age groups; and there are no longitudinal studies of pain catastrophising. Therefore, future research should address the development of pain catastrophising across the life span.

Secondly, the research subjects in this thesis were predominant to females, except for Experiment 6 which used both genders. Pain catastrophising has been suggested to partially mediate the gender differences in pain intensity (Keefe et al.,

2000, Sullivan et al., 2000b, Edwards et al., 2004). Females reported more frequent catastrophic thinking about pain than men (Sullivan et al., 1995), although, male patients with acute whiplash injury reported more pain catastrophising than did female patients with the same injury (Rivest et al., 2010). Previous neuroscience studies of pain catastrophising did not mention the gender differences in the experimental pain perception (Gracely et al., 2004, Seminowicz and Davis, 2006, Lloyd et al., 2008, Jensen et al., 2010, Burgmer et al., 2011, Vase et al., 2012, Lin et al., 2013). The knowledge of males with high pain catastrophising is limited. Future research should investigate whether male subjects exhibit similar or different neural mechanisms to females.

Last but not least, this thesis focused only on healthy people. However, pain catastrophising has been considered to be maladaptive coping mechanism which heightens severe pain and other aversive outcomes in chronic pain patients (Sullivan et al., 2001b, Quartana et al., 2009). Due to the relevance of pain catastrophising to clinical symptoms of chronic pain patients, it is necessary to explore the behavioural and cognitive mechanisms of pain catastrophising in chronic pain patients when under the same experimental setups.

6.7. Further Research

Considering the failure findings of the eye tracking studies of this thesis, future research should be considered to use the clinical population. For example, attentional effects on pain catastrophising could be evaluated by the attentional differences in healthy people and chronic pain patients. Future eye tracking studies also should combine with EEG or fMRI technique to investigate the differences of cortical activations between high and how pain catastrophisers during viewing pain cues, and whether brain activations in high pain catastrophisers may correlate with eye movement data, such as, attentional orientation and attentional maintenance.

Relative to low pain catastrophisers, high pain catastrophisers demonstrated augmented aversion and arousal, and attributed more pain when observing pain pictures. This finding was accompanied with alterations in ERP components and source activation patterns. High pain catastrophisers also reported a reduced pain during viewing of comforting postures, and manifested altered cortical responses to physical pain, which was modulated by the context of social-emotional cues. The results enhance the current understanding of the psychological aspects of pain catastrophising, and particularly the pain processing regions which may exhibit altered functions in high pain catastrophisers during observation of comforting postures. The role of pain processing regions (such as, the operculo-insular cortex) in alteration to noxious pain in the context of comfort-giving in healthy people with

high pain catastrophising is interesting. The original paradigm could be expanded to include patients with chronic pain, in order to explore whether such pain-reducing effects seen in the clinical population. Alternatively, to further investigate the broader catastrophising, it would be useful to utilise the original paradigm with targeted stimuli to the specific groups of catastrophising, such as, anxiety.

With regards to the structural findings of this thesis, future functional and anatomical imaging research should prioritise subcortial alterations in high pain catastrophisers, especially the dorsal striatum. In addition, the influenced factors of brain structural alterations associated with pain catastrophising are not clear. Therefore, future research should employ genetic and neuroimaging techniques to evaluate the potential anatomical changes associated with pain catastrophising. Also, future studies should look for the longitudinal effects on pain catastrophising, in order to investigate the process of brain structural changes across the life span.

6.8. Conclusion

The thesis employed new experimental paradigms and methods to explore the behavioural responses and cortical activation patterns to pain-related stimuli in healthy people scoring high or low pain catastrophising. Novel findings of this thesis included reporting greater pain to pain and non-pain scenes, reduced capability to

differentiate pain and non-pain events, alterations to processing of pain viewed in others, pain modulation by the context of emotional-social cues, and morphological alterations of brain structures in people with high pain catastrophising. The findings of this thesis added to theories of pain catastrophising such as the appraisal model, the attentional model, and the communal coping model. These data suggest that pain catastrophising is associated with affective and attentional aspects of pain. It also advocates new areas for further research in pain catastrophising. For example, the interactional effects of genotype and environment on structural brain changes associated with pain catastrophising still remains to be investigated. As pain catastrophising plays a role in the development of certain types of chronic pain and contributes to clinical outcomes of pain therapy, the findings of this thesis may be used in behavioural interventions involving modification of catastrophising attitudes towards pain

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