The influence of pain on reward processing

Wiebke Gandhi (née Tiede)

Faculty of Dentistry

McGill University, Montréal

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Contributions of authors

Data presented in chapter 3, 5, 6, and 7 compose the body of this thesis. While parts of the data shown in chapter 3 are already published (Gandhi et al., 2013), manuscripts of the studies presented in chapter 6 and 7 are in preparation, and data shown in chapter 5 as well as parts of chapter 1 will be subject of future manuscripts.

Chapter 3: The influence of acute pain on motivational and emotional aspects of reward processing: behavioral studies in healthy people.

Study design: Wiebke Gandhi, Petra Schweinhardt

Execution of the experiment: Wiebke Gandhi (Experiment 1), Michael Wodzinski under supervision of Wiebke Gandhi (Experiment 2)

Data analysis: Wiebke Gandhi

Writing of the manuscript: Wiebke Gandhi, Petra Schweinhardt

Supervision: Petra Schweinhardt

Chapter 5: Characteristics of helplessness following unrewarded pain avoidance attempts in healthy people

Study design: Wiebke Gandhi, Petra Schweinhardt

Execution of the experiment: Wiebke Gandhi (lead), Cecile de Vos (in support), Richard Hoge (parameter adaptation of the applied MR sequences)

Data analysis: Wiebke Gandhi

Supervision: Petra Schweinhardt

Chapter 6: Activation of the periaqueductal grey (PAG) predicts pain-induced changes in pain avoidance behavior

Study design: Wiebke Gandhi, Petra Schweinhardt

Execution of the experiment: Wiebke Gandhi (lead), Cecile de Vos (in support), Richard Hoge (parameter adaptation of the applied MR sequences)

Data analysis: Wiebke Gandhi

Writing of the manuscript: Wiebke Gandhi, Petra Schweinhardt

Supervision: Petra Schweinhardt

Chapter 7: Pain avoidance in patients with a history of unavoidable pain – behavioral, neural, and clinical correlates

Study design: Wiebke Gandhi, Petra Schweinhardt

Execution of the experiment: Wiebke Gandhi (lead), Cecile de Vos (in support), Richard Hoge (parameter adaptation of the applied MR sequences), Marie-Eve Hoeppli (programming of the motor-visual control task)

Data analysis: Wiebke Gandhi, Richard Hoge (finite impulse response estimation)

Writing of the manuscript: Wiebke Gandhi, Petra Schweinhardt

Supervision: Petra Schweinhardt

Original contributions

This thesis revealed novel and original findings contributing to our understanding of the interplay between pain and reward. They highlight the role of reward processing in coping with pain and suggest the PAG as the central structure underlying these coping mechanisms. Finally, I proposed a vicious circle demonstrating how helplessness relates to altered PAG activity and, ultimately, worsens clinical characteristics in migraineurs. Interrupting this vicious circle may provide a promising avenue to reduce suffering and promote well-being and life quality in pain patients.

Chapter 2

In chapter 2 we described a novel pain model for acute tonic pain in humans mimicking inflammatory pain that can last for an hour – or possibly longer if needed – without known adverse long-term effects.

Chapter 3

In chapter 3 we demonstrated that acute unavoidable pain increases the motivation to obtain reward. Based on a significant correlation between pain unpleasantness and motivation to obtain reward, we concluded that participants tried to compensate for the unpleasant state that pain causes by reaching for rewards.

Chapter 5

In chapter 5 we revealed cognitive and motivational changes in pain avoidance following unrewarded previous avoidance attempts. More precisely, healthy participants felt less able to avoid an upcoming painful stimulus when they had been unsuccessful in avoiding the previous stimulus. Similarly, their efforts shown towards avoiding pain were reduced following an unrewarded pain avoidance attempt.

Chapter 6

In chapter 6 we identified PAG activation in response to a physical threat to be the key predictor for the subsequent behavioral measure of pain avoidance motivation. This highlights the central role of the PAG in the preparation to actively cope with pain in humans. We have further demonstrated a functional network of the PAG in preparation to actively cope with pain, encompassing regions associated with motor-preparation and attention. This network seemed to be reduced in subsequent trials after unsuccessful pain avoidance attempts.

Chapter 7

In chapter 7 we revealed that episodic migraineurs are even more affected in their motivation to avoid pain than healthy people when previous avoidance attempts were unsuccessful. While the underlying brain circuitries seemed comparable between

migraineurs and healthy controls, I have shown that migraine patients who report higher helplessness have a stronger pain-induced reduction in PAG activation than patients with lower self-reported helplessness. Linking the neural and behavioral results in migraineurs with the clinical characteristics of these patients, I was able to describe a vicious circle of helplessness.

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ACC	anterior cingulate cortex
ATP	adenosine triphosphate
BDI	Beck's depression inventory
BOLD	blood oxygenation level-dependent
CBF	cerebral blood flow
dlPAG	dorsolateral periaqueductal grey
EPI	echo planar imaging
fig.	Figure
FIR	finite impulse response
fMRI	functional magnetic resonance imaging
FSL	FMRIB Software Library
GLM	general linear model
HHS	hope- and helplessness scale
HRF	hemodynamic response function
ICA	independent component analysis
IDT	Incentive delay task
KPI	Kieler Pain Inventory
MRI	magnetic resonance imaging
OFC	orbitofrontal cortex
PAG	periaqueductal grey
PE	parameter estimate

PET	positron emission tomography
PPI	psychophysiological interaction analysis
RF	radio frequency
RoI	region of interest
SD	standard deviation
SEM	standard error of the mean
TE	echo time
TR	repetition time
VAS	visual analogue scale
vlPAG	ventrolateral periaqueductal grey
VPL	ventral posterolateral nucleus
VPM	ventral posteromedial nucleus
VTA	ventral tegmental area

Abstract

Avoiding pain and seeking reward are motivational states crucial for survival. When activated simultaneously, they are likely to interact (Becker et al., 2012; Navratilova and Porreca 2014). Chronic pain, for example, has been associated with anhedonia, the inability to feel pleasure (Marbach and Lund 1981; Marbach et al., 1983). However, these studies did not control for depression, a common co-morbidity of chronic pain. Thus it remains unknown how pain *per se* changes reward processing in humans. Addressing this question, evidence from a rodent study suggests an increased motivation to obtain food reward in acutely injured rats (Low and Fitzgerald 2012). No data in humans exist, however, to confirm this interaction of pain and reward. Therefore, the first aim of this thesis was to investigate the influence of acute pain in healthy people on motivational and hedonic aspects of reward processing. Using a monetary reward task we showed that acute pain increased the motivation to obtain reward while hedonic ('liking') ratings were unaffected by pain. The increase in motivation was correlated to perceived pain unpleasantness. Therefore, we concluded that people with acute pain try to compensate for the unpleasant state their pain provokes by obtaining higher wins. This mechanism implies an adaptive, active coping mechanism in a situation where pain itself cannot be avoided.

After I had investigated the influence of acute pain on positive rewards, I was next interested in the effect of pain on the avoidance of negative states (i.e. pain). Using a pain-avoidance task we could show that a painful stimulus which participants had unsuccessfully tried to avoid, led (i) to decreased expectations to be able to avoid the next painful stimulus, and (ii) to decreased pain avoidance behavior. We conclude that

characteristics of helplessness (Abramson et al., 1978) can be induced within our experimental setting.

Further, we sought to characterize the neural underpinnings of the pain-induced reduction in the motivation to avoid pain. Using functional magnetic resonance imaging (fMRI), we engaged healthy participants in a similar pain avoidance task. We replicated our previous finding: an unsuccessful avoidance attempt reduced the motivation to avoid pain. The pain-induced reduction in motivation was predicted by a decrease in periaqueductal grey (PAG) activation, highlighting a key role of the PAG and its network in human pain avoidance behavior.

Based on the concept of learned helplessness we hypothesized that the observed influence of pain on pain avoidance should be amplified in patients with a history of unavoidable pain. Therefore, we performed the same fMRI experiment in a group of migraineurs. We found that migraineurs were, indeed, more affected by previous pain in their avoidance behavior. Similar to healthy controls, the decrease in pain avoidance following pain was explained by a pain-induced reduction in PAG activation; these changes of the PAG correlated positively with self-reported helplessness in migraineurs.

These studies improve our understanding of the interplay between pain and reward; they highlight the role of reward processing in coping with pain and suggest PAG as a central structure underlying these coping mechanisms. In this context, a vicious circle will be proposed demonstrating how helplessness relates to altered PAG activity and, ultimately, worsens clinical measures in migraineurs. Interrupting this circle may provide promising avenues to reduce suffering and promote well-being in pain patients.

Résumé

Éviter la douleur et rechercher les récompenses sont des états émotionnels essentiels à la survie. Quand ils sont activés simultanément, ils sont susceptibles d'interagir. La douleur chronique, par exemple, a été associée dans certaines études à l'anhédonie, l'incapacité de ressentir du plaisir. Cependant, ces études ne mesuraient pas la dépression, une comorbidité courante de la douleur chronique. On ne sait donc pas comment la douleur proprement dite modifie le traitement de la récompense chez l'être humain.

Tentant de répondre à cette question, des données probantes provenant d'une étude réalisée à l'aide de rongeurs suggèrent une motivation accrue d'obtenir une récompense alimentaire chez les rats gravement blessés. Aucune donnée n'existe chez les humains, cependant, pour confirmer cette interaction entre la douleur et la récompense. Par conséquent, le premier objectif de la présente thèse est d'analyser, chez les personnes en santé, l'influence de la douleur aigue sur les aspects émotifs et hédoniques non influencés par le traitement de la douleur. À l'aide d'une tâche récompensée financièrement, nous avons montré que la douleur aigue accroissait la motivation à obtenir une récompense, alors que les taux hédoniques (le fait d'apprécier quelque chose) n'étaient pas influencés par la douleur. L'accroissement de la motivation a été associé au caractère désagréable perçu de la douleur. Par conséquent, nous avons conclu que les personnes souffrant de douleur aigue tentaient de compenser pour l'état désagréable que provoquait leur douleur en obtenant des

gains plus élevés. Ce mécanisme sous-entend un mécanisme compensatoire actif et adaptatif dans une situation où la douleur elle-même ne peut être évitée.

Après que j'aie étudié l'influence de la douleur aigue sur les récompenses positives, je me suis ensuite penchée sur l'effet de la douleur sur l'évitement d'états négatifs (c.-à-d. la douleur). À l'aide d'une tâche visant à éviter la douleur, nous pouvions montrer qu'un stimulus douloureux que les participants avaient essayé, sans succès, d'éviter a mené (i) à une diminution des attentes quant aux capacités d'éviter le prochain stimulus douloureux et (ii) à une diminution du comportement de l'évitement de la douleur. Nous concluons que les caractéristiques du sentiment d'impuissance peuvent être induites dans le cadre de notre milieu expérimental.

De plus, nous avons cherché à caractériser les fondements neuraux de la réduction induite par la douleur de la motivation à éviter cette douleur. À l'aide de l'imagerie par résonance magnétique fonctionnelle (IRMf), nous avons fait participer des sujets sains à une tâche semblable d'évitement de la douleur. Nous avons obtenu des conclusions identiques aux précédentes : une tentative non réussie d'éviter la douleur a réduit la motivation à éviter la douleur. La réduction induite par la douleur de cette motivation était prédite par une diminution de l'activation de la substance grise périaqueducale (SGP), mettant en évidence un rôle clé de la SGP et de son réseau dans le comportement de l'évitement de la douleur chez l'être humain.

En nous fondant sur le concept d'impuissance acquise, nous avons émis l'hypothèse que l'influence observée de la douleur sur l'évitement de la douleur devrait être amplifiée chez les patients ayant des antécédents de douleur inévitable. Par

conséquent, nous avons effectuée la même expérience d'IRMf auprès d'un groupe de personnes souffrant de migraines. Nous avons découvert que le comportement d'évitement de ces personnes était, effectivement, davantage influencé par la douleur précédente. Comme avec les sujets en santé, la diminution de l'évitement de la douleur à la suite de celle-ci s'expliquait par une réduction induite par la douleur de l'activation de la SGP; ces modifications de la SGP étaient positivement associées à l'impuissance autodéclarée chez les personnes souffrant de migraines.

Ces études améliorent notre compréhension du lien entre douleur et récompense; elles mettent en relief le rôle du traitement de la récompense pour faire face à la douleur et laissent entendre que la SGP est une structure centrale sous-jacente à ces mécanismes de compensation. Dans ce contexte, un cercle vicieux démontrant comment l'impuissance est associée à l'activité modifiée de la SGP sera proposé et, ultimement, comment cette impuissance nuit aux mesures cliniques chez les personnes atteintes de migraines. L'interruption de ce cercle peut fournir des avenues prometteuses pour réduire la souffrance et promouvoir le bien-être chez les patients atteints de douleurs.

Chapter 1:

General introduction

1.1 Statement of the problem

Chronic pain is a debilitating condition with a large number of sufferers – over 100 million pain patients are estimated for the U.S.A. (Institute of Medicine 2011) and approximately 7 million for Canada (Moulin et al., 2002; Schopflocher et al., 2011). Dealing with frequent pain leads to changes in the way patients perceive their surroundings and how they interact with their environment. For example, chronic pain has been associated with anhedonia, the inability to perceive pleasure (Marbach and Lund 1981; Marbach et al., 1983), reduced motivational drive (Fishbain et al., 2004) and high helplessness (Matatko et al., 2009; Nicassio et al., 1999; Siniatchkin et al., 1999), i.e. the perception of lacking control over their pain. All of these factors have been associated with negative consequences, including physical and mental impairment, and lower treatment success (Camacho et al., 2013; Keefe et al., 2004). These consequences are likely contributing to personal suffering and a reduction in life quality.

The described consequences of chronic pain suggest that pain interferes with reward processing, encompassing many aspects such as the motivation to obtain reward, perceiving pleasure when being rewarded, and the motivation to avoid aversive events, including pain. However, previous studies did not control for depression, a common co-morbidity of chronic pain (Goesling et al., 2013). Thus, the influence of pain *per se* remains unclear. One rodent study shed light on this question and provides evidence for increased motivation; acutely injured rats were more motivated to reach rewarding food pellets located in the centre of an open field arena when compared to control

animals (Low and Fitzgerald 2012). Although spending more time in proximity to the reward, acutely injured animals did not differ from control animals in the number of pellets consumed. The results imply an influence of pain specifically on the motivational aspect of reward processing in rodents, but not on the hedonic component (i.e. the pleasure of the reward).

In order to improve our understanding of the interplay between pain and reward processing – including the pursuit of positive rewards as well as the avoidance of negative events – we conducted a series of experiments studying the influence of acute pain on reward in healthy people and pain patients. The studies described in this thesis sought to:

1) Examine the influence of acute pain on motivational and hedonic aspects of reward processing in humans.
2) Investigate the influence of acute pain on cognitive and motivational aspects of pain avoidance.
3) Determine the neural underpinnings of the motivation to avoid pain.
4) Investigate the influence of acute pain on pain avoidance behavior and its neural correlates in patients with a history of unavoidable clinical pain.

1.2 Background

1.2.1 Pain

1.2.1.1 Pain as a personal and societal burden

Pain is the number one reason for patients to seek health care (Institute of Medicine 2011). When it becomes chronic, pain is commonly associated with co-morbidities such as depression (Choiniere et al., 2010; Goesling et al., 2013), sleep disorders (Diaz-Piedra et al., 2015; Karaman et al., 2014; McBeth et al., 2015; Roberts and Drummond 2015), and cognitive impairment (Berryman et al., 2014; Martinsen et al., 2014; Moriarty et al., 2011; Wolrich et al., 2014), all of which contribute to an amplification of disability, diminished life quality, and reduced productivity. In addition to the personal burden of pain, it also has a major impact on society: the costs associated with health care and lost productivity are estimated at $ 560-630 billion per year in the U.S.A. (Institute of Medicine 2011) and $ 56-60 billion per year in Canada (the Canadian Pain Society, “Pain in Canada fact sheet”, June 2014). Current treatment of chronic pain is often insufficient, possibly leading to the sensation of helplessness, or in other words, the perceived lack of control which is theorized to cause a tendency to give up (Abramson et al., 1978). Helplessness in chronic pain patients has been associated with lower mental and physical health as well as poorer treatment outcomes (Camacho et al., 2013; Keefe et al., 2004). Therefore, it is of high clinical relevance to gain a better understanding of pain coping mechanisms in situations where pain itself cannot be avoided.

1.2.1.2 The definition of pain

The International Association for the Study of Pain (IASP) defines pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage”. (IASP Taxonomy Working Group, 2011). This broad definition encompasses pain perceived as the result of an acute injury as well as pain syndromes such as idiopathic pain (i.e. perceived pain without a known physical cause). It highlights two further characteristics of pain: it is a warning system informing us about (potential) harm (“associated with actual or potential tissue damage”) and it is “unpleasant” (IASP Taxonomy Working Group, 2011). Both features imply that we would naturally want to avoid situations and events that are (potentially) painful, because it is neither enjoyable nor safe. This means that pain ultimately initiates coping.

1.2.1.3 The neurobiology of pain: from nociceptive processing to the perception of pain

In response to an injury, free nerve endings in the periphery are being activated by the nociceptive stimulus – from here, the nociceptive signal is conducted via the spinal cord to the midbrain and the thalamus, before reaching higher cortical centers (Fields 1987; Marchand 2008; Willis 1985; Willis and Westlund 1997).

Nerve endings originating in the periphery are activated by thermal, mechanical, and/or chemical nociceptive stimuli. Once activated, the nociceptive signal is being conducted

by the primary somatosensory neuron to the dorsal horn of the spinal cord. Two types of afferent fibers of the primary neuron are involved in conveying nociceptive signals:
(1) Relatively large, myelinated Aδ fibers conducting nociceptive signals at a velocity of 5-30 m/s and causing a sharp sensation that is well localizable (causing the sensation of so called *first pain*); and
(2) thin, non-myelinated c fibers conducting nociceptive signals at a velocity of 0.5-2 m/s and mediating a rather diffuse and dull ache (so called *second pain*).
The nociceptive afferent fibers make synaptic contact with the secondary neuron forming the spinothalamic (lateral) and the spinoreticular (medial) tract which both travel to supraspinal centers after crossing to the contralateral side at spinal cord level.
The afferences of the spinothalamic tract have synaptic contact in the thalamus, a 'relay station' sending the signal on to a network of cortical structures.
Afferences of the spinoreticular tract make secondary synaptic contact in the medial nucleus of the thalamus, as well as in brain stem structures, including the periaqueductal grey (PAG) and nucleus raphe magnus. The two latter brain stem structures are important for pain modulation and play a key role in the initiation of behavioral reactions to pain [i.e. either a fight or flight reaction, or passive endurance of pain (Keay et al., 2002; Lovick and Bandler 2005; Lumb 2002)].
The mechanisms described thus far can be summarized as *nociceptive processing,* i.e. "the neural process of encoding noxious stimuli" (IASP Taxonomy Working Group, 2011). The previous paragraph on nociceptive processing is based on the article "The Physiology of Pain Mechanisms: from the Periphery to the Brain" which

comprehensively summarizes the neurobiological processing of pain and the signaling pathways of nociceptive inputs (Marchand 2008).

The actual experience of pain requires the nociceptive signal to reach the cortex. Pain is a complex sensation engaging a large number of cortical and subcortical brain regions, often referred to as the “pain matrix” (Brooks and Tracey 2005).

The “pain matrix” describes a large network of brain areas consistently showing activation in response to acute painful stimuli across different human brain imaging studies; this network includes the primary and secondary somatosensory cortex (S1 and S2), anterior cingulate cortex (ACC), the insula, prefrontal cortex (PFC), thalamus, basal ganglia and cerebellum (for review see Schweinhardt and Bushnell 2010). The involvement of such a large network implies that specific aspects of the nociceptive input are mediated by specific brain areas (Apkarian et al., 2005), which are then integrated (Buechel 2002) and finally leading to the complex sensation of pain.

With the advance of brain imaging techniques in the 1990s, researchers started to explain the specific role of different brain regions in pain processing. In a simplified fashion, the involved cortical and sub-cortical areas can be subdivided into structures contributing either to sensory aspects, or affective aspects of pain. The sensory qualities – i.e. localization of the (potential) injury, duration, and intensity of the painful stimulus – originally transmitted via the spinothalamic tract, are relayed in the ventrobasal complex – consisting of the ventral posteromedial nucleus (VPM) and the ventral posterolateral nucleus (VPL) – of the thalamus and processed by S1, S2, and posterior parietal cortex (Hofbauer et al., 2001; Kulkarni et al., 2005; Treede 2002). The affective qualities – i.e. the unpleasantness of the pain – are relayed by the medial

nucleus of the thalamus and further processed in the ACC and insular cortex (IC) (Kulkarni et al., 2005; Rainville et al., 1997; Vogt 2005). Further, an unconscious response to pain encompassing arousal, autonomic changes, and changes in the muscle tonus is mediated by midbrain circuits with a central role of the PAG (Keay and Bandler 2001; 2002; Lumb 2002).

Finally, the resulting pain experience is hugely determined by descending control which originates from supraspinal sites and acts via the midbrain and medullary sites to bi-directionally modulate nociceptive transmission in the dorsal horn of the spinal cord (Millan 2002; Willis 1988; Willis and Westlund 1997). Psychological factors such as attention and distraction, as well as different emotional states have been shown to modulate the perception of pain (see reviewed in Schweinhardt and Bushnell 2010; Villemure and Schweinhardt 2010). Positive mood states (Meagher et al., 2001; Roy et al., 2012; Villemure and Bushnell 2009; Villemure et al., 2003; Wiech et al., 2008), rewarding stimuli (Becker et al., 2013; Becker et al., 2015), and distraction (Schmahl et al., 2004; Schreiber et al., 2014; Tiede et al., 2010) decrease the perception of concurrent pain, while aversive events – i.e. losing money (Becker et al., 2013), and observing facial expressions of pain in others (Khatibi et al., 2014) lead to pain facilitation. Historically the first brain region demonstrated to activate an endogenous pain inhibitory system in animals and humans is the PAG (Reynolds 1969; Richardson and Akil 1977a; b; Tsou and Jang 1964). Nowadays, the PAG is well understood as a central structure for descending inhibition of nociceptive inputs (Fields et al., 1991). Human brain imaging studies suggest that the PAG receives input from cortical regions which are involved in the mediation of psychological factors such as distraction and

emotional states. The rostral anterior cingulate cortex [rACC (Eippert et al., 2009; Petrovic et al., 2002)] and orbitofrontal cortex (Villemure and Bushnell 2009) are examples for theses brain regions. The PAG then modulates nociceptive input at the dorsal horn of the spinal cord mainly via reciprocal connections to the rostroventromedial medulla [RVM (Fields et al., 2006)].

1.2.1.4 Pain avoidance: from reflexes to innate and learned coping mechanisms

Pain warns the organism of (potential) harm and calls for a quick action. This action could include the withdrawal of the affected body part from a harmful source or the escape from an unsafe environment all together. Ultimately, the affected person will likely learn from the unpleasant experience and, in the future, try to avoid the behavior that previously led to pain. Accordingly, Morrison and colleagues portrayed pain as an "action problem" (Morrison et al., 2013) highlighting the necessity of immediate nocifensive behavior when facing potential injury. In the following paragraph, I will be describing acute actions of pain avoidance, subsequent learning mechanisms, and their neural correlates. Further, I will introduce 'learned helplessness' as a consequence of repeated, unsuccessful attempts to avoid pain.

1.2.1.4.1 Withdrawal reflexes

At the dorsal horn of the spinal cord the afferent nociceptive signal is conveyed directly or indirectly to spinal motor neurons to facilitate a withdrawal reflex. The withdrawal

reflex is a rapid, involuntary movement ensuring the removal of the threatened body part from the stimulation. It is elicited at stimulation intensities below the point of actual tissue damage and, thus, serves as preventative action to avoid injury (for review Morrison et al., 2013).

1.2.1.4.2 Complex nocifensive behavior and its neural correlates

While initial reflexes provide a rapid action to prevent harm and injury, more complex mid-brain and cortex-regulated mechanisms refine nocifensive behaviors.
Some evidence has been provided that the posterior parietal cortex seems to play an important role for sensorimotor transformation of threat-relevant visual stimuli (Buneo et al., 2002; Calton et al., 2002; Fogassi and Luppino 2005; Rizzolatti et al., 1997). Many neurons within posterior parietal cortex respond to both tactile and visual stimuli and therefore facilitate the movement of the eyes and body towards a threatening or actual nociceptive stimulus.
Facing threats, the organism will ‘decide’ how to cope by either showing a ‘freezing’ or ‘fight or flight’ response – referred to as passive and active coping, respectively. On a neural level, the periaqueductal grey has been described to play a central role in mediating coping responses (Bandler and Carrive 1988; Depaulis et al., 1992): Stimulation of the PAG by an electrical current of increasing intensity turned a resting animal into an alert one (Vianna et al., 2001). Further increasing the intensity of the electrical stimulation, the alert animal would next freeze and eventually escape. The dorsolateral aspect of the PAG has especially been associated with a readiness to

actively cope with threats indicating potential harm and show confrontational defense behavior in animals (Keay and Bandler 2001; 2002; Lovick and Bandler 2005; Lumb 2002; Vianna et al., 2001). Behavioral changes are accompanied by autonomic changes, namely increases in blood pressure, heart rate, respiration, and muscle tone (Lovick and Bandler 2005) and thus preparing the body to cope with the threat or actual harm.

1.2.1.5 Learned helplessness: a phenomenon of maladaptive pain avoidance behavior

The motivation to avoid harm and injury is crucial for survival. Escape-avoidance behavior can be impaired, however, when the organism has previously been exposed to inescapable aversive stimulations (Overmier and Seligman 1967). This phenomenon has been termed “learned helplessness” and could be demonstrated in several species, including dogs, rats, mice, fish, and humans (e.g. Landgraf et al., 2015; Okamoto et al., 2012; Overmier and Seligman 1967; Seligman and Beagley 1975; Seligman et al., 1968; Thornton and Jacobs 1971; Vollmayr and Henn 2001). The initial experiments in canines demonstrated that naïve dogs receiving escape-avoidance training show fear-like behavior in response to electrical stimulation that typically includes running about, howling, urinating, defecating, and trembling, until the dog finally escapes to safety (e.g. jumping over a barrier to the ‘safe’ compartment of a shuttle box (Solomon and Wynne 1953). With every new exposure to the same aversive stimulation, the dog will show the escape response faster and faster; it, thus, improves its avoidance-escape behavior.

However, a dog that is being exposed to unavoidable electrical foot shocks several hours before starting the escape-avoidance training will initially show the same fear-like response to the electrical stimulation as naïve dogs. In contrast to the naïve dogs, though, this dog will soon show a maladaptive response: it discontinues any attempts to avoid or escape; instead, it 'gives up' and will passively endure the shocks (Overmier and Seligman 1967; Seligman et al., 1968). During the inescapable shock procedure (performed in a Pavlovian harness apparatus), the animal seems to have learned that shock termination is independent of its behavioral response. Receiving shocks in a new situation (i.e. in a shuttle box), the expectation of not being in control is then being generalized and the organism fails to learn appropriate avoidance or escape behavior (reviewed in Maier and Watkins 2005). While the classic experiments typically used trans-situational settings (i.e. exposure to inescapable pain and the actual testing session took place in different environments), more recent studies also confirm the occurrence of learned helplessness when both sessions take place in the same or similar environments [e.g. (Anisman and Merali 2001; Chourbaji et al., 2005; Malberg and Duman 2003)]. In humans, both trans-situational effects of learned helplessness (Alloy et al., 1984; Hiroto 1974; Hiroto and Seligman 1975; Klein and Seligman 1976; Thornton and Jacobs 1971) and learned helplessness effects across different stressors have been demonstrated to exist (Alloy et al., 1984; Benson and Kennelly 1976; Hiroto and Seligman 1975; Kuhl 1981; Miller and Seligman 1975). Learned helplessness seems particularly generalizable when two aspects are fulfilled: (1) the pre-treatment and the test situation are similar (Alloy et al., 1984; Pasahow et al., 1982); and (2) the person in question has a specific attribution style, as formulated by the attribution theory

(Abramson et al., 1978; Alloy et al., 1984). According to this theory, people who attribute a lack of control over negative events ‘globally’ and ‘internally stable’ are more likely to generalize helplessness. People with a global and internally stable attribution style have a tendency to never feel in control of any stressful situation after only one negative experience, because of a perceived personal lack of necessary skills – as opposed to blaming the situation, certain circumstances, or others (Abramson et al., 1978; Alloy et al., 1984; Raps et al., 1982). Abramson, Seligman and Teasdale conceptualized that learning that aversive outcomes are not controllable leads to a cognitive and motivational deficit in humans (Abramson et al., 1978). Initially, the person comes to expect that outcomes are out of their control (i.e. cognitive change). This expectation is followed by the motivational deficit consisting of a delayed initiation of escape-avoidance behavior.

Two lines of evidence support the hypothesis that cognitive changes occur first, while motivational changes follow. First, exposure to escapable pain does not cause the helplessness effect, even though they are physically identical to the inescapable one (Seligman and Maier 1967). This implies that the organism has to learn first that its behavior has no effect on the stressor. The resulting expectation of not being in control will then lead to the observed motivational deficit. The second line of evidence is provided by experiments testing the reversal of learned helplessness (Seligman et al., 1968). When animals had persistently shown to fail pain avoidance in the shuttlebox, the experimenters removed the hurdle and forced the animal to move to the safe side of the box. The animal had no motivation to move and had to be dragged. Once it reached the safe side, the aversive stimulation was discontinued. After 30 to 50 times of forcing

the animal to terminate the stimulation, they started to show avoidance behavior by themselves again. They continued to escape the shock even after the replacement of the hurdle (Seligman et al., 1968). Again, this implies that the expectation to be in control had to be established first, before a motivational change followed.

1.2.1.5.1 The neurobiology of learned helplessness

While the neurobiology of learned helplessness in humans is still poorly understood, extensive research has been performed in animals. The findings here are diverse and numerous neurotransmitters seem to play a role in moderating or modulating effects of learned helplessness, including serotonin, acetylcholine, dopamine and endogenous opioids (Peterson et al., 1993). The two probably most extensively studied neurotransmitters to play a role in learned helplessness are norepinephrine, and gamma-aminobutyric acid (GABA).

Historically the first neurochemical to be investigated in its role for learned helplessness was the catecholamine norepinephrine with a study by Weiss and colleagues (Weiss et al., 1970). They showed that the whole brain's norepinephrine content was reduced following the rat's exposure to inescapable shock, but not to escapable shock. While the norepinephrine system is being activated following both escapable and inescapable shocks, utilization of norepinephrine can be matched by synthesis only following escapable shocks; following inescapable shocks, however, utilization of norepinephrine succeeds synthesis and thereby depletion of norepinephrine follows (Anisman and

Zacharko 1986). A depletion of norepinephrine following inescapable stress would therefore lead to the motor deficits observed in helpless animals (Weiss et al., 1970). This view was supported by a depletion study in rats (Anisman et al., 1979) showing that the lack of norepinephrine led to passivity and omission of escape behavior in the shuttlebox even without the prior experience of inescapable shocks. Measuring the duration of norepinephrine changes by inescapable and escapable shocks in numerous brain regions, Weiss and colleagues found norepinephrine depletion only in the locus coeruleus to correlate to helpless behavior following inescapable shock (Weiss et al., 1981).

Taken together, the literature suggests that an activation of the norepinephrine system in the locus coeruleus that exceeds its synthesis – and thus causing depletion – mediates behavioral passivity following inescapable shocks in rodents.

GABA is the major inhibitory neurotransmitter of the brain; when it binds to its receptor an influx of negatively-charged chloride into the neuron follows, causing hyperpolarization of the neuron. An early study providing evidence for a role of GABA in learned helplessness was undertaken by Petty and Sherman (Petty and Sherman 1981). They showed that GABA levels of the hippocampus were reduced in rats that were previously exposed to inescapable shock, but not in rats that had experienced escapable shock. When they injected GABA directly into the hippocampus of rats, the inability to learn escape behavior was reversed. These findings were supported by further results showing that animals that were previously exposed to inescapable stress showed a reduced amount of chloride ion influx when GABA receptors were activated

(Drugan et al., 1989). In line with these studies, the administration of benzodiazepines before inescapable shock exposure prevents the inability to learn escape behavior 24 hours later in the shuttlebox (Sherman et al., 1979). Benzodiazepines are known to increase the inhibitory effect of GABA by binding to the benzodiazepine binding site of $GABA_A$ receptors. Once bound benzodiazepines facilitate GABA's binding to its receptor and thereby increase the number of chloride channel openings by a given GABA concentration. These drugs have been identified to decrease anxiety and fear among other effects (Paul et al., 1981). Interestingly, the administration of benzodiazepine only prevents the inability to learn escape in the shuttlebox when given before the exposure to inescapable shock. On the contrary, administering benzodiazepine directly prior to the shuttlebox experience revealed no effect on helpless behavior (Peterson et al., 1993).

Taken together, GABA activity in the hippocampus seems to mediate learned helplessness. Increasing the inhibitory effect of GABA by benzodiazepines during the exposure to inescapable shock can reduce subsequent behavioral correlates of learned helplessness. Given the anxiolytic action of benzodiazepines, GABA's role in learned helplessness can be interpreted as mediating learned helplessness by reducing the anxiety-related aspects of uncontrollable pain during the exposure phase.

1.2.1.5.2 A potential role of the PAG in learned helplessness

The periaqueductal grey (PAG) has been described to play a central role in mediating coping responses: the organism can either avoid or escape threatening situations (i.e. active coping) or rather freeze and endure the pain (i.e. passive coping) (Bandler and Carrive 1988; Depaulis et al., 1992). As mentioned above, specifically the dorsolateral aspect of the PAG has been associated with a readiness to actively cope with threats, i.e. to show confrontational defense or escape behavior in animals (Keay and Bandler 2001; 2002; Lovick and Bandler 2005; Lumb 2002; Vianna et al., 2001). In a threatening situation more specifically linked to learned helplessness, one study demonstrated that baseline levels (measured in the shuttle box before electrical shocks commenced) of serotonin in the dorsal PAG were increased in animals who were exposed to *escapable* shocks 24 before, but not in animals that were previously exposed to *inescapable* shocks (Amat et al., 1998). Further, the mean absolute serotonin levels of the dorsal PAG were inversely correlated to freezing, implying less freezing (i.e. more active coping) with higher levels of serotonin measured in dorsal PAG (Amat et al., 1998).

In short, the findings coming mainly from the survival behavior literature, supported by one study testing learned helplessness specifically, suggest that dorsolateral PAG might be the central structure underlying the motivation to escape and avoid painful stimulation. This assumption has been supported by a lesion study in rodents. Pain escape responses are significantly diminished in rats following electrolytic lesion of the dorsolateral PAG (Lei et al., 2014). Further, the PAG has direct anatomical connections to key brain structures shown to be involved in learned helplessness such as the locus

coeruleus (Aston-Jones et al., 1991; Mantyh 1983), and the hippocampus probably via the paraventricular nucleus of the hypothalamus (Cameron et al., 1995). Therefore, the PAG is anatomically well suited to mediate different aspects of helplessness.

No data, however, seem to exist to confirm the role of the human PAG in coping with threats of pain, nor do we have evidence confirming that helplessness in humans is, in fact, linked to the PAG. Understanding the underlying mechanisms of maladaptive passive coping in patients exposed to pain as an unavoidable chronic stressor may provide targets for pharmaceutical interventions and/or cognitive behavioral therapy to improve treatment outcomes (Keefe et al., 2004) and enhance life quality in these patients.

1.2.1.5.3 Helplessness in migraine patients

In the last experiment of my thesis I investigated pain avoidance behavior in episodic migraineurs (see chapter 6). Episodic migraine is characterized by up to 14 attacks of debilitating, pulsating headache per month, often accompanied by nausea and vomiting [International Headache Society classification, (ICHD-II 2004)]. Patients describe their satisfaction with acute migraine treatment as low to modest at best (Silberstein 2010). This dissatisfaction is likely caused by an unreliable efficacy of acute migraine treatments: a lack of treatment success has been described in approximately half of all attacks; a quarter of migraine patients have been classified as non-responders to commonly administered acute migraine remedies, such as triptans (reviewed in

Silberstein 2010). The symptomology of episodically reoccurring headaches that are often unpredictable and unavoidable, in combination with little or unreliable pain relief in response to treatment may offer an explanation why migraineurs feel helpless with regard to their pain. In fact, reported helplessness scores in migraineurs are higher not only compared to healthy controls (Siniatchkin et al., 1999), but also compared to other pain patients, such as back pain sufferers (Matatko et al., 2009). Based on the concept of learned helplessness *(see above)*, we assume that migraineurs are more affected in their motivation to avoid pain when previous pain avoidance attempts were unsuccessful. However, to our knowledge no studies have yet investigated the mechanisms of pain avoidance in pain patients.

1.2.2 Reward

In a psychological context, reward is defined as “any pleasant event that follows a response and therefore increases the likelihood of the response recurring in the future” (Collins English Dictionary – Complete and Unabridged, 12th Edition 2014 © Harper-Collins Publishers). The definition highlights the pleasant aspect of reward and its purpose to facilitate learning in order to maximize pleasant events (or minimize negative events, i.e. punishment) in the future. Pursuing reward is crucial for survival and thus one of our strongest motivators.

We generally distinguish between two types of reward: primary and secondary rewards. Primary rewards on one hand have an innate value and include for example food, sex,

and shelter. Secondary rewards, on the other hand, do not serve survival directly and include monetary gains and power. The latter rewards only gain value by learned association with primary rewards; money for instance can buy you food or a safer shelter (Sescousse et al., 2013). Despite the difference in their evolutionary origin, primary and secondary rewards share common neural reward circuitries, including brain structures such as bilateral striatum, bilateral anterior insula, mediodorsal thalamus, bilateral amygdala, orbitofrontal cortex (OFC) and ventromedial prefrontal cortex (vmPFC) as comprehensively demonstrated by a recent meta-analysis which included 87 fMRI studies (Sescousse et al., 2013). The involved brain regions have been related to different aspects of reward processing. The personal reward value for instance has been associated with vmPFC and OFC. Their activity increases with higher objective reward values, decreases when saturation is reached, and varies with personal preferences (Breiter et al., 2001; Knutson et al., 2001; Knutson et al., 2003; O'Doherty et al., 2001; O'Doherty et al., 2000; O'Doherty et al., 2003; Peters and Buchel 2010; Small et al., 2003; Small et al., 2001). The ventral striatum has been associated with prediction errors, i.e. it codes the receipt of unexpected rewards or unexpectedly high rewards, as well as the omission of anticipated rewards (Bray and O'Doherty 2007; Contreras-Vidal and Schultz 1999; Delgado 2007; O'Doherty 2004). Prediction errors are essential learning signals: the organism learns to predict the consequences of their actions and will use this knowledge to (1) maximize the likelihood of rewards and to (2) minimize punishment in the future. If the comparison of one’s expectation and the actual outcome yield a difference (i.e. prediction error) the knowledge can be updated and the future prediction will be more accurate (Niv and

Schoenbaum 2008). The anterior insula has been associated with interoceptive and emotional awareness for both positive and negative events, including pain and monetary loss (Craig 2002; Naqvi and Bechara 2010; Petrovic et al., 2008). It further plays an important role in attention processes and has been discussed as the switch for attentive states (Menon and Uddin 2010). Therefore, the anterior insular cortex may increase general alertness in the presence of reward or punishment as well as reward-promising or physically threatening environments. Thus, it may facilitate learning processes within an emotional setting.

The previous paragraph emphasizes that reward processing is conceptually complex, embracing several facets. Some of these facets I will investigate in more detail within the experiments of this thesis. These aspects include the emotional response to reward, i.e. the ability to either feel pleasure when receiving a desired stimulus, or relief after a negative event has been avoided. Another central component is motivation which encompasses the willingness to pursue reward-promising cues (i.e. incentives) and to avoid negative situations. It further implies vigilance – increased attention – towards these incentives in the environment, so called *salience* or stimulus awareness. Incentive salience is the result of an implicit process of transforming sensory information of a stimulus (e.g. smell, sights) into an appetitive, attractive cue (Berridge and Robinson 2003). The salient incentive can then trigger appropriate behavior aimed at obtaining reward.

1.2.3 The pain-reward interaction

Based on the knowledge that winning decreases the perception of concurrent pain (Becker et al., 2013; Becker et al., 2015), reaching for rewarding stimuli offers itself as an adaptive coping mechanism for painful stimuli that are not per se avoidable. However, do people actually pursuit positive means when in pain? Or do they rather feel discouraged by the unpleasant sensation? Surprisingly little is known about the influence of pain on the motivation to obtain reward. In part 1 of this thesis (see chapter 3), I will be reporting my findings with respect to the influence of pain on motivational and emotional aspects of reward processing. Based on the current knowledge, the following paragraphs will portray why we believe that pain is in fact likely to have an influence on reward. Neuroanatomical and neurochemical overlaps between pain and reward processing, for instance, offer a common neural substrate for pain and reward systems and, therefore, support the hypothesis that the two may interact. Many of the following thoughts I have also described as part of a published book chapter entitled "The influence of pain on reward processing: current literature and prospects" (Gandhi et al., 2014).

1.2.3.1 Common neuroanatomical substrates for pain and reward

Several brain regions, including the dorsal and ventral striatum, orbitofrontal cortex, and the insula are involved in both pain and reward processing (Becker et al., 2012; Leknes and Tracey 2008; Navratilova et al., 2015).

For reward processing, the contributions of the ventral striatum and the orbitofrontal cortex have been studied most extensively. As discussed above, the ventral striatum has been associated with prediction errors (Bray and O'Doherty 2007; Contreras-Vidal and Schultz 1999; Delgado 2007; O'Doherty 2004). It is therefore considered a key structure underlying learning processes following unexpected rewards and omissions of expected rewards (e.g. Gottfried et al., 2003; McClure et al., 2003; Pagnoni et al., 2002; Schultz 2007).

The role of the ventral striatum in nociceptive processing is not certain. However, ventral striatum activation has been identified in response to pain (reviewed in Borsook et al., 2010; Leknes and Tracey 2008). It seems to be involved in pain modulation (Gear et al., 1999; Scott et al., 2008), probably through indirect connections via the cingulate cortex, amygdala, medial thalamus, and hypothalamus (Fields et al., 2006; Groenewegen and Russchen 1984; Williams et al., 1977).

As highlighted previously, the OFC encodes the personal reward value (Breiter et al., 2001; Knutson et al., 2001; Knutson et al., 2003; O'Doherty et al., 2001; O'Doherty et al., 2000; O'Doherty et al., 2003; Peters and Buchel 2010; Small et al., 2003; Small et al., 2001). It is further engaged in updating expectations of future reward, probably in close interaction with the ventral striatum (Gottfried et al., 2003; Hampton et al., 2006; O'Doherty et al., 2002; Schoenbaum et al., 1998).

The OFC further seems to be a key structure for the modulation of pain by distraction and emotional processing. Its increased activity during distraction away from pain has been identified to correlate with decreased pain ratings (Bantick et al., 2002; Petrovic et al., 2000; Valet et al., 2004). Separating attentional and emotional processing, one

study demonstrated that the activity of the OFC was correlated with emotional modulation of the perceived pain intensity (Villemure and Bushnell 2009). It further co-varied with pain-related activity in the anterior cingulate cortex and the PAG, suggesting a pain-modulatory effect of the OFC via these structures. Based on these findings, the orbitofrontal cortex might also play a role in pain modulation by the pleasure felt when being rewarded, possibly via projections similar to those described here.

1.2.3.2 Common neurochemical substrates for pain and reward

Beside anatomical overlaps, pain and reward share at least two neurochemical modulators, namely dopamine and opioids.

Dopamine is central for reward processing (Schultz 2007). Its role in the motivation to obtain reward has been repeatedly documented by studies in animals and humans (Cagniard et al., 2005; Cooper and Knutson 2008; Pecina et al., 2003; Smith et al., 2011; Yin et al., 2006; Zink et al., 2004; see Berridge 2007 for review). Dopamine has been identified to be needed and to be sufficient to trigger the motivation to obtain reward. In contrast, dopamine release is insufficient to explain hedonic responses to reward (Berridge and Robinson 1998; Leknes and Tracey 2008; Wise 2004). Hedonic responses are, in fact, mediated by opioids (Berridge 2003; Pecina et al., 2003). Activating μ-opioid receptors in rodents by injecting an opioid agonist to specific sites of the nucleus accumbens is associated with increased pleasure and with decreased aversiveness (Berridge 2003).

Endogenous opioids further play a well established role in pain modulation. In humans the μ-opioid receptor system is activated in response to pain in several brain regions including the anterior cingulate cortex, lateral prefrontal cortex, anterior insular cortex, thalamus, ventral basal ganglia, amygdala, hypothalamus, and the PAG (Zubieta et al., 2001). In this study, opioid activation in the ventral basal ganglia, ipsilateral thalamus, and amygdala was associated with lower pain ratings. Therefore, supraspinal opioid activity seems to mediate pain inhibition.

The role of dopamine in pain processing is still less certain and conflicting results have been found across species. In humans, the evidence shows that dopamine is released in the ventral and dorsal striatum in response to experimental pain (Scott et al., 2006; Wood 2006). While the magnitude of the dopamine release in these human studies was positively correlated with pain sensitivity in humans (Scott et al., 2006; Wood 2006), rodent studies reported an attenuation of pain behaviors associated with the activation of dopamine receptors (Altier and Stewart 1999; Dennis and Melzack 1983; Taylor et al., 2003). Investigating the role of dopamine in pain modulation further, evidence from our own laboratory revealed that dopamine per se does not decrease pain sensitivity in humans, but seems to play a role in the decision whether the person should focus on their pain – and find a way to escape it – or focus on other, positive means such as any available rewarding stimuli (Becker et al., 2013). Considering the evidence discussed here, it could be hypothesized that a pain-induced release of dopamine in the ventral striatum may lead to greater saliency (stimulus awareness) of incentives and therefore facilitate the focus on positive means while in pain.

1.2.3.3 The influence of acute and long-term pain on reward

The extensive overlap of pain and reward in the brain suggest interactions between them. In this section I will discuss how pain may influence reward processing. Here, I will distinguish between chronic and acute pain, because evidence suggests that reward systems might be altered with long-term exposure to pain.

1.2.3.3.1 Chronic pain

The common observation that chronic pain patients often experience anhedonia (Marbach and Lund 1981) and report low motivation (Barendregt et al., 1998; Fishbain et al., 2004), suggests that the long-term exposure to pain impacts on the reward system. Experimental studies support this idea. Chronic pain patients suffering from fibromyalgia or complex regional pain syndrome show deficits to improve their performance on reward-dependent learning tasks (Apkarian et al., 2004a; Becker et al., 2011). This deficit implies impairments of their reward sensitivity.

Alterations of the dopaminergic and opioid systems in chronic pain patients may underlie these observed behavioral phenomena. In fact, dopamine release in response to experimental pain is reduced in patients with chronic widespread pain (Martikainen et al., 2015; Wood et al., 2007). Tonic dopamine levels and phasic dopamine release are inversely related (Floresco et al., 2003; Grace 1991; Schultz 2007). This implies that the observed decrease of dopamine release in chronic pain patients might be

related to increased tonic dopamine levels (Wood 2006). However, no direct evidence of increased tonic dopamine levels induced by chronic pain exists to my knowledge. Therefore, it is currently only safe to conclude that dopaminergic neurotransmission is altered in patients with chronic pain. Given the central role of dopamine for motivational processes, altered dopaminergic neurotransmission in pain patients may underlie the decreased motivation commonly reported by chronic pain patients.

While alterations of the dopamine system offer a likely explanation for motivational changes in chronic pain patients, anhedonia would rather be expected to be mediated by changes in the opioid system. Using opioid receptor PET, studies identified decreased resting binding potentials in chronic pain patients with neuropathic pain (Maarrawi et al., 2007) and fibromyalgia (Harris et al., 2007). The interpretation of PET results is somewhat ambiguous. Reduced resting binding potentials can either result from increased endogenous opioid levels or from a decreased receptor density/affinity. However, both of these mechanisms may contribute to the finding in pain patients. The presence of pain may chronically activate the opioid systems in patients, possibly to attempt pain reduction. However, when the level of agonists is constantly high, internalization of the receptor may follow (Laruelle 2000). Internalization is a protective mechanism of the cell and attenuates cellular responses. With the receptors internalized, the density of available receptors is consequentially decreased (Laruelle 2000). Considering the important role opioid plays in the hedonic responses to rewarding stimuli, this attenuation of opioid responses by internalization may provide a neurochemical substrate for anhedonia in chronic pain patients.

1.2.3.3.2 Acute pain

The influence of acute, short-term pain on reward processing has rarely been investigated. Nevertheless, the existing findings do suggest an interaction between acute pain and reward. One human imaging study found that the attractiveness of reward was decreased when short painful stimuli accompanied the reward (Talmi et al., 2009). The authors identified a neural signature underlying the individual variability in reward-related decisions which were modulated by pain. Here, the activation of the orbitofrontal cortex was modulated by pain-related activity in the insular cortex. This result is in line with the suggested role of the orbitofrontal cortex in encoding personal reward value. The experience of concurrent pain seems to modulate this subjective reward value via neural connections from the insula to the orbitofrontal cortex.
The currently central study investigating the influence of acute pain on hedonic and motivational aspects of reward is provided by the rodent literature. Low and Fitzgerald demonstrated that acutely injured rats spent more time in proximity to food pellets in the middle of an open field arena than control animals (Low and Fitzgerald 2012). This implies that the animals accept the exposure to a potentially riskier environment in order to obtain reward. Therefore, Low's result suggests an increased motivation in the injured animals to obtain reward. In contrast, the hedonic component of reward seemed unaffected in this study. Both groups – acutely injured and control animals – consumed similar amounts of food pellets.

In our laboratory, we conducted the first study in humans to confirm the effect of acute pain on motivational and hedonic aspects of reward (Gandhi et al., 2013). This study will be presented as part of this thesis (chapter 3).

1.3 Rationale of this thesis

The primary objective of this thesis was to explore how acute pain influences reward. Within this framework, I investigated how pain affects different aspects of reward processing, including the motivation to obtain reward, the pleasure felt when being rewarded, and the motivation to avoid unpleasant states, namely pain. In this thesis, I will present data on pain-induced changes in both reward-related behavior and neural underpinnings of certain aspects of reward processing as identified by BOLD fMRI. Finally, I will discuss my findings within the framework of active pain coping, an adaptive mechanism that is easily disturbed when coping attempts remain unsuccessful.

PART 1

ACTIVE COPING WHEN PAIN ITSELF CANNOT BE AVOIDED: REACHING OUT FOR POSITIVE MEANS

Chapter 2:

Methods – Part 1

2.1 Methods and procedures

2.1.1 Participants

Two sets of healthy participants were recruited to take part in two independent experiments.

In the first experiment, forty-four healthy volunteers participated of which two dropped out after the first session and two had to be excluded as they either perceived the painful stimulation as not painful or the warm stimulation (control condition) as painful. The final sample of experiment 1 consisted of 40 healthy participants (20 male, 20 female, aged 18-46, M= 23.73 years, SD=6.26 years).

For the second experiment, we recruited thirty-six healthy volunteers (17 male, 19 female, aged 18-38, M=23.36 years, SD=4.55 years).

The studies complied with the revised Declaration of Helsinki (2008) and were approved by McGill's Institutional Review Board (see IRB approval in appendix A). Informed consent was obtained from each participant at the beginning of the first session.

2.1.2 Monetary Reward Task

The Incentive delay task (IDT) has previously been used to investigate reward processing in humans (Knutson et al., 2000). Participants played the task on a laptop positioned in front of them. During each trial, participants saw a certain amount of money being displayed first (incentive cue). The amount of each incentive cue was

either $ 0.04, $ 1.00, or $ 4.00; and the cue was displayed for 750 ms. After a randomized interval of 1000 to 4000 ms a target cue appeared on the computer screen. Participants were instructed to press the space bar on a key board with their dominant hand as quickly as possible when the target cue appeared. Immediately after their response, feedback was displayed on the screen for 1000 ms. Participants won the amount of money they had seen at the beginning of the trial if they responded to the target cue within an individually adjusted time frame. However, if they pressed too early (before the target cue had appeared), too late, or not at all, participants did not win the money ($ 0). After the feedback slide participants were asked to rate how much they liked or disliked their latest win/omission of a win on a 200 mm visual analogue scale with the anchors ‘strongly dislike’ and ‘strongly like’. In experiment 1, participants moved the cursor – indicating their rating on the visual analogue scale – by pressing the left or right arrow key on the keyboard. Each button press corresponded to a shift of the cursor by 5 mm. In experiment 2, participants indicated their ‘liking’ rating on the same VAS scale, but on a 19 inch touch screen (model *PT1945R*, Planar®) by a single tab of the corresponding spot on the horizontal line with the index finger of their dominant hand.

Figure 1 depicts an example of a single trial of the IDT. In each session, participants performed 75 trials in total, 25 trials for each incentive occurring in a pseudorandomized order. After every 25th trial, participants were asked to take a short break during which the experimenter asked for a pain rating. The task took approximately 12 minutes in total.

Participants were familiarized with the IDT prior to the experiment. During the familiarization participants played 12 trials knowing that the money won during this phase would not be counted towards their final win. Participants' reaction times were recorded and used to adjust the time allowance for the response after each target cue accordingly. The time allowance was adjusted to 200 ms, 225 ms, 250 ms, 275 ms, or 300 ms, based on the time that was associated with a success rate of approximately 50-75% in the familiarization phase. The time allowance was individually adjusted once per subject and was not changed between first and second session. In the actual test runs of experiment 1 the average percentage of rewarded trials was close to 75% ($M_{control}$= 77%; M_{pain}= 78%). In experiment 2 they were closer to 50% ($M_{control}$= 50%; M_{pain}= 54%).

The two outcome measures of the IDT were 1) the reaction time in response to the target cue as a measure of motivation to work for a given incentive [with lower reaction times being indicative of increased motivation (Delmonte et al., 2012; Tobler et al., 2007)], and 2) the VAS rating after each feedback as a measure of the hedonic response to rewarding stimuli of different intensities ($ 0.04, $ 1.00, $ 4.00).

The design of the task allowed a comparison across the different incentive values between the pain and control condition. This way, we could control for sensorimotor components as well as other psychological phenomena that could potentially decrease motor responses such as attention.

2.1.3 Experimental Conditions

Participants were tested in two experimental sessions which took place on two separate days with at least 4 days in between sessions (experiment 1: M= 7 days, SD=1 day; experiment 2: M= 9 days, SD= 3 days) to avoid carry-over effects of the capsaicin-induced sensitization (*see below)*. Counterbalanced across the group, participants were either assigned to start with the painful condition or the non-painful control condition.

2.1.3.1 Pain condition

For the painful condition we applied a tonic thermal stimulation after capsaicin-induced sensitization of the skin using 0.075% topical capsaicin cream. The cream was applied to one of the participant's upper calf over an area of 10 cm by 10 cm using the left leg in 50% and the right leg in the other 50% of participants (each group had equal numbers of men and women). Capsaicin is the pain-inducing component of chili pepper and induces heat sensitization by activating temperature-dependent ion channels (Holzer 1991).

The cream was removed after 20 minutes (Dirks et al., 2003). Using an electrical heating pad with a surface area of 13 cm by 19 cm (TC-1000, CWE Inc., PA, USA) a tonic thermal stimulus was applied to the treated skin starting at a temperature of 35.5˚C. An adjustment period of ten minutes followed to ensure that all participants perceived the stimulation as moderately painful. During the adjustment period participants' pain ratings were taken every two minutes. According to these ratings the temperature was individually adjusted to ensure that participants felt moderate pain

(corresponding to a rating of 130-160 out of 200 on the VAS intensity scale, *see below*) throughout the experiment.

After the adjustment period participants first performed the motor control task followed by the IDT. The motor control task was performed to ensure that pain did not influence motor reactivity per se (see further details below). Before and after the motor control task, as well as before, after, and in the two short breaks of the IDT, pain ratings were assessed again and temperatures adjusted accordingly. The average applied temperature during the tasks was 38.05±2.62˚C (range: 31˚C to 42.7˚C).

2.1.3.2 Control condition

In the control condition, participants were treated with vehicle cream. Thermal stimulation was similar to the above described stimulation protocol with the difference that temperatures were perceived as non-painful. We aimed at a low warm sensation and adjusted the temperatures according to subjective ratings of approximately 5-20 out of 200 on the VAS intensity scale (*see below*). The average applied temperature throughout the control condition was 37.49±2.07˚C (range: 32.73˚C to 42.03˚C).

2.1.4 Manipulation Checks

Since we were applying a novel experimental pain model as well as a reward task that has rarely been used in a parametric fashion we performed manipulation checks in experiment 1 on different levels:

Stimulation temperatures were adjusted and pain intensity and unpleasantness ratings were recorded to ensure that participants perceived the painful condition as painful and unpleasant throughout the experiment; and as warm, but not painful or unpleasant in the control condition.

A motor control task was performed to ensure that pain did not influence motor reactivity per se. This task was important because the main outcome measure of the reward task (IDT) is reaction time measured as the delay of a button press in response to a target cue.

Skin conductance was recorded as an autonomic measure to confirm whether the painful condition was more arousing than the control condition (skin conductance levels) and whether increasing incentives in the IDT were associated with increasing arousal (skin conductance amplitudes). Generally, skin conductance levels are a measure of overall conductivity. It reflects longer-term manifestations of arousal (Figner and Murphy 2011) and is hence suitable to measure arousal in response to the tonic pain stimulus used in our experiment. In contrast, skin conductance amplitudes are short fluctuations in skin conductance. They reflect short modifications of arousal and were therefore used to measure alterations in arousal in response to the different short-lived incentives in our reward task (Figner and Murphy 2011).

2.1.5 Visual Analogue Scales (VAS) for pain ratings

Subjects were familiarized with the VAS before the experiment was commenced. The differences between the intensity and the hedonic (unpleasantness/pleasantness) scales were explained carefully using explanations similar to those published by Price and colleagues (Price et al., 1994). Participants were given sufficient time to ask questions until they felt comfortable using the scales.

2.1.5.1 Pain intensity scale

Participants rated the perceived intensity of the thermal sensation on a 200-point VAS with 0 meaning “no sensation”, 100 being the pain threshold and 200 being equivalent to “the most intense pain tolerable”.

2.1.5.1 Pain affective scale (pleasantness/unpleasantness)

Participants rated the pleasantness/unpleasantness as the affective component of the perceived pain or warm sensation evoked by thermal stimulation. The verbal anchors of the affective VAS are “highly unpleasant” (-100), “neutral” (0), and “highly pleasant” (+100). The intensity and affective scales have been used successfully to differentiate sensory and affective components of pain perception (Villemure and Bushnell 2007; Villemure et al., 2003)

2.1.6 Motor control task

To control whether motor responses per se were influenced by pain participants played a computerized motor control task (MCT): across ten trials, participants were asked to press the space bar on a keyboard in front of them as fast as possible when the target cue appeared on the screen. Reaction times were recorded and compared between conditions.

2.1.7 Physiological measurement and analysis

Skin conductance responses (SCR) were recorded at the third phalanx of the index and middle finger of the participant's non-dominant hand with Ag-AgCl surface electrodes (Type EL-507) using the BIOPAC MP150 system (BIOPAC Systems Inc., Goleta, USA). Skin conductance was sampled at 1000 Hz and high-pass filtered (0.05 Hz). To quantify SCR, onset-to-peak amplitudes as well as skin conductance levels (tonic activity) within 1-4 seconds after the incentive cue were used. SCR were averaged across trials separately for the two conditions (pain vs. control) and the three incentives ($ 0.04; $ 1.00; $ 4.00) for each participant. Skin conductance was analyzed using Ledalab V3.2.9 (Benedek and Kaernbach 2010).

2.1.8 Statistical analysis

All statistical analysis was performed using PASW Statistics 17 (SPSS Inc., Chicago, Il, USA). A p-value of <0.05 was considered significant and data are presented by means

± standard error of the mean (SEM). Since our data revealed no effect of gender data for male and female participants were pooled.

2.1.8.1 Sample size calculation

This was the first formal investigation on the interaction between pain and reward processing, and therefore, the effect size was unknown. Consequently, we based the sample size calculation on a small effect size. In the context of ANOVAs, effect size can be expressed as Cohen's f2, and f2=0.04 (f=0.2) is considered a small effect size (Cohen, 1988).

A repeated measure ANOVA with two within subject factors ('incentive' and 'pain condition') with three-by-two levels was conducted. In order to detect a small interaction effect with a 5% probability of committing a Type 1 error (alpha=0.95) and a 20% probability of committing a Type 2 error (beta=0.8), a minimum of thirty-four participants were needed to be tested.

2.1.8.2 Statistical analysis of the incentive delay task

To assess the influence of pain and incentives on motivation to work for reward a repeated-measures ANOVA was conducted with two within-subject factors: pain condition (two levels: pain and control condition) and incentive (three levels: $ 0.04; $

1.00; $ 4.00). Reaction time in response to the target cue was used as dependent variable.

To assess the influence of pain and incentives on hedonic responses to reward a second repeated measures ANOVA was calculated with condition and incentive as factors and VAS 'liking' ratings as dependent variable.

Following significant main or interaction effects of the ANOVAs, post-hoc paired student's t-tests were conducted to compare mean values between conditions and across incentives.

Pearson's correlation was carried out between changes in reaction times between conditions (pain minus control condition) and changes in unpleasantness ratings to assess the association between pain-induced changes in motivation and the affective component of pain perception, which is supposedly more closely linked to motivation than the sensory component of pain (Heckhausen 2000). Cook's distance was applied to identify multivariate outliers using a cut-off value of d>1/n (with n being the number of observations).

2.1.8.3 Statistical analysis of the motor control task

To assess whether pain had an effect on simple motor responses a paired student's t-test was calculated for average reaction times from the motor control task between the pain and control conditions.

2.2 Figures and tables

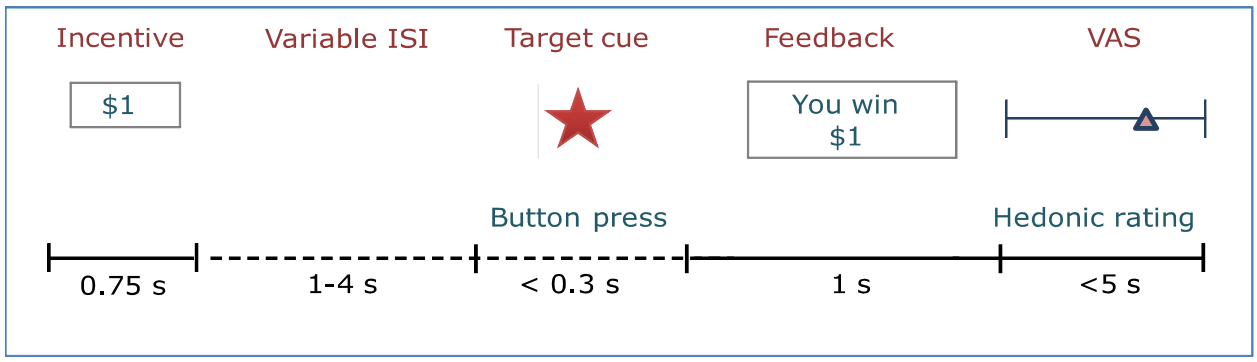

Fig. 1 The incentive delay task: outline of one trial including timeline. Participants saw the incentive being displayed first. Shortly after, the target cue appeared. If participants reacted fast enough in response to the target cue they won the amount of money that was displayed beforehand. They got feedback right away, followed by their rating on how much they liked/disliked the most recent win/omission of a win.

Chapter 3

The influence of acute pain on motivational and emotional aspects of reward processing: behavioral studies in healthy people.

3.1 Rationale

Escaping pain and obtaining reward are two fundamental motivations. When these motivations occur simultaneously, they seem to interact (Becker et al., 2013; Fields 2006; Navratilova and Porreca 2014). When an organism faces a potentially rewarding stimulus whilst being in pain, it supposedly takes a ‘decision’, according to the Motivation-Decision Model (Fields 2006). It will either prioritize one or the other, depending on situational and personal factors, and the state of the organism. To withdraw attention from pain and have the person concentrate instead on pleasurable activities is a central feature of behavioral pain therapy. While not eliminating the pain, this approach focuses on improving the functioning and life quality of patients suffering from pain (Gatzounis et al., 2012).

Pleasure is the hedonic response to reward. In the attempt to maximize pleasure, individuals show an effort to obtain the potentially rewarding stimulus. Both aspects, perceived pleasure and motivational drive, are important components of reward processing. While results in rodents suggest that acute pain influences the motivational – but not hedonic – aspect of reward processing (chapter 1, section 1.2.3.3.2), no data in humans exist to confirm the influence of acute pain on reward.

Therefore, we conducted two psychophysical experiments in healthy participants that investigated the effects of acute pain on the two identified aspects of reward

processing, namely: the motivation to receive reward, and the hedonic response to reward.

Based on the findings in rodents, I hypothesized that 1) the motivation to work for monetary reward will be increased when simultaneously presented with pain. Further, the hedonic responses to reward will be unaltered by pain.

In order to test these hypotheses, I engaged healthy people in a monetary incentive delay paradigm. To assess motivation with this paradigm, I measured reaction time in response to target cues that promised monetary wins of different values. The hedonic response to reward was assessed by obtaining ratings on a visual analogue scale. For the latter, I employed two different methods between experiment 1 and experiment 2. Both studies followed the same within-subject design. Participants underwent the paradigm twice: once while they were simultaneously given heat pain and once when given a non-painfully warm stimulation. The session order was counter-balanced, meaning that half of the participants started with the painful condition and the other half with the non-painful control condition.

3.2 EXPERIMENT 1

3.2.1 Results

3.2.1.1 Manipulation checks

3.2.1.1.1 Pain Ratings and applied temperatures

The tonic heat stimulation in the pain condition induced a moderately painful sensation (average intensity rating across all participants and time points per task; IDT: 135.86±3.33; MCT: 146.06±3.39), and was described as unpleasant (average unpleasantness ratings per task. For IDT: -35.81±4.00; for MCT: -44.91±4.33). In the control condition, the thermal stimulation was rated as non-painful (average intensity rating across all participants and time points per task; IDT: 18.36±1.98; MCT: 19.00±2.44) and described as pleasant (IDT: 24.98±4.54; MCT: 29.29±4.64). In both conditions, a majority of participants showed some adaptation to the applied temperature over time but by increasing stimulation temperatures intensity ratings were kept constant (fig. 2). In the painful condition the initial average temperature of 37.08±0.43˚C at time point 1 (before motor control task) was increased to the final average temperature of 38.53±0.42˚C at time point 6 (after IDT). In the control condition the initial average temperature of 35.75±0.25˚C at time point 1 was increased to the final average temperature of 37.86±0.38˚C at time point 6.

3.2.1.1.2 Motor control task

No differences in reaction times were found between pain and control condition in the motor control task (Control: 280.05±5.93 ms; Pain: 280.69±7.69 ms,; t_{39}=-0.07; p=0.95). This indicates that reaction times per se were not altered by pain.

3.2.1.1.3 Skin Conductance: Amplitudes and tonic levels

Skin conductance amplitudes

Whereas pain had no significant main effect on skin conductance amplitudes recorded during the IDT (F=2.79; p=0.10), the main effect of incentives on skin conductance amplitudes was highly significant (F=14.06; p<0.001) with lowest amplitudes for the lowest incentive ($ 0.04), medium amplitudes for the medium incentive ($ 1.00), and highest amplitudes for the highest incentive ($ 4.00). No interaction between condition and incentives was found (F=0.96; p=0.39). Figure 3a depicts results for skin conductance amplitudes for each incentive and pain condition.

Skin conductance levels

Pain had a significant main effect on skin conductance levels (F=4.23; p=0.047), with higher skin conductance levels in the pain condition compared to the control condition. The main effect of incentives on skin conductance levels was also significant (F=4.70; p=0.01) with highest levels for the lowest incentive ($ 0.04), medium levels for the

medium incentive ($ 1.00), and lowest level for the highest incentive ($ 4.00). No interaction between condition and incentives was found (F=0.92; p=0.40). Post-hoc paired student t-tests revealed a trend for higher levels in the pain compared to control condition for the lowest incentive (t_{36}=-1.84; p=0.074) and for the medium incentive (t_{36}=-1.95; p=0.059), and a significantly higher level for pain compared to control condition for the highest incentive (t_{36}=-2.22; p=0.033). In the pain condition, skin conductance levels did not differ significantly between incentives. In the control condition, levels were significantly higher for the lowest compared to the highest incentive (t_{36}=-2.98; p=0.005).

Figure 3b depicts the skin conductance levels in each pain condition and for all incentives. Our results on skin conductance demonstrate increasing arousal with increasing incentives (evidenced by the SCR amplitudes), thereby supporting the parametric design of the IDT, and generally higher levels of arousal in the pain compared to the control condition (evidenced by the SCR levels).

In summary, using measures on different perceptional and behavioral levels, the presented manipulation checks confirmed the feasibility and quality of our pain stimulation technique and our parametric reward task.

3.2.1.2 The influence of pain on the measures of Reward

3.2.1.2.1 The influence of pain on motivation

Three participants were excluded as outliers from the analysis, because their reaction times increased or decreased more than 2 standard deviations from the group mean between control and pain condition. Thus, the differences in reaction times for these three participants laid beyond the expected range for changes in reaction time due to increased/decreased motivation. Hence, the following results are reported for a sample of N=37.

Two-way repeated measures ANOVA with pain condition and incentives as within-subject factors showed a significant main effect of incentives on reaction time ($F_{2,37}$=13.72, p<0.001), but no main effect of pain on reaction time ($F_{1,37}$=0.01, p=0.93). However, incentives significantly interacted with pain ($F_{2,37}$=5.03; p=0.009), with decreased reaction time for the highest incentive, but not for the low or medium incentives in the pain condition compared to control condition. Post-hoc paired student's t-test revealed a trend for decreased reaction time in the pain compared to control condition for the highest incentive (t_{36}=1.91, p=0.065). In the control condition, reaction times were lower for medium than for low incentives (t_{36}=-3.41, p=0.002), and lower for high than for low incentives (t_{36}=-2.74, p=0.009). In the pain condition, reaction times were lower for medium than for low incentives (t_{36}=-2.97, p=0.005), lower for high than for low incentives (t_{36}=-5.39, p<0.001) and lower for high than for

medium incentives (t_{36}=-2.27, p=0.029). Figure 4 depicts reaction times in each condition and for all incentives.

3.2.1.2.1 The influence of pain on hedonic responses

Two-way repeated measures ANOVA with pain condition and incentives as within-subject factors showed a significant main effect of incentives on hedonic ratings ($F_{2,37}$=89.12, p<0.001), but no main or interaction effect of pain on hedonic ratings ($F_{1,37}$=0.09, p=0.77 and $F_{2,37}$=0.22, p=0.70). In both conditions, hedonic ratings were highest for the high incentive and lowest for the low incentive (fig. 5), with all differences among incentives being statistically significant (paired Student's t-tests, all p<0.001).

3.2.1.2.1 The relation between pain-induced changes in pain unpleasantness ratings and the increase in motivation

Two more participants had to be excluded as they were identified as multivariate outliers according to Cook's distance with a cut-off value of d>4/n. Hence, the following results are reported for a sample of N=35. Pearson's correlation revealed a highly significant positive correlation between pain-induced changes in pain unpleasantness (unpleasantness perceived in pain condition minus unpleasantness perceived in control condition) and pain-induced changes in motivation to receive the highest incentive (reaction time for $ 4.00 in the pain condition minus reaction time for $ 4.00 in control

condition) of r=0.52 (p=0.001). The greater the pain-induced increase in unpleasantness the shorter the reaction time to response to the target cue in the $ 4.00 trials (indicating increased motivation to receive the reward). Figure 6 depicts the correlation between pain-induced changes in subjective unpleasantness and the increase in motivation.

3.3 EXPERIMENT 2

3.3.1 Preamble

With experiment 2, I followed up on the observed similarity in hedonic responses to reward between the painful and pain-free condition. My concern with experiment 1 was that participants might have not been able to introspect accurately enough to express subtle hedonic changes on the employed VAS. A further potential issue might have been that participants actually followed a categorical way to rate each incentive independent of the pain condition. In other words, the participants might have responded with a certain number of key presses which they associated with each of the three incentive categories (e.g. always moving the cursor 5 units to the right when winning $1, and 10 units when winning $4). This potential problem might have led to the observed lack of differences in 'liking' ratings between the pain and control condition. To extend our understanding whether acute pain does or, in fact, does *not* influence hedonic responses to monetary reward, we repeated experiment 1 in a new sample of 36 participants (see chapter 2, section 2.1.1). While we employed the same VAS as before, we now used a touch screen for participants to indicate their rating by a single touch. The advantage of this method is twofold: first, even minor changes in 'liking' could be expressed, because ratings were no longer limited to the minimum unit which the cursor could be moved by (i.e. 5 mm per key press). Second, this method avoids – at least to some extent – the problem of countable key presses for each incentive.

3.3.2 RESULTS

3.3.2.1 Manipulation checks

3.3.2.1.1 Pain Ratings and applied temperatures

The tonic heat stimulation in the pain condition induced a moderately painful sensation (average intensity rating across all participants and time points per task; IDT: 154.21±4.03; MCT: 142.22±4.65), and was described as unpleasant (average unpleasantness ratings per task. For IDT: -53.93±3.96; for MCT: -44.25±4.61). In the control condition, the thermal stimulation was rated as non-painful (average intensity rating across all participants and time points per task; IDT: 19.19±1.91; MCT: 23.00±2.81) and described as pleasant (IDT: 8.43±4.05; MCT: 13.03±3.70). In both conditions, a majority of participants showed some adaptation to the applied temperature over time but by increasing stimulation temperatures intensity ratings were kept constant (Fig. 7). In the painful condition the initial average temperature of 38.85±0.39˚C at time point 1 (before motor control task) was increased to the final average temperature of 40.44±0.59˚C at time point 6 (after IDT). In the control condition the initial average temperature of 36.94±0.35˚C at time point 1 was increased to the final average temperature of 38.16±0.64˚C at time point 6.

3.3.2.1.2 Motor control task

Replicating the results of experiment one, no differences in reaction times were found between pain and control condition in the motor control task (Control: 258.21±4.83 ms, Pain: 267.82±10.73 ms, t_{35}=-0.99; p=0.33). This indicates that reaction times per se were not altered by pain.

3.3.2.2 The influence of pain on the measures of Reward

3.3.2.2.1 The influence of pain on motivation

While reaction times were normally distributed in experiment 1, those in experiment 2 had to be corrected for non-normality by applying $f(x)=x^2$. Trials with reaction times identified as extreme outliers (outside the range of the average transformed RT ± 3 SD) were excluded; kurtosis and skewness were smaller than a value of 2 after the correction and the exclusion of extreme outliers.

Two-way repeated measures ANOVA with pain condition and incentives as within-subject factors showed a significant main effect of incentives on reaction time ($F_{2,36}$=6.28, p<0.01), and a main effect of pain on reaction time ($F_{1,36}$=4.45, p=0.04). However, there was no significant interaction for incentive and pain ($F_{2,36}$=1.04; p=0.36). Post-hoc paired student's t-test revealed a significantly decreased reaction time in the pain compared to control condition for the medium incentive (t_{35}=2.62, p=0.01). In the control condition, reaction times were lower for medium than for low incentives (t_{35}=-2.35, p=0.03), lower for high than for low incentives (t_{35}=-3.80, p<0.01),

and lower for high than for medium incentives (t_{35}=-2.83, p<0.01). In the pain condition, reaction times were lower for medium than for low incentives (t_{35}=-2.74, p=0.01), lower for high than for low incentives (t_{35}=-2.91, p<0.01), and comparable for high and medium incentives (t_{35}=-0.07, p=0.94). Figure 8 depicts reaction times in each condition and for all incentives.

3.3.2.2.2 The influence of pain on hedonic responses

Using a different method to indicate the perceived 'liking' of a just obtained reward – one being probably more sensitive to subtle changes – yield comparable results to those already reported for experiment 1.

A two-way repeated measures ANOVA with pain condition and incentives as within-subject factors replicated the significant main effect of incentives on hedonic ratings ($F_{2,36}$=49.46, p<0.001), but no main or interaction effect of pain on hedonic ratings ($F_{1,36}$=0.34, p=0.56 and $F_{2,36}$=0.35, p=0.70). In both conditions, hedonic ratings were highest for the high incentive and lowest for the low incentive (Fig. 9), with all differences among incentives being statistically significant (paired Student's t-tests, all p<0.001).

3.4 Discussion and conclusions

With part 1 of my thesis, I demonstrated that acute pain increased the motivation to obtain reward, while hedonic responses were not influenced by pain. The result that participants liked their reward equally in the painful and control condition was demonstrated using two different methods to indicate hedonic ratings on a VAS. I interpret the results presented in this chapter as an adaptive coping attempt. While pain itself is inescapable, people try harder to reach out for positive means.

Our results are in line with findings in rodents. Acutely injured rats have been demonstrated to spend more time in proximity to rewarding food pellets than control animals (Low and Fitzgerald 2012). The consumption of the pellets, however, was comparable between both groups. In accordance with our results, these data imply a pain-induced increase in the motivation to obtain reward, while rewards are similarly liked independent of the presence or absence of pain.

The result of unchanged ‘liking’ ratings suggests that pain might simply not influence the hedonic response to reward. Yet, one consideration might be that participants are simply not able to introspect accurately enough to express subtle hedonic changes on a VAS. However, the replication (experiment 2) of the results found in experiment 1 – now using an improved method to acquire ‘liking’ ratings – strengthens the finding that pain has indeed no effect on the hedonic component of reward processing.

Investigating the question how pain influences the motivation to obtain reward, we observed slightly different results for experiment 1 and experiment 2. While in experiment 1 the reaction time was significantly decreased for the highest incentive ($ 4) during the pain compared to the control condition, a similar difference was found only for the medium incentive ($ 1) in experiment 2. In both experiments participants were in a highly attentive and motivated state which resulted in fast reaction times throughout the experiment. This might have resulted in floor effects. Floor effects imply that participants have a certain minimum reaction time that constitutes their personal limit. Beyond this limit, further increasing motivation would no longer be reflected in decreasing reaction times. Our data suggest floor effects in both experiments. In experiment 1, participants were generally very fast in their responses to the target cue, already in the control condition. Here we observed that participants seemed to respond with their personally fastest reaction time for $ 1 already. Apparently, they were not able to react any faster than that, which resulted in indistinguishable reaction times for $1 and $ 4 in the control condition. However, when participants were in pain they managed to actually overcome this floor effect when playing for the highest incentive and responded with even lower reaction times than what had seemed their personal limit whilst not in pain. In experiment 2, participants generally had slightly lower average reaction times than the sample in experiment 1. While the group in experiments 2 decreased in their reaction times linearly with increasing incentives during the pain-free control condition, they showed a floor effect during the pain condition. Compared to the pain-free condition, they responded significantly faster in the pain condition when playing for the medium incentive ($ 1). However, they were unable to further decrease

their reaction time when playing for the highest incentive ($ 4). I speculate that this floor effect might have prevented an interaction effect between pain and incentive in experiment 2. Despite these differences, however, both experiments do confirm that pain increases the motivation to obtain reward.

To assess motivation, I measured reaction times in response to an external stimulus. Interestingly, reaction times have also commonly served as a measure of attention (reviewed in Callahan and Terry 2015). In contrast to our study, the performance during attention tasks is generally worse when in pain (e.g. (Buhle and Wager 2010; Eccleston 1994; Van Damme et al., 2008b; Van Ryckeghem et al., 2012). To resolve the apparent contradiction between my findings and those from attention studies, it may be important to take a closer look at the tasks people are engaged in while in pain, and – probably even more important – whether the outcome of the task is of relevance to the participant's state. In general, individuals are more sensitive to information that is relevant to reach a certain goal; goal-irrelevant information, in contrast, is likely to be ignored (Van Damme et al., 2010). Similarly, while in pain, the sensitivity towards incentives associated with rewarding outcomes are increased, because it assists in achieving the goal to re-establish hedonic homeostasis. Conversely, during goal-irrelevant tasks that do not impact on the homeostatic balance while in pain, such as mental arithmetic, memory or discrimination tasks, the performance is worse compared to a pain-free state, as shown in many experimental studies on attention (e.g. Buhle and Wager 2010; Eccleston 1994; Van Damme et al., 2008b; Van Ryckeghem et al., 2012).

The observed correlation between pain unpleasantness and the motivation to obtain reward supports the idea that a pain-induced increase in motivation serves the purpose of re-establishing the hedonic homeostasis. This correlation revealed that participants who experienced the pain as being more unpleasant were more motivated to obtain reward. Consequentially, I interpret the increased effort to obtain reward as an attempt to compensate for the negative state that was induced by the pain. Although not terminating the pain, it may help to re-establish the hedonic homeostasis. In addition, evidence from our own laboratory suggests that receiving a rewarding stimulus whilst being in pain has indeed analgesic effects (Becker et al., 2013; Becker et al., 2015). Although I did not assess the analgesic effect of winning in the current experiments, I speculate that pain perception was probably reduced when obtaining reward. This means that the increased effort to obtain reward (i.e. faster responses to the target cue) was not only reinforced by winning money, but probably also by a decrease in the perceived pain itself.

Interestingly, the current finding that acute pain increased motivation is in contrast to studies of long-term pain. Pain patients typically show a low motivational drive. This has been demonstrated in studies using self-report questionnaires (Barendregt et al., 1998; Fishbain et al., 2004) or experimental paradigms (Apkarian et al., 2004a; Becker et al., 2011). The conflicting findings for chronic and acute pain may imply a bimodal effect of pain on motivation (i.e. increased motivation with acute pain and decreased motivation with chronic pain). This notion is supported by rodent studies on stress.

Animals exposed to acute physical stress show enhanced reward seeking behavior. These behaviors involve an increased intake of palatable food (Hagan et al., 2002) and saccharine (Pucilowski et al., 1993), an increase in voluntary exercising (Sibold et al., 2011), and enhanced sexual behavior in males (Barfield and Sachs 1968; Caggiula 1972; Goldfoot and Baum 1972; Retana-Marquez et al., 1996; Sharma and Hays 1974). Likewise, humans acutely exposed to stress have been identified to show elevated risk taking behavior (Lighthall et al., 2009), presumably to increase immediate reward.

On the contrary, rodents exposed to long-term physical stress reveal decreases in reward behaviors, including reduced sexual behavior (Retana-Marquez et al., 1996) and decreased saccharine intake (Pucilowski et al., 1993).

Further, the nature of the stressor seems to play an important role. Animals exposed to social rather than physical stress are decreased in their motivational drive, independent of the duration of exposure. Animals that experience single (Meerlo et al., 1996) or repeated defeat (Rygula et al., 2005; Rygula et al., 2008) show diminished locomotion, sniffing and rearing in the open field, and are more immobilized in the forced swim test (Rygula et al., 2005; Rygula et al., 2008). Chronic pain patients are not only frequently exposed to physical stress in form of their pain, but may also face many social stressors, including the loss of independence or fewer social interactions. Based on the rodent literature on stress, it is plausible to assume that physical and social stress may contribute to decreased reward processing in chronic pain patients.

In analogy to the bimodal effect of pain on reward seeking, phasic dopamine release in response to stress has been identified to follow a biphasic curve as a function of time (Puglisi-Allegra et al., 1991). High release of dopamine in the ventral striatum has been reported in rodents exposed to short-term stress (Puglisi-Allegra et al., 1991). In chronically stressed rats, however, the dopamine release in the ventral striatum is reduced (Gambarana et al., 1999; Puglisi-Allegra et al., 1991). Effects of acute and chronic pain on dopamine are comparable to the ones demonstrated for stress. Some evidence exists that dopamine is being released in the striatum in response to acute pain (Scott et al., 2006; Wood et al., 2007), but is diminished in patients with chronic pain (Martikainen et al., 2015; Wood et al., 2007). A change in dopamine sensitivity with prolonging exposure to pain may constitute the neural substrate underlying the bimodal effect of pain on reward behavior.

In summary, part 1 of my thesis revealed that acute inescapable pain leads to an increased motivation to obtain reward. Once obtained, the reward is perceived as equally pleasant as in non-painful situations. My results are in accordance with previous rodent studies investigating the influence of pain and physical stress on reward behavior. I propose that reaching out for positive means in situations when pain cannot be escaped, is an adaptive coping strategy. While not eliminating the pain, it may help to re-establish the hedonic homeostasis and therefore improve well-being. The increase in motivational drive is likely mediated by the dopaminergic system. A decrease in sensitivity of this system as a consequence of long-term exposure to pain

might be the neural underpinning of decreased motivation, which is commonly described in chronic pain patients. This idea, which is supported by rodent studies on long-term stress, could have important clinical implications for patients suffering from chronic pain.

3.5 Figures and tables

EXPERIMENT 1

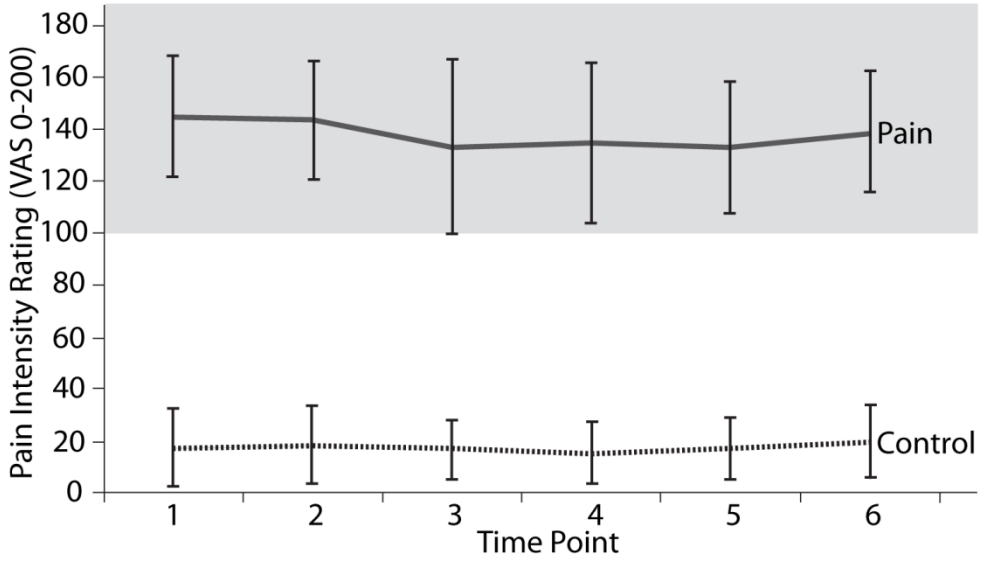

Fig. 2 Intensity ratings over the course of testing
Intensity ratings in the control condition were consistently in the non-painful range (white background) whereas intensity ratings in the painful condition were consistently in the painful range (grey background). Depicted is mean intensity rating across the group +/- standard deviation.

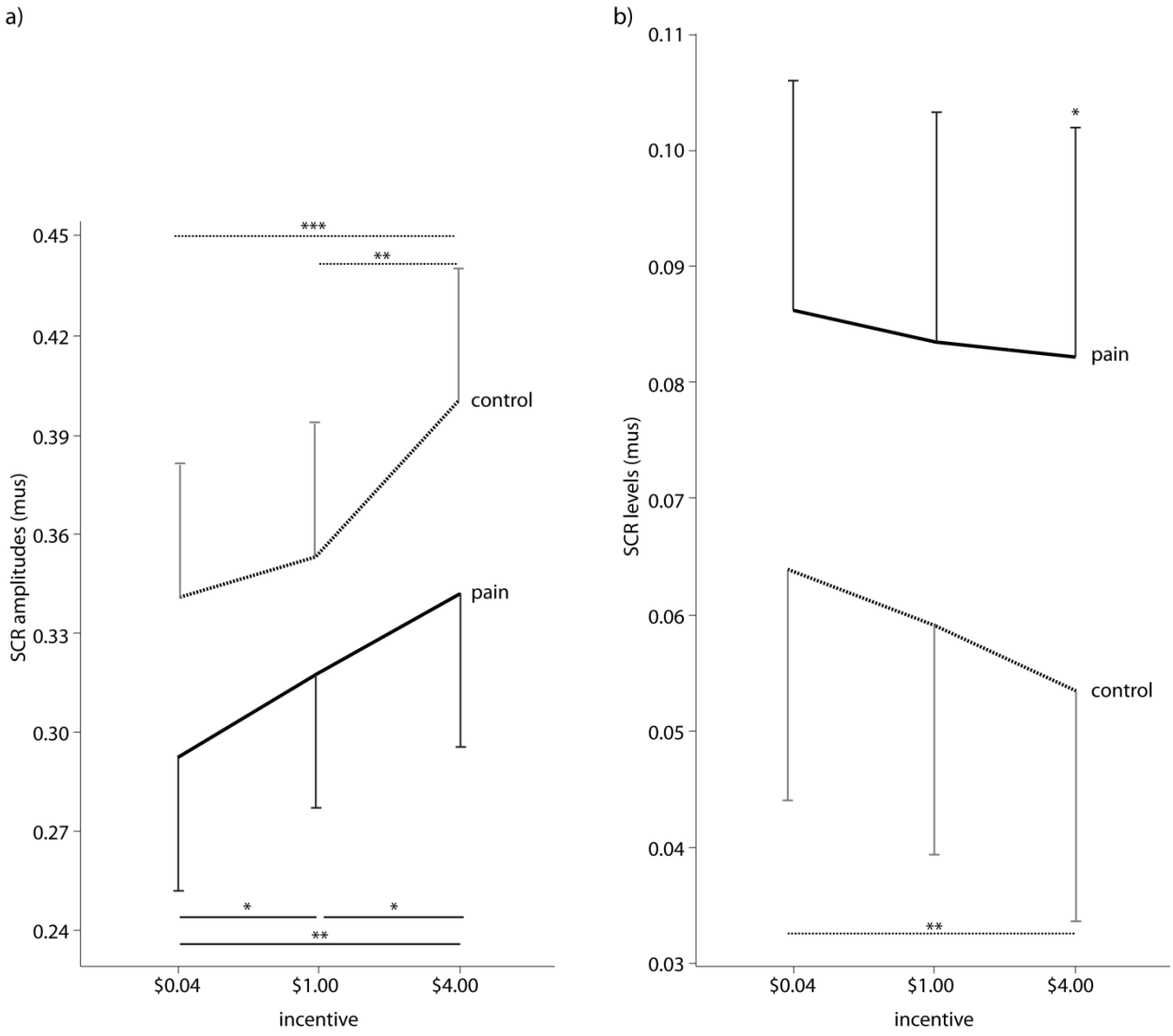

Fig. 3 Skin conductance responses (A) and levels (B) during the IDT
Skin conductance responses are higher the greater the incentive value. Skin conductance levels are generally higher in the pain compared to control condition. (* p<0.05; ** p<0.01; *** p<0.001). Mean+/-SEM.

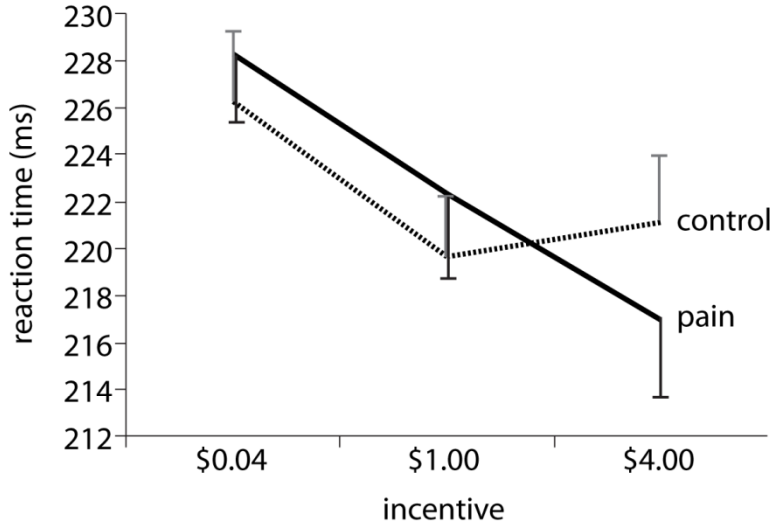

Fig. 4 Pain increases the motivation to obtain reward if incentive is high.
Incentives and pain showed a significant interaction on reaction time (p=0.009), with decreased reaction time for the highest incentive (p=0.065), but not for the low or medium incentives in the pain condition compared to control condition. Mean+/-SEM.

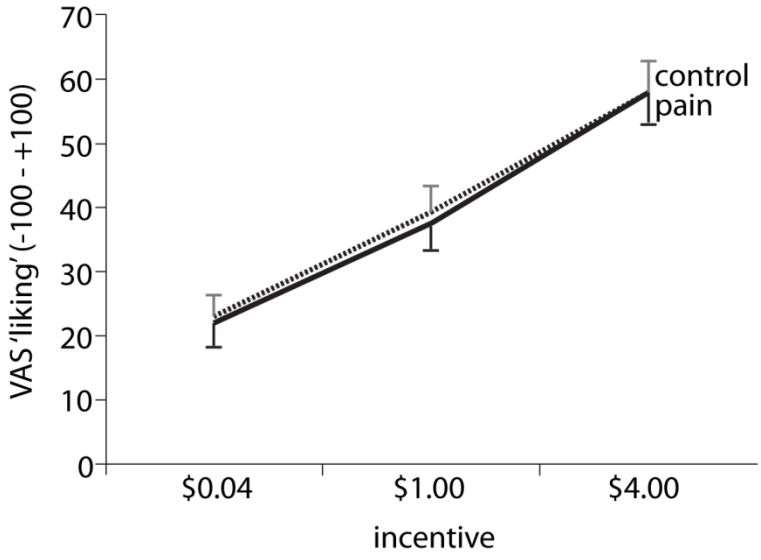

Fig. 5 Pain has no influence on hedonic responses to reward.
Higher pain ratings were associated with higher incentive values; no differences were found for hedonic ratings between conditions. Mean +/- SEM.

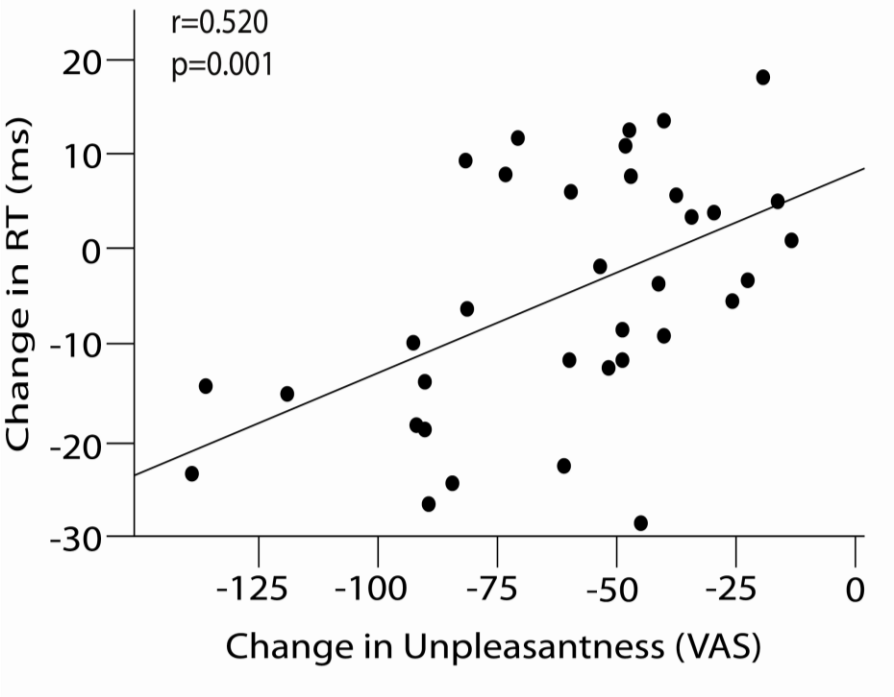

Fig. 6 A greater increase in pain unpleasantness is associated with a greater increase in motivational drive.
The bigger the negative shift participants perceived towards unpleasantness in the painful compared to the control condition the lower their reaction time in response to the target cue of the highest incentive in the pain compared to the control condition.

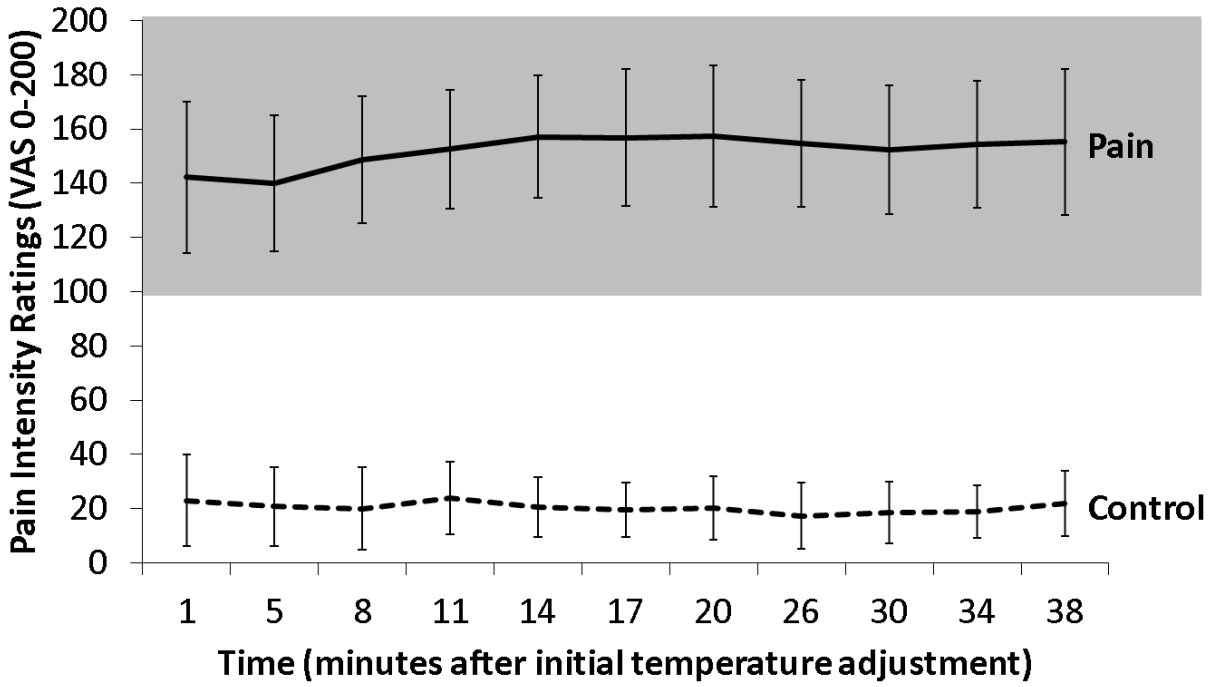

Fig. 7 Intensity ratings over the course of testing
Similar to the first experiment, intensity ratings in the control condition were consistently in the non-painful range (white background) whereas intensity ratings in the painful condition were consistently in the painful range (grey background). Depicted is mean intensity rating across the group +/- standard deviation.

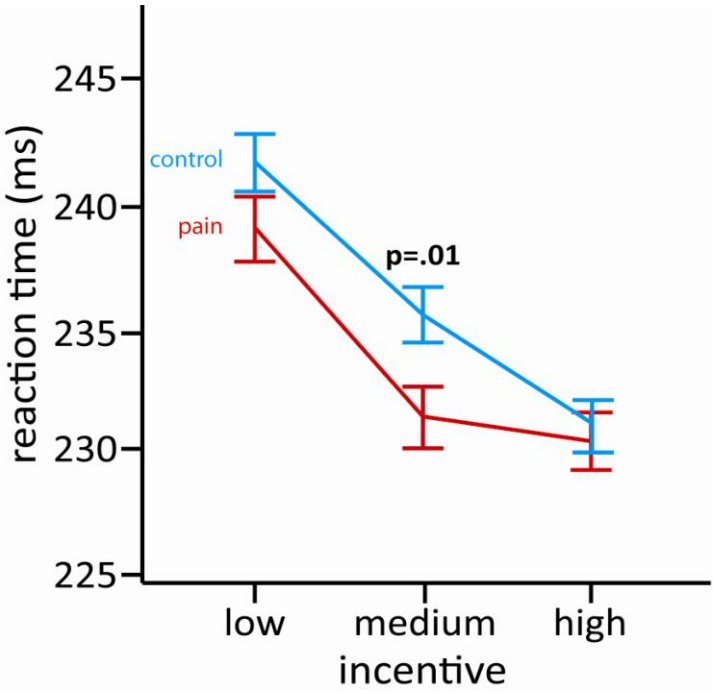

Fig. 8 Pain increases the motivation to obtain reward.
Similar to experiment 1, reaction times were lower in the pain condition. However, instead of an interaction between pain condition and incentive, we observed a main effect of pain (p=0.04), with significantly lower reaction times in the pain condition for the medium incentive (i.e. $1), but not for low or high incentives. The lack of a difference in reaction times between conditions for the high incentive might be explained by a floor effect. Mean+/-SEM.

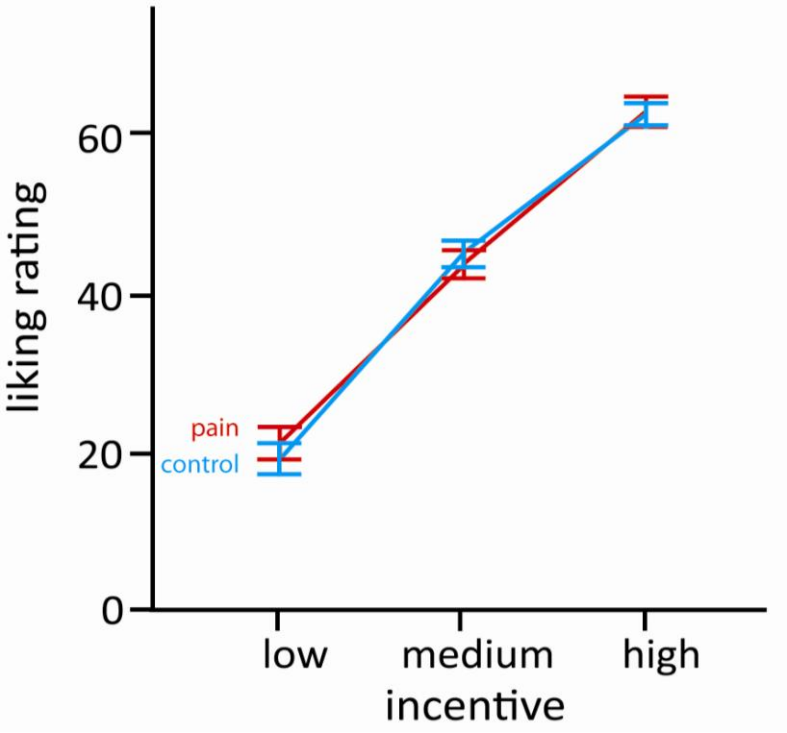

Fig. 9 Replication of the finding that pain does not influence hedonic responses. Higher pain ratings were associated with higher incentive values; no differences were found for hedonic ratings between conditions. Mean +/- SEM.

PART 2

WHEN ACTIVE COPING REMAINS UNREWARDED: BEHAVIORIAL AND NEURAL CHANGES FOLLOWING UNSUCCESSFUL ATTEMPTS TO AVOID PAIN

Preamble

Pain initiates coping with the aim either to eliminate or reduce pain, or to pursue rewarding activities to compensate for the hedonic homeostatic imbalance that pain causes (reviewed in Gandhi et al., *in review*). While having focused on active compensatory coping when pain itself is unavoidable in part 1 of this thesis, in part 2, I will address active coping in situation where acute pain is, in fact, avoidable. However, in order to avoid pain, effort is required and even despite trying hard, not every attempt necessarily leads to success. In the following chapters, I am specifically interested in the effect of unrewarded pain avoidance attempts on the subsequent motivation to avoid pain and its underlying neurobiology. I will further present how a clinical history of frequent, unavoidable pain in migraineurs amplifies the behavioral effect of pain on subsequent pain avoidance and how its neural correlates relate to clinical characteristics of these patients.

Chapter 4:

Methods – Part 2

4.1. Methods Background

4.1.1 Basic principles of magnetic resonance imaging (MRI)

A majority of MRI techniques take advantage of the magnetic properties of hydrogen (^{1}H) nuclei – with hydrogen being the most prevalent atom of the human body (reviewed in Blink 2004; Roberts and Mikulis 2007). The hydrogen atom has a nucleus with only one proton (i.e. an odd number of protons), and one electron. The proton is electrically charged and rotates around its axis, which causes an electrical current and its associated magnetic field. Therefore, it compares to a bar magnet with a net magnetic moment, called 'spin'.

Bringing the participant to a strong external magnetic field (B_0), such as the one in an MR scanner, the spins of the hydrogen nuclei are forced to align either parallel or anti-parallel to the main direction of B_0 (i.e. the z-axis). More atoms will align parallel to B_0, because it is the state of lower energy compared to the anti-parallel alignment. This is called a net magnetic moment (magnetization, M_z) parallel to the z-axis. Next, a brief radio frequency (RF) pulse will be turned on. Its frequency is optimized to excite the targeted protons (Larmor frequency). Commonly, an RF pulse of 90° flip angle is being used. This pulse forces the spins of the hydrogen nuclei to flip from the z-axis to the xy-plane and, therefore, causing a new net magnetiziation (M_{xy}). M_{xy} induces a signal that can be detected by the receiver coil. Further, the RF pulse also forces the spins of the hydrogen nuclei into phase with each other, meaning that all magnetic moments are now in the same phase on their spinning path around the z-axis.

Turning the RF pulse off again, the hydrogen nuclei start to relax; they are approaching a lower-energy state again which is in parallel to the z-axis (i.e. the main direction of the strong external magnetic field). Accordingly, the signal associated with M_{xy} begins to decay. This process encompasses two important components: (1) the recovery of M_z magnetization, and (2) the decrease of M_{xy} magnetization.

The recovery of M_z magnetization is determined by the longitudinal relaxation time, T1. It describes an interaction between the spin and the magnetic environment, implying that the recovery of M_z magnetization is dependent on the field strength of the magnetic field, with longer T1 for higher field strengths. Contrary, the rate of decrease in M_{xy} magnetization is independent of the field strength; it rather reflects the effect of spin-spin interactions, and is described by the transverse relaxation time T2. Both, T1 and T2 relaxation times are constant lengths distinctively specified by each particular tissue, such as fat and water.

Now, to generate an actual contrast with MRI a pulse sequence has to be applied. A pulse sequence includes excitatory RF pulses, signal detection, and periods of recovery (a pause in between excitatory pulses). The sequence is determined mainly by the repetition time (TR) and the echo time (TE). TR, on one hand, describes the time in between two RF pulses and sets thus the amount of T1 recovery when the signal is being read. TE, on the other hand, determines the amount of T2 decay when the signal is being read. As briefly mentioned above, T1 and T2 relaxation times are tissue-specific constants. Fat, for instance, has a short T1 relaxation time. Therefore, fat-rich tissues – such as the brain's white matter – appear light (i.e. high signal) on a T1-weighted image. Contrary, water has a long T1 relaxation time causing cerebrospinal

fluid to appear dark (i.e. low signal) on a T1 weighted image. Exploiting these physical characteristics, a contrast between different brain tissues can therefore be imaged. The information provided here is based on a text book and a review article on MR physics (Blink 2004; Roberts and Mikulis 2007).

Finally, T2* images are determined by T2 decay and local field inhomogeneities. The latter causes additional dephasing of the hydrogen nuclei, and thus makes T2* even shorter than T2 relaxation time. T2* is essential for blood-oxygenation-level-dependent (BOLD) functional MRI which is typically performed to investigate local increases in brain activation (Mikulis and Roberts 2007; Roberts and Mikulis 2007).

4.1.2 Blood-oxygenation-level-dependent (BOLD) functional MRI

Functional magnetic resonance imaging (fMRI) has been around for approximately 25 years – the first published research article appeared in 1991 (Belliveau et al., 1991). This non-invasive technique enables us to map human brain activation either at rest or during an external task. In the final chapters of this thesis I undertook fMRI experiments to investigate the brain activation associated with the preparation of pain avoidance behavior in humans in the face of a threatening cue.

FMRI is based on the principle that a local increase in neural activity requires the supply of energy in form of adenosine triphosphate (ATP). A majority of the ATP supply of the brain is obtained from oxidative glucose metabolism – an aerobic mechanism requiring oxygen. The increase in the consumption of oxygen and glucose leads to an

increase in cerebral blood flow (CBF). CBF increases to a greater extent than the oxygen consumption which results in a net increase of oxygen in the blood vessels and in the tissue. This oversupply of oxygen is the basis for BOLD fMRI, which detects alterations in the ratio of deoxygenated to oxygenated hemoglobin. This is physically possible because of the different magnetic characteristics of deoxygenated and oxygenated hemoglobin – deoxygenated blood is paramagnetic (i.e. it causes an inhomogeneous magnetic field in its vicinity, meaning signal loss), while oxygenated blood is diamagnetic (i.e. it does not cause a change in the magnetic field). Because active brain areas have a greater ratio of deoxygenated to oxygenated hemoglobin than relatively inactive brain areas, we will thus observe an overall improvement of the local field homogeneity, meaning an increase in signal of a T2* image (reviewed in Huettel et al., 2004).

BOLD fMRI can further be used to investigate 'effective connectivity' between different brain regions based on the observation of temporally correlated signal changes associated with specific events during an external task. A so called 'psychophysiological interaction analysis' [PPIs; (Friston et al., 1997)] can be performed; it provides a model of how a certain psychological context changes the influence of one brain area (i.e. the *seed* region) on either another area specifically, or a widespread network of brain regions (i.e. *region of interest, RoI*). I employed this specific technique within my fMRI experiment to explore effective networks underlying the preparation of active coping when participants were visually presented with pain-indicating threats.

4.2 Methods and procedures

4.2.1 Participants

The study was approved by the local Ethics Committee (Comité mixte d'éthique de la recherché, Regroupement Neuro-Imagerie Québec – CMER-RNQ, see appendix B) and informed consent was obtained from all participants according to the revised Declaration of Helsinki (2008). Exclusion criteria for healthy participants included excessive smoking (more than 10 cigarettes a day), regular use of recreational drugs (more than once in three months), alcohol consumption of > 10 UK units per week, pregnancy, the presence or history of chronic pain conditions, major medical, neurological or psychiatric conditions, and MRI contradictions. Further exclusion criteria specific to the group of migraine patients included less than 1 or more than 15 migraine attacks per month, headache at the time of testing, and chronic pain conditions other than migraine. All included migraine patients reported to take acute pain medication on demand when migraine attacks commence; one patient reported the daily use of preventative migraine medication (for details, see Table 1). All included patients met the criteria of episodic migraine (Katsarava et al., 2012); four patients had migraines with aura and 13 patients migraine without aura. Importantly, all patients perceived their migraine attacks as unavoidable, aversive events, which occur regularly. Further, migraine headaches were experienced as distinctive attacks with pain-free periods in between attacks. The total study sample consisted of 17 episodic migraine patients (3 males, 14 females; mean age 26±5, range 19-35 years) and 17 age- and gender-matched healthy controls (3 males, 14 females; mean age 28±5, range 19-38 years),

with no differences in depressions scores between the groups (mean Beck's depression Inventory (BDI) score for patients: 5.0±5.2; mean BDI score for healthy people: 4.2±4.3, p=.627; Table 1).

4.2.2 Experimental procedure

A parametric between-subject design (within-between factor interaction) was used to address the aims of this research. Data collection was performed in a single session per participant. Upon arrival, informed consent was obtained, and the study aims, pain rating scale and tasks were explained to the participant. Once positioned on the scanner bed, pain sensitivity was tested (details below) to familiarize participants with the sensation of the electrical stimuli and to determine the stimulation intensities. Participants were reminded of the task instructions and practiced one trial of the pain avoidance task (details below) using visual feedback instead of electrical shocks. Before testing was commenced, participants received one more painful and one more non-painful stimulus to confirm the stimulation intensities. Then, functional image acquisition was started during which participants performed the two pain avoidance tasks – first the 'threat delay task' and second the 'click challenge task'. To reduce carry-over effects from the first to second pain avoidance task, we acquired a 20 minute MR sequence measuring cortical blood perfusion (methods and results not further reported here). During this scan participants were asked to keep their eyes open and relax. The pain avoidance tasks were then followed by a high-resolution anatomical scan of the brain. We finalized the scanning session with another functional

scan throughout which participants were engaged in a non-incentive motor-visual control task. After participants had been removed from the scanner, they completed the Beck's depression inventory [BDI-II, (Beck et al., 1996)], and the avoidance-endurance questionnaire (KPI-AEQ), of which the hope- and helplessness subscales were of specific interest here [HHS, (Hasenbring et al., 2009)].

4.2.3 Electrical Stimulation

As part of the pain avoidance tasks, participants received transcutaneous electrical stimuli using pairs of 1 cm^2 MRI-compatible surface electrodes (Vermed®). Depending on the participant's task performance, stimuli were either painful or non-painful. *(i)* Painful stimuli were applied to degreased skin over the retromaleolar path of the right sural nerve using a Grass-S48 stimulator (Astro-Med Inc.). Each stimulation consisted of four repetitions of a 45 ms train (15 1-ms long pulses per train). The time in-between the four repetitions was 500 ms. *(ii)* Non-painful stimuli were applied to degreased skin over the right anterior tibialis muscle using a Constant Voltage Isolated Linear Stimulator (STMISOLA, Biopac Systems, Inc.). Each stimulation consisted of three repetitions of three 1-ms long pulses. The time in-between the three repetitions was 750 ms.

Stimulation intensities for painful and non-painful stimuli were individually determined prior to the scan. We aimed at painful stimuli rated as 75 on a scale ranging from 0 ('no sensation') to 100 ('extremely painful/unpleasant') with 10 being the pain threshold ('just

painful/unpleasant'), i.e. to be strongly aversive and painful. Stimulation intensities for the non-painful stimuli had to be perceivable (>0) but non-painful (<10). Stimulation intensities were determined using a staircase method: first, using the stimulation parameters for the painful pulses, intensity started at 0.5 mA and increased for each subsequent stimulus. If the stimulus was rated below 75, more stimuli were applied with increasing intensities by steps of 1 mA up to a rating of approximately 50, and steps of 0.5 mA until a rating of 75 or higher was reached. In case of ratings higher than 80, stimulation intensity was decreased. The intensity rated around 75 three times in a row was used for the painful stimulation during the pain avoidance task. For the non-painful stimuli, the stimulation intensity that the participant rated consistently around 5 on the rating scale was determined.

4.2.4 The behavioral tasks

4.2.4.1 The click challenge task

In the Click Challenge Task, the aim was to avoid painful stimuli by pressing a button on the button box often enough within a 2 second response period. A target cue was presented indicating the beginning of the 2 second period. As soon as the participants saw the target cue, they were instructed to start pressing the button until the target cue disappeared. If they managed to press the button often enough (i.e. successful trials) they avoided the painful stimulation, and received a non-painful electrical stimulus instead. There were three different difficulty levels: 'easy', 'difficult', and 'extremely difficult'. The success rate of the easy condition was aimed to be 66%; for the difficult

condition we aimed for 33%, and in extremely difficult' for 0%. Throughout the task the number of button presses needed to avoid the painful stimuli was adjusted automatically to ensure similar success rates across participants. The number of button presses needed to avoid the painful stimulus was unbeknownst to the participants. They only knew that the number was lower in the easy than in the difficult condition and highest in the 'extremely difficult' condition. The level of difficulty was indicated by a cue at the beginning of each trial. At the same time as the difficulty cue was being presented, a rating scale was displayed on the screen. We asked the participants to rate how confident they felt to be able to succeed and consequently avoid the pain. Shortly after their rating, the target cue appeared. If participants did not manage to press the button often enough they received the painful stimulus once the target cue had disappeared (i.e. unsuccessful trials).

After the stimulation, a fixation cross appeared on the screen for 7-14 s (with an average of 11 s). Figure 10 shows a schematic illustration of one trial of the click challenge task. In total there were 29 trials, with 12 repetitions for the easy and difficult condition each, and 5 repetitions for 'extremely difficult'. The duration of the task was approximately 10 minutes.

4.2.4.2 The threat delay task

We used an adaptation of the Incentive Delay Task, which has previously been used to investigate motivated behavior in humans including by our lab (Gandhi et al., 2013; Knutson et al., 2000). In the modified version (i.e. 'threat delay task'), the participants'

goal was to avoid a painful stimulus and to receive a non-painful one instead. During each trial, participants saw one of three words (safe; easy; difficult) displayed for 2-12 s (average 6 s). Then, a target cue appeared in the centre of the screen. Participants were instructed to press a button on a button box as fast as possible when the target cue appeared. They were told that they had to press the response button quickly in the easy condition to avoid the painful stimulus, and even more quickly in the difficult condition; in 'safe' trials participants knew they would receive the non-painful stimulus as long as they pressed the button eventually. Despite being safe in 'safe' trials regardless of reaction times, we asked participants to respond to the target cue immediately in order to continue the game without delays. After their response, participants received a painful or a non-painful electrical stimulus, dependent on their reaction time. Participants received the non-painful stimulus (i.e. they avoided the painful stimulus) if they responded to the target cue within 310 ms for the easy, and within 230 ms for the difficult condition. Conversely, they received the painful stimulus if they failed to press the button within the allotted time window of each condition. In the safe condition participants always received the non-painful stimulus regardless of their reaction time. Trials of the three different conditions were pseudo-randomly intermingled. After the stimulation, a fixation cross appeared on the screen for 6-12 s (average 9 s). Figure 11 shows a schematic illustration of one trial. In total there were 36 trials, with 12 repetitions per condition (safe, easy, difficult). The duration of the task was approximately 11 minutes.

4.2.4.3 The motor-visual control task

The control task served the aim to compare the hemodynamic responses between migraineurs and healthy controls. Importantly, in this task behavior was not motivated by explicit threats or incentives.

During the control task, participants first saw a fixation cross projected onto a screen for one second. The fixation cross was followed by the presentation of a circular checkerboard that flickered at a frequency of 3 Hz for a duration of 1.7 seconds. The participants were asked to press a button on a response unit using their dominant index finger once per trial, namely when they saw the presentation of the flickering checkerboard commencing. The presentation of the checkerboard was followed by an inter-trail-interval of 6-20 seconds. During the inter-trial-interval a fixation cross was displayed on the screen again. Figure 12 illustrates a trial of the motor-visual control task. There were 30 trials in total.

4.2.5 MRI data acquisition

Brain images were acquired using a 3 T Siemens Magnetom TRIO scanner (Siemens, Erlangen, Germany) with a standard 32-channel head coil. Functional MRI data were acquired using a blood oxygenation level-dependent (BOLD) protocol with a T2*-weighted multiband accelerated gradient echo planar imaging (EPI) sequence (for the first and third scan – while participants performed the threat delay task and the control task, respectively. The following acquisition parameters were used: repetition time (TR) 854 ms, echo time (TE) 30 ms, flip angle 52°, resolution 2 × 2 × 2 mm, acceleration

factor 6. For the second functional scan – i.e. while participants performed the click challenge task – a similar sequence with the following acquisition parameters was used: repetition time (TR) 1354 ms including a 500 ms acquisition gap at the end of each volume, echo time (TE) 30 ms, flip angle 52°, resolution 2 × 2 × 2 mm, acceleration factor 6). Axial slices were oriented 30° from the line between the anterior and posterior commissure, covering the entire brain. After discarding the first three volumes to allow for steady-state magnetization, 721 volumes were acquired for scan 1 (threat delay task), 478 volumes for scan 2 (click challenge task), and 436 volumes for scan 3 (control task). In a final scan, anatomical images were acquired using a T1-weighted 3D magnetization prepared rapid acquisition by gradient echo (MP-RAGE) sequence (repetition time (TR) 2300 ms, echo time (TE) 2.98 ms, flip angle 9°, field of view 256 mm, resolution 1 × 1 × 1 mm). Throughout the session, participants wore earplugs and their heads were immobilized.

4.2.6 Statistical analysis of the behavioral data

4.2.6.1 Sample size calculation

This was the first formal investigation on the interaction between pain and psychological aspects of pain avoidance, and therefore, the effect size was unknown. Consequently, we base the sample size calculation on a small effect size. In the context of ANOVAs, effect size can be expressed as Cohen's f2, and f2=0.04 (f=0.2) is considered a small effect size (Cohen, 1988).

A repeated measure ANOVA with two within subject factors (‘difficulty level’ and ‘outcome on previous trial’) with three-by-two levels and one between-subject factor (group) with two levels was conducted. In order to detect a small interaction effect with a 5% probability of committing a Type 1 error (alpha=0.95) and a 20% probability of committing a Type 2 error (beta=0.8), a minimum of twenty-eight participants (14 per group) were needed to be tested.

4.2.6.2 The click challenge task

Data from two female migraine patients were excluded because one did not comply with the instructions of the task and the other one did not receive a majority of the painful electrical shocks, because one of the stimulation electrodes had come loose. Further, data from one female healthy person was excluded because she did not comply with the instructions of the task.

Confidence ratings were transformed from the 6-point Likert scale to actual numbers varying from -2.5 (i.e. ‘definitely not able to avoid the pain’) to +2.5 (i.e. ‘definitely able to avoid the pain’) with steps of 1 in between representing each point of the Likert scale. Values for confidence ratings were normally distributed (kurtosis and skewness <2) and no outliers were observed. To test the effects of difficulty level, and previous outcome on the expectation to be able to avoid the pain, confidence ratings were analyzed with a repeated measurement ANOVA design, using mixed model procedures with the factors ‘difficulty level’ (3 levels: easy, difficult, extremely difficult’), and

‘outcome on previous trial’ (2 levels: painful vs. non-painful), separately for the two groups.

The number of button presses within the 2 second target period were corrected for non-normality by applying $f(x)=x^2$, and extreme outliers ($x > mean \pm 3SD$) were excluded (kurtosis and skewness <2 after corrections). We refer to this measure as ‘number of clicks’ hereafter, with a higher number of clicks being indicative of increased motivation (Venugopalan et al., 2011). To test the effects of difficulty level, and previous outcome on the motivation to avoid pain, the number of clicks was analyzed with a repeated measurement ANOVA design, using mixed model procedures with the factors ‘difficulty level’ (3 levels: safe, easy, difficult), and ‘outcome on previous trial’ (2 levels: painful vs. non-painful), separately for the two groups.

Each ANOVA analysis was followed by post-hoc univariate repeated measures ANOVAs or pairwise comparisons, and calculation of Cohen’s d as a measure of effect size (Cohen, 1988) when appropriate.

4.2.6.3 The threat delay task

Data from two female migraine patients were excluded because they did not comply with the instructions of the pain avoidance task. Further, we included only trials with reaction times greater than 150 ms and below 1000 ms to exclude reaction times that were unlikely to reflect motivated behavior. Across all trials of all participants (n=1152), two trials were excluded because the reaction time was below 150 ms and 8 trials were

excluded because the reaction time was above 1000 ms. In two participants, two trials were excluded, in six participants one trial was excluded, and in 24 participants zero trials were excluded.

Reaction times were corrected for non-normality by applying f(x)=1/x (kurtosis and skewness <2 after correction). We refer to this measure as ‘reaction speed’ hereafter, with higher reaction speed being indicative of increased motivation (Delmonte et al., 2012; Tobler et al., 2007). To test the effects of group, difficulty level, and previous outcome on the motivation to avoid pain, reaction speed was analyzed with a repeated measurement ANOVA design, using mixed model procedures with the factors ‘group’ (2 levels: patients and controls), ‘difficulty level’ (3 levels: safe, easy, difficult), ‘outcome on previous trial’ (2 levels: painful vs. non-painful), and ‘trial number’ (12 levels: one through twelve within each difficulty level). Trial number was included as a factor to test for changes in reaction speed over the course of the task, which indicates general tendencies of learning over time. Each ANOVA analysis was followed by post-hoc univariate repeated measures ANOVAs or pairwise comparisons, and calculation of Cohen’s d as a measure of effect size (Cohen, 1988) when appropriate.

To test for linear relations between different clinical characteristics of the migraine patients, clinical characteristics and pain avoidance behavior, or clinical characteristics and the mean brain activation of the PAG, Pearson’s product-moment correlation coefficients (*Pearson’s r*) was measured between the respective variables.

The significance level was set to 5% for all analyses and results were Bonferroni-corrected to account for multiple testing. All statistical analyses were performed using PASW Statistics 17 (SPSS Inc. Chicago, USA).

4.2.7 Statistical analysis of fMRI data

4.2.7.1 The motor visual control task: estimation of the hemodynamic response function

Data from one female migraine patient was included in the analysis of the visual responses only, but excluded from the analysis of the motor responses because she failed to give a majority of the required motor responses. Data from one further female participant was not acquired because her scan was discontinued by the experimenters after she had been incompliant with the instructions of the previous two tasks.

Using FSL 5.0.8 [FMRIB's Software Library; http://www.fmrib.ox.ac.uk/fsl; (Smith et al., 2004)], the following preprocessing steps were applied to each functional dataset: spatial smoothing (Gaussian kernel, full width at half-maximum: 5 mm), motion correction, and temporal highpass filtering (Gaussian-weighted least-squares straight line fitting with sigma = 90 s). After this, a general linear model (GLM) was applied to each functional dataset, modeling one event (visual-motor event) in order to test the pattern of brain activation related to participants' visual and motor response while being exposed to the flickering checkerboard and simultaneously pressing the response button. Hereafter, I will refer to this analysis as the 'initial GLM'.

For the actual evaluation of the hemodynamic response function (HRF) we performed a well-established finite impulse response (FIR) estimation (Dale and Buckner 1997; Orban et al., 2015) as implemented in the software NeuroLens2 (scripted in Python™). We applied this model-free analysis to estimate the shape of the HRF in the primary visual cortex (V1) in response to the onset of the visual stimulus (i.e. flickering checkerboard), and in the hand area of the contralateral primary motor cortex (M1), as well as in the putamen in response to the button press. The coordinates of the regions of interest (RoI) were based on the respective peak activations resulting from the 'initial GLM' (*see* above). Voxels exceeding a z value of 2.3 were included in the RoIs and multiplied with anatomical masks of the left visual cortex, the left motor cortex, and the right putamen as defined by the 'Harvard-Oxford Cortical Structural Atlas' and the 'Harvard-Oxford Subcortical Structural Atlas' implemented in FSL. RoIs for V1 and M1 were further manually restricted to avoid large RoIs actually exceeding the area of V1 and the hand area of M1, respectively.

To estimate the shape of the HRF for each of the RoIs, an additional GLM was fitted for every individual dataset using 41 delta functions as regressors with one sample estimate per repetition time (TR = 854 ms, resulting in a time window of 41 x 0.854 s = 35 s), and a third order polynomial function as a regressor of no interest to control for slow drifts in the signal over time. The resulting HRF estimates were then further analyzed using a repeated measure ANOVA with 'time' as within-subject factor and 'group' (migraineurs vs. healthy controls) as between subject factor, performed separately for the three RoIs. This analysis served the aim to compare the HRF shape

between migraineurs and healthy controls and was carried out using PASW Statistics 17 (SPSS Inc. Chicago, USA).

4.2.7.2 'Threat delay task'

All image processing and statistical analysis was performed using the software package FSL 5.0.8 [FMRIB's Software Library; http://www.fmrib.ox.ac.uk/fsl; (Smith et al., 2004)]. For one healthy control participant only 500 volumes (out of 721) were included in the analysis, because the scan had stopped early due to technical failure.

Subject level analysis. The following preprocessing steps were applied to each functional dataset: denoising using MELODIC (Multivariate Exploratory Linear Optimized Decomposition into Independent Components) within FEAT (FMRI Expert Analysis Tool), spatial smoothing (Gaussian kernel, full width at half-maximum: 5 mm), motion correction, and temporal highpass filtering (Gaussian-weighted least-squares straight line fitting with sigma = 90 s). Susceptibility-related distortions were corrected using FSL field map correction routines.

A general linear model (GLM) was applied to each functional dataset, modeling six conditions (safe with previous outcome non-painful, easy with previous outcome non-painful, difficult with previous outcome non-painful, safe with previous outcome painful, easy with previous outcome painful, difficult with previous outcome painful; 'basic GLM') in order to test the pattern of brain activation related to participants' preparatory state while waiting for the target cue. The time points of the target cue, button press,

and electrical stimulation were included in the model as nuisance variables. A further general linear model (GLM) was applied to each functional dataset, modeling two conditions (previous outcome non-painful and previous outcome painful) with each trial weighted according to the level of difficulty (safe = 1, easy = 2, difficult =3; 'linear GLM') in order to test the pattern of increasing brain activation related to participants' increasing motivation while waiting for the target cue. The same nuisance variables as described for 'basic GLM' were included. In both GLMs, regressors were convolved with a gamma hemodynamic response function and the first temporal derivatives were included. Voxel-wise parameter estimates (PEs) were derived using the appropriate contrasts. Individuals' functional images were first registered to their own structural scan and subsequently to the International Consortium for Brain Mapping (ICBM) 152 *non-linear 6th generation* symmetric template in MNI standard space using linear [FLIRT; (Jenkinson et al., 2002)] and non-linear transformations (FNIRT, warp resolution=6 mm).

Group level analysis. Second level analyses were performed using a mixed-effects model, implemented in FLAME (Beckmann et al., 2003). Statistical inference was based on a voxel-based threshold of z = 2.3, cluster corrected across the whole brain at $p < .05$.

To identify brain areas that were correlated in their activation to changes in pain avoidance behavior due to previous pain in the difficult condition, we added a regressor to the second level analysis of the contrast 'difficult previous stimulation non-painful vs. painful ('basic GLM + speed regressor'). This regressor coded the difference in average

reaction speed for difficult trials following non-painful vs. painful stimulation for each participant.

Localization of activation was achieved by inspecting the group activation maps overlaid on the non-linear ICBM-152 template.

To test whether the influence of unsuccessful pain avoidance attempts (experienced inability to avoid pain) on PAG activation was related to the helplessness scores of migraineurs, the mean differences in brain activation of the PAG between trials following a non-painful vs. painful outcome were correlated with the helplessness scores as assessed by the KPI-AEQ.

Connectivity analyses. To investigate the connectivity between the PAG and brain regions increased with increasing task difficulty, depending on the type of previous stimulation (painful vs. non-painful), psychophysiological interaction analyses [PPIs; (Friston et al., 1997)] were performed. The PAG served as seed region because it is a core region implicated in survival behavior (Bandler and Carrive 1988; Depaulis et al., 1992; Vianna et al., 2001); further, after identifying PAG activation as predictor for pain-induced changes in pain avoidance behavior (*see* chapter 6), we sought to identify the brain network functionally connected to the PAG. The coordinates of the PAG seed were based on the PAG activation resulting from the analysis 'basic GLM + speed regressor' (*see* above) with a peak activation at x; y; z = 2 mm; -34 mm; -6 mm. Voxels of the identified PAG activation exceeding a z value of 2.3 were included in the seed. Two PPI regressors were computed, each as the scalar product of the time series of the activity averaged across the voxels in the PAG seed and a vector coding for the

type of previous stimulation (difficult_painful vs. difficult_non-painful). Both PPI regressors were included in the same GLM and in addition all regressors and nuisance variables as described for ‘basic GLM’, as well as the average time course extracted from the seed. The ‘preparatory matrix’ as identified by the ‘linear GLM’ following nonpainful stimulation, served as regions of interest (RoI). Voxels exceeding a z value of 2.3 were included in the RoI. Statistical inference of the PPI analysis was based on a voxel-based threshold of z=2.3, cluster corrected at $p < 0.05$.

Localization of activation was achieved by inspection of group activation maps overlaid on the non-linear ICBM-152 template. Images are displayed in radiological convention, i.e., right side of the brain is on the left. Coordinates are given in MNI space.

4.3 Figures and tables

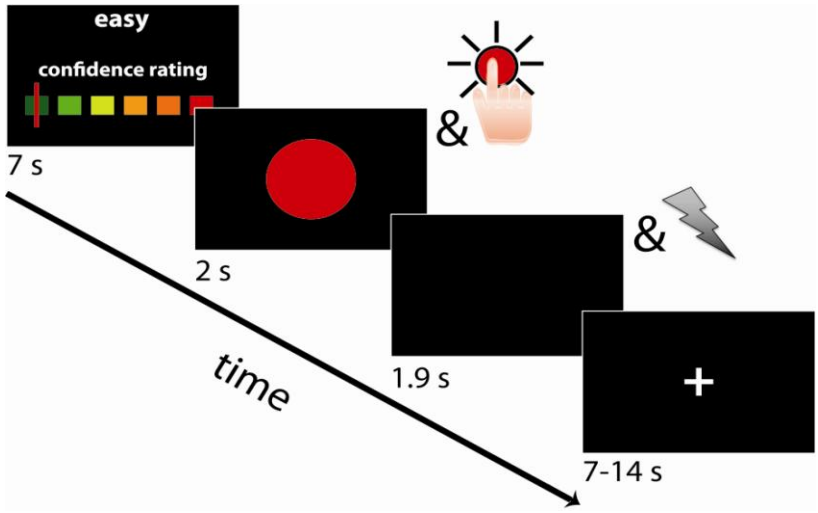

Fig. 10 The click challenge task: outline of one trial including timeline. Participants first saw how difficult it would be to avoid the upcoming pain. Simultaneously, they were asked to rate how confident they were to be successful in their avoidance. Shortly after, the target cue appeared. Only if participants pressed the response key often enough during this period they avoided the painful stimulus and received a non-painful one instead. The electrical shock was administered subsequent to the response period. This was followed by the presentation of a fixation cross, before the next trail commenced.

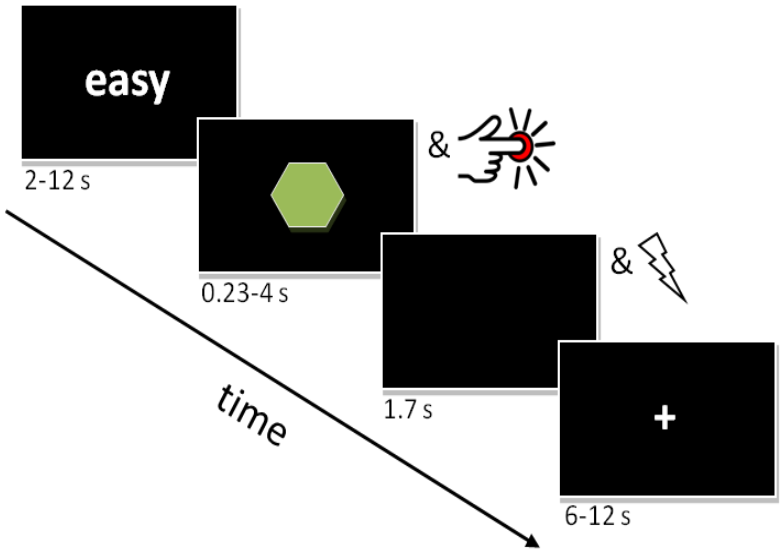

Fig. 11 The threat delay task: outline of one trial including timeline.

Participants first saw how difficult it would be to avoid the upcoming pain. We refer to this phase as the ‘preparatory phase’ during which we analyzed the underlying brain activation. Shortly after the preparatory phase, the target cue appeared. Only if participants reacted fast enough in response to the target cue they avoided the painful stimulus and received a non-painful one instead. The electrical shock was administered subsequent to the response period. This was followed by the presentation of a fixation cross, before the next trail commenced.

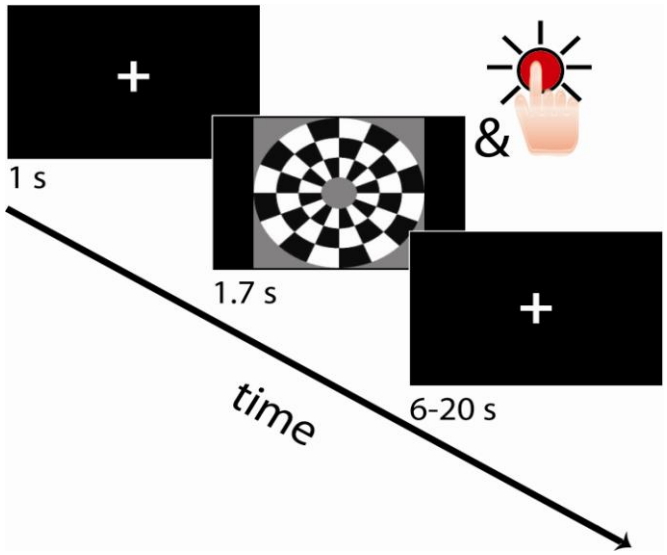

Fig. 12 The motor-visual control task: outline of one trial including timeline. Participants first saw the display of a fixation cross followed by a flickering checkerboard. Participants were instructed to press the response button once during the period of the flickering checkerboard. The display of the checkerboard was followed by the presentation of another fixation cross, before the next trail commenced.

Table 1 Characteristics of the study sample.

	Controls n=17 Mean (SD) Range	**Migraineurs** n=17 Mean (SD) Range	P Value
Age	28 (5) 19-35	25 (5) 19-38	0.11
Gender			
Male	3	3	
Female	14	14	
Handedness			
Left	1	1	
Right	16	16	
Migraine Characteristics			
Duration (years)		12 (7) 2-24	
Attacks/month		5 (4) 1-14	
Typical duration of an attack (hrs)		22 (19) 3-50	
Experience of auras (n patients)		4	
Migraine medication, acute			
NSAIDS		3	
Triptans		3	
Acetominophen		8	
Ibuprofen		9	
Migraine medication, prevention			
Topiramate		1	
Affective Measures			
Depressive symptoms (BDI)	4.2 (4.3) 0-15	4.8 (5.0) 0-18	0.70
Helplessness (KPI-HHS)	9.1 (10.6) 0-28	21.7 (12.8) 0-48	0.007*

Chapter 5:

Characteristics of helplessness following unrewarded pain avoidance attempts in healthy people

5.1 Rationale

The motivation to avoid or escape pain is of paramount importance for survival (Esch and Stefano 2004). Therefore, experiencing acute escapable pain, generally triggers active coping, namely confronting the harmful source, avoiding the pain, or escape the situation when possible (Keay and Bandler 2001). Active coping serves the aim to eliminate the pain and thus prevent harm and injury. Escape behavior encompasses a wide range of possible responses. While reflexes constitute the simplest form of pain escape, multifaceted voluntary movements involving higher cognition, such as planning and decision making, represent the more complex end of the spectrum (Morrison et al., 2013). Importantly, any of these responses are incorporated into the context of an experience within brain networks. Every experience may contribute to subsequent cortical processing of stimuli that are similar to the one that triggered the response (Gandhi et al., in review). Even spinally-mediated reflexes, such as the nociceptive flexion reflex, are associated with specific brain activity (Piche et al., 2010) and can be modulated by top-down factors such as attention and emotional states (Khatibi et al., 2014; Roy et al., 2012). Consequently, active coping behavior is influenced by memory and the individuals' history.

In fact, the motivation to avoid pain is disrupted – or even entirely lacking – in organisms with a history of repeated inescapable pain; a phenomenon termed 'learned helplessness' (Maier and Seligman 1976). Learned helplessness has been conceptualized as a maladaptive coping strategy, encompassing lowered expectations towards one's own ability to avoid stress, resulting in reduced avoidance behavior

(Abramson et al., 1978). In classical learned helplessness paradigms, participants are initially exposed to an inescapable stressor. This experienced inability to control an aversive event is then generalized to a new situation in which the stressor is actually controllable. Nevertheless the participant has given up based on their previous experience and will show delayed or reduced motivation to avoid the new stressor (Alloy et al., 1984; Hiroto 1974; Hiroto and Seligman 1975; Klein and Seligman 1976; Thornton and Jacobs 1971). It remains unknown, however, if single stimuli of pain, interleafed with successfully avoided stimuli, already reduce (i) the *confidence* to be able to avoid pain, and (ii) the *motivation* to avoid it. It is important to fill this knowledge gap, because many people suffering chronic or sub-chronic pain often experience periods where they have little or no control over their pain. It may be of clinical relevance if short periods of perceived inability to avoid/escape pain are sufficient to lead to characteristics of learned helplessness, especially assuming that these characteristics further consolidate with repeated exposure. Helplessness in patients has been associated with a wide range of negative clinical consequences (Camacho et al., 2013; Keefe et al., 2004).

In this behavioral study I investigated the influence of pain – as a result of unsuccessful avoidance attempts – on the subsequent motivation to avoid pain in healthy people. Further, I assessed participants' confidence to be able to avoid the next painful stimulus depending on the previous success to avoid pain. Based on the literature of learned helplessness I hypothesized that preceding pain (i.e. the inability to prevent pain on the previous trial) decreases (i) the expectation to be able to avoid the upcoming pain stimulus and (ii) the motivation to avoid pain. As discussed earlier (chapter 1, section

1.2.1.5), a reduction in motivation following the perceived lack of control over pain seems to be the consequence of the reduced expectation to be able to avoid the pain. This low expectation is based on previous experiences with stressors.

5.2 Results

To answer the question whether pain influences the cognitive and motivational aspects of pain avoidance behavior, we analyzed the behavioral data of the 'click challenge task'. In this task participants were required to press a button a certain number of times within a 2-second period in order to avoid the painful shock and receive the non-painful stimulus instead. Here, we found that participants generally indicated that they expected to be able to avoid the painful stimulus in the easy condition, while they believed not to be able to avoid the painful stimulus in the difficult or extremely difficult condition. As expected, the lowest confidence ratings were observed for the extremely difficult condition (main effect of 'difficulty level' $F_{2,137}$=394,38, p<0.001). Interestingly though, the outcome of the previous trial and difficulty level interacted significantly ($F_{2,113}$=6.23, p=.003). As depicted by figure 13, the post-hoc tests revealed that participants were significantly less confident following unsuccessful pain avoidance attempts to be able to avoid the painful stimulus in the easy and difficult condition (mean difference for easy -0.60, p<.001, Cohen's *d*=.48; mean difference for difficult -0.55, p=.001, Cohen's *d*=.41), but not in the extremely difficult condition (mean difference for extremely difficult +0.43, p=.107). In the extremely difficult condition the confidence to be able to avoid the pain was probably reaching a floor effect. Even in trials following non-painful stimulations I observed a mean rating of -2.1±0.2 which is very close to the lowest possible ratings of -2.5 (i.e. equivalent to 'not at all likely' to avoid the pain). Consequently, pain ratings could not decrease much below the ratings found for the extremely difficult condition following successful pain avoidance attempts.

Pain on the previous trial not only decreased the expectation to be able to avoid the next painful stimulus, but also the motivation to avoid pain. While the motivation to avoid pain was comparable across conditions (no main effect of difficulty level, $F_{2,121}$=1.01, p=.367), it was significantly reduced following painful stimulations (main effect of previous outcome, $F_{1,126}$=10.58, p=.001). As depicted by figure 14, the post-hoc tests revealed that participants pressed the button during the response phase significantly less often following pain in the easy, and difficult conditions (mean difference for easy -38.29, p<.001, Cohen's *d*=.52; mean difference for difficult -28.71 ms, p=.004, Cohen's *d*=.37); but not in the extremely difficult conditions (mean difference for extremely difficult -7.01, p=.709).

5.2.1 Limitations of the paradigm

The main limitation of the employed paradigm is certainly the low number of repetitions of the extremely difficult condition. We only repeated this condition five times, while the other two conditions ('easy' and 'difficult') were repeated twelve times each. The extremely difficult condition was originally intended to serve as a control condition in which pain should always be an expected outcome (i.e. no occurrence of negative prediction errors). Investigating motivation as one of my central outcomes, my main aim was to use a task that would provide me with a sufficient number of repetitions for a meaningful analysis of variance, and yet was short enough to keep participants engaged throughout. Consequently, I decided to compromise by keeping the number of repetitions in the control condition ('extremely difficult') lower than for the two other

conditions (‘difficult’ and ‘easy’). While I did not follow up on the intended analysis of prediction errors, I still left the extremely difficult condition in this current analysis for completeness. Dividing the five repetitions of the extremely difficult condition by the two conditions of the previous outcome (painful vs. non-painful), left me with a very small number of trials to compare to each other. It is therefore possible that I could have found a difference between trials following successful and unsuccessful pain avoidance attempts for the extremely difficult condition if I had had a higher number of repetitions. This speculation will have to be confirmed in future experiments though. Because no valid conclusion can be drawn from the results for the extremely difficult condition, I will focus hereafter on the interpretation of the findings for the difficult and easy condition.

A further limitation of the employed paradigm is that the results for the measure of motivation (i.e. the number of button presses within the 2 s response period) did not confirm the intended parametric nature of the design. We failed to find a main effect of difficulty level on motivation and, thus, found comparable numbers of responses across all difficulty levels. A possible explanation for this finding might lie in the algorithm we used to individually adjust the difficulty within each condition. While the implementation of this algorithm ensured that all participants received the same number of painful and non-painful stimuli, it sometimes adjusted the criterion to achieve pain avoidance for the easy and difficult condition in a way that both conditions were actually comparable with regard to their difficulty at certain times. Consequently, participants might have pressed the response button as often as they could, irrespective of the actual difficulty level. Despite this caveat, we still observed the reduction of responses in trials

subsequent to unsuccessful pain avoidance attempts. This reduction was significant for the easy and the difficult condition – a valid and central finding that I will further interpret and discuss.

5.3 Discussion and conclusions

This study demonstrates that our experimental paradigm was, in fact, able to induce symptoms of learned helplessness in healthy people (i.e. reduced expectations to be able to avoid pain, and reduced motivation to avoid pain) as defined by Abramson (Abramson et al., 1978).

The experience of unsuccessful pain avoidance in our experiment led to a negative appraisal of the subsequent stressor (Lazarus and Folkman 1987; Smith and Kirby 2009). This was indicated by the reduced level of self-reported confidence of my participants in their ability to successfully avoid subsequent pain when the previous pain avoidance attempt remained unrewarded. Based on the discussion above (chapter 1, section 1.2.1.5), I conclude that this cognitive process (i.e. the diminished expectations with regard to the avoidance ability) probably caused the observed reduction in subsequent avoidance behavior. Similar passivity as a consequence of inescapable or uncontrollable aversive events has been reported in a large number of experimental helplessness studies in rodents and humans (e.g. Alloy et al., 1984; Jackson et al., 1980; Maier and Seligman 1976; Maier and Watkins 1995; Peterson et al., 1993; Seligman and Beagley 1975).

In contrast to the classic paradigm of learned helplessness in humans, however, our paradigm did not induce helplessness in an initial separate session through exposure to an aversive stimulus that was inescapable (Alloy et al., 1984; Hiroto 1974; Hiroto and Seligman 1975; Klein and Seligman 1976; Thornton and Jacobs 1971). In fact, our

paradigm did not require different test environments or different types of aversive stimuli. Characteristics of learned helplessness were observed in trials following unsuccessful attempts to avoid pain when compared to trials that had followed successful pain avoidance. We could further demonstrate that our paradigm offers an opportunity to investigate helplessness with regard to pain avoidance in a brain scanner. Therefore, it offers an opportunity to investigate neural underpinnings of the observed behavioral effect in humans using modern imaging techniques, including fMRI and PET. To date, I am aware of only four human imaging studies that had investigated helplessness in humans in a scanner (Peng et al., 2014; Salomons et al., 2012; Schneider et al., 1996; Strigo et al., 2008). Among these studies, only one (Schneider et al., 1996) actually induced helplessness. The others, in contrast, used self-reports of helplessness and correlated those to their respective neural measures. Schneider and colleagues used unsolvable anagrams to induce helplessness – a non-physical stressor. A non-physical stressor is likely to have a different effect than a physical stressor such as pain, because the act of giving up when trying to solve anagrams would not actually cause harm to the body. This implies that the underlying neurobiology may also differ between physical and non-physical stressors. Taken together, the paradigm used in the current study offers a novel opportunity to study neural underpinnings to investigate cognitive and motivation changes induced by the experience of an inability to avoid pain.

The fact that we observed cognitive and motivational changes with regard to pain avoidance after unsuccessful avoidance attempts in healthy people without a history of unavoidable clinical pain is quite remarkable and highlights how easily signs of

helplessness can occur. Translating these results to clinical settings may have significant implications for patients who experience episodes of uncontrollable pain on a regular basis. With repeated exposure to unavoidable pain, helplessness may even become stronger and potentially interfere with the handling of various situations in daily life. Therefore, the cognitive and motivational consequences caused by an inability to avoid pain may not only play an important role in the manifestation of chronic pain, but it may also lead to a lower life quality in patients (Camacho et al., 2013; Keefe et al., 2004).

5.4 Figures and tables

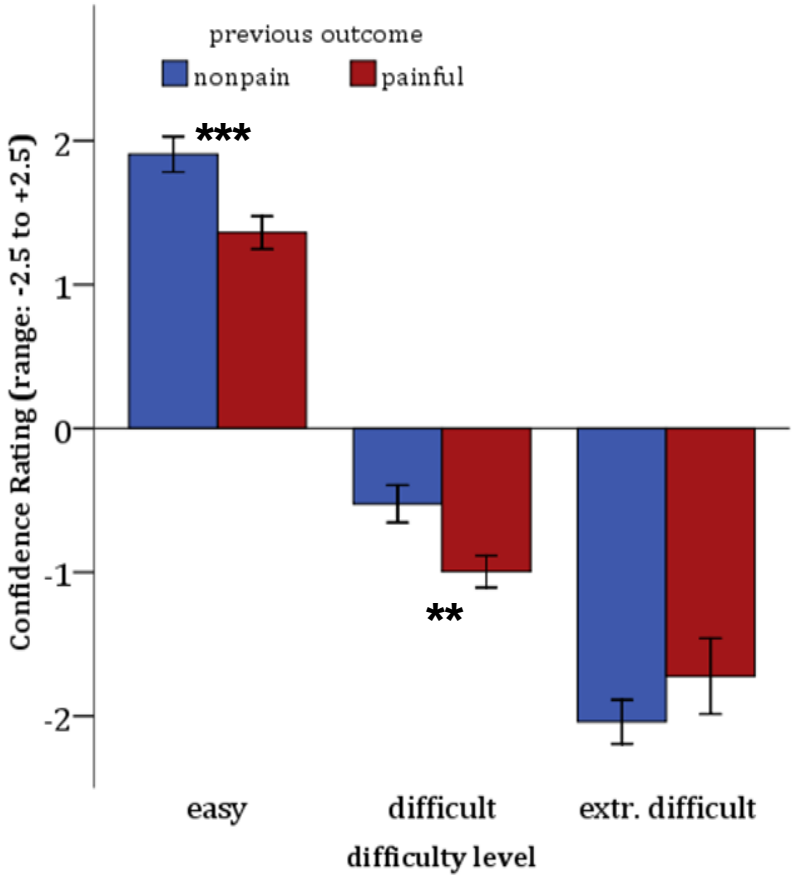

Fig. 13 Reduced confidence when previous attempts were unrewarded
Participants rated their ability to be able to avoid the upcoming pain lower when their pain avoidance attempt on the previous trial was unsuccessful, but only for the easy and difficult condition (significant interaction between pervious outcome and difficulty level, p=0.003). For the extremely difficult condition, the confidence ratings were consistently low, independent of the previous outcome. (** p<0.01; *** p<0.001). Mean+/-SEM.

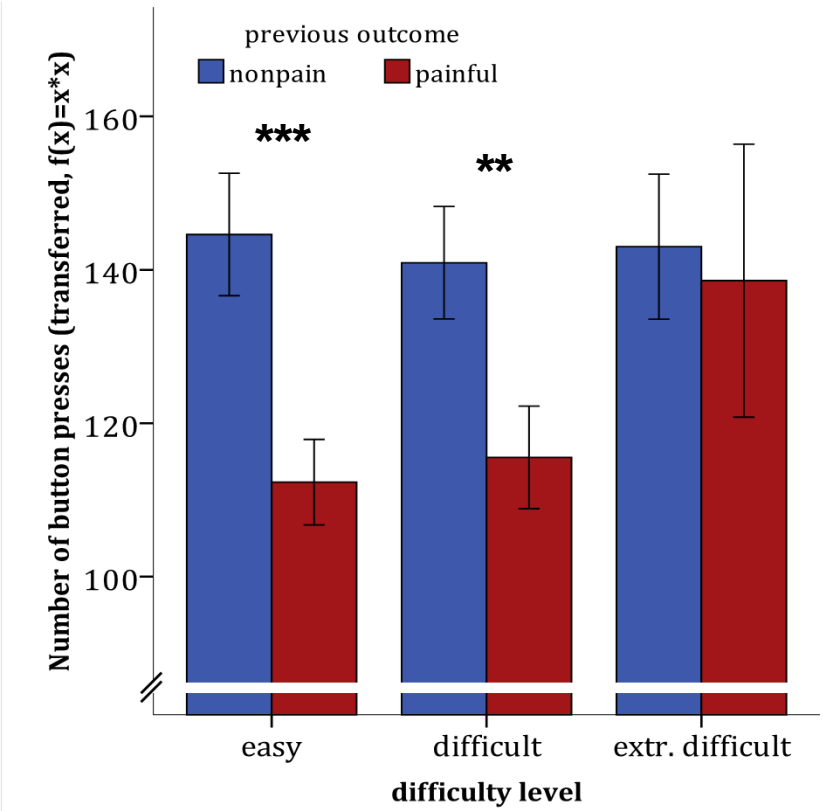

Fig. 14 Reduced motivation to avoid pain when previous attempts were unrewarded Participants responded with fewer button presses when their pain avoidance attempt on the previous trial was unsuccessful and ended with a painful outcome (main effect of previous outcome, p=0.001). The effect of reduced pain avoidance following unrewarded attempts was significant in the easy and difficult condition, but not in extremely difficult. The latter condition has to be interpreted with caution, because we only included 5 extremely difficult trials that are further divided here by two different previous outcomes. (** p<0.01; *** p<0.001). Transformation $f(x)=x^2$. Mean+/-SEM.

Chapter 6:

Activation of the periaqueductal grey (PAG) predicts pain-induced changes in pain avoidance behavior

6.1 Rationale

The presence of a physical threat forces the organism to react quickly and to cope. Coping is defined as solving ‘personal and interpersonal problems, and seeking to master, minimize or tolerate stress or conflict’ (Cram101 Textbook Reviews 2016). While in psychology, coping typically refers to conscious efforts (Cram101 Textbook Reviews 2016), coping with pain includes non-conscious and reflexive behaviors (Morrison et al., 2013) with the aim to avoid or escape pain, and minimize harm and injury.

For threats indicating acute, escapable pain, active coping strategies are likely to be most adaptive (Gandhi et al., *in review*), encompassing ‘fight and flight’ behaviors. On a neural level, the periaqueductal grey (PAG) has been described to play a central role in coping with physical threats and actual acute pain (Bandler and Carrive 1988; Depaulis et al., 1992): In rodents, stimulation of the PAG by a low electrical current turned a resting animal into an alert one (Vianna et al., 2001). Further increasing the intensity of the electrical stimulation, the alert animal would next freeze and eventually escape. The dorsolateral aspect of the PAG has been especially associated with a readiness to actively cope with threats and show confrontational defense or escape behavior in animals (Keay and Bandler 2001; 2002; Lovick and Bandler 2005; Lumb 2002; Vianna et al., 2001). Behavioral changes are accompanied by autonomic changes, namely increases in blood pressure, heart rate, respiration, and muscle tone (Lovick and Bandler 2005). The efferent connections of the PAG form a wide network including structures such as the thalamus, hypothalamus, reticular formation, ventral tegmental

area (VTA), and substantia nigra pars compacta (Cameron et al., 1995), providing the anatomical substrate for its central role in orchestrating behavioral, and autonomic responses to threats and aversive events. In short, the PAG seems to prepare the body for an action necessary to avoid harm – probably via a larger network of motor and attention-related brain regions.

Despite extensive work in animals, no studies in humans exist to confirm the role of the PAG and its network in active coping with acute pain. To close this knowledge gap we conducted an fMRI study in healthy people, seeking to characterize the neural underpinnings of the motivation to avoid pain.

Based on my behavioral results discussed above (see chapter 5), I will now present how activation of the dorsolateral PAG changes with preceding pain, and how this decrease in activation correlates with the motivation to avoid subsequent pain. In accordance with my previous results, I hypothesize that preceding pain (i.e. the inability to prevent pain on the previous trial) decreases the motivation to avoid pain. Based on the rodent PAG literature, I anticipate the reduced motivation to avoid pain to be reflected in a decreased activation of the dorsolateral PAG in response to a threat signaling potentially upcoming pain. Further, using functional connectivity analyses, I will describe the network associated with the PAG following successful and unsuccessful avoidance attempts on the previous trial. Here I hypothesize that brain areas associated with attention and motor-preparation areas are functionally connected to the dorsolateral PAG.

6.2 Results

The following results are based on the threat delay task (fig. 3, see chapter2). Participants first saw a cue indicating how difficult it would be to avoid an upcoming painful stimulus. We refer to this phase as the 'preparatory phase', during which we analyzed the underlying brain activation. During this phase, there was no further stimulation, but the display of the difficulty level (indicated by the word "safe", "easy", or "difficult"). Shortly after the preparatory phase, the target cue appeared. Only if participants reacted fast enough in response to this target cue they avoided the painful stimulus and received a non-painful one instead. For the behavioral analysis, I will be reporting the reaction speed, meaning one divided by the time elapsed between initial occurrence of the target cue and the participant's response (i.e. to press a button on the response unit). This transformation of reaction times was required in order to reach normal distribution of the data to allow for parametric testing. The electrical shock was administered subsequent to the response period and could either be painful or non-painful, depending on the individual performance. The stimulation was followed by the presentation of a fixation cross, before the next trail commenced. Please note that the brain activity I analyzed corresponded to a time period which occurred chronologically *before* the behavior of interest was actually carried out. Therefore, I will report that the brain activity observed during the preparatory phase is not only correlated to the observed behavior, but can be seen as a predictor of the subsequent motor response.

6.2.1 Behavioral findings

Reaction speed in healthy participants was influenced by the factors ‘difficulty level’ and ‘outcome on previous trial’. As depicted in Figure 15, participants reacted faster with increasing difficulty for trials preceded by a painful shock and trials preceded by a non-painful shock (main effect of ‘difficulty level’ $F_{2,157}$=15.69, p<0.001). The reaction speed was decreased when healthy controls received a painful shock in the previous trial (main effect of ‘outcome on previous trial’ $F_{1,271}$=5.18, p=0.024); in post-hoc pairwise comparisons the difference between reaction speed depending on the previous outcome was statistically significant for the difficult condition (mean difference -25.21 ms, p=0.001, Cohen’s *d*=0.49), but not for safe and easy. No interaction between ‘difficulty level’ and ‘outcome on previous trial’ was found ($F_{2,176}$=2.39, p=0.094).

6.2.2 Neural underpinnings of the motivation to avoid pain

Activations associated with increasing difficulty of the task following non-painful trials (difficult > easy > safe for previous stimulation ‘non-painful’; linear GLM) revealed typical brain regions related to alertness and motor preparation, including bilateral anterior insula, parietal cortex, ACC, pre-motor areas, and basal ganglia (we will refer to this network as ‘preparatory matrix’ hereafter, fig. 16a and table 2a,b). Modeling the outcome of the previous trial (i.e. painful vs. non-painful), we found the activation of alertness-related brain areas (e.g. anterior insular cortex) as well as motor-preparation areas (e.g. cerebellum, pre-motor cortex) to be reduced following trials of unsuccessful pain avoidance compared to successful trials (Fig. 16b, table 2c).

Because we were specifically interested in the brain activations associated with the pain-induced decrease in response speed significantly shown for the difficult condition we added the mean behavioral difference per person to the higher level analysis of the contrast ‘difficult_previous-non-painful’ vs. ‘difficult_previous-painful’ which was part of the ‘basic GLM’. Using a whole-brain analysis, significant brain activation for this regression was found in the PAG (fig. 17a). No further brain region was associated in its activation with the subsequent pain avoidance behavior. Extracting the mean activation per participant and condition from the identified PAG region confirmed the significant correlation between changes in PAG activation from ‘no pain’ to ‘pain’ and the pain-induced reduction in pain avoidance behavior for the difficult condition ($r=0.75$, $p=0.001$, fig. 17b).

In the next step we tested how activation of the PAG was related to activation of the preparatory matrix following painful and non-painful stimulation. The psychophysiological interaction analysis (PPI) showed significant functional connectivity of the PAG with the bilateral cerebellum, contralateral putamen, and posterior parietal cortex following non-painful stimulation (fig. 18a). Following painful stimulation, PAG was still connected to posterior parietal cortex, however no longer to areas related to motor preparation (i.e. cerebellum or putamen, fig. 18b). Contrasting the conditions directly (previous outcome non-painful > painful) did not reveal significant differences between the two connectivity matrices. Because PPI analyses are considered to be very conservative the chance of false negatives is high (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/PPICaveats).

To understand why this caveat might have affected my data, it may be useful to take a closer look at the analysis approach I took (i.e. the FSL standard approach). With my PPI analysis I investigated the question whether the PAG is functionally connected to certain brain areas within the preparatory matrix only under specific circumstances, i.e. when the previous pain avoidance attempt was successful versus unsuccessful. This means I analyzed a task-specific change in the correlations between the PAG and my target regions (i.e. the preparatory matrix) which cannot be simply explained by a shared effect of the task. In order to do so, I included the same regressors as used for the basic GLM in the new GLM of my PPI analysis, in addition to the physical regressor (i.e. the time course of the PAG), and the PPI regressors. The PPI regressors, I generated by finding the scalar product of the task regressors (previous outcome painful and previous outcome non-painful) and the time course from the PAG.
The resulting design typically lacks power, because physiological (PAG time course), psychological (task regressors), and interaction variables (PPI regressors) are highly correlated. Further, the task regressors and the physiological regressor already explain variance. This results in a lower probability that even more variance can be explained by the PPI regressors. According to these two issues, a high change in signal is needed to obtain significant results, which consequentially leads to high chances of false negatives.

Considering this caveat, I decided to report findings for the contrast ‘previous outcome non-painful > painful’ although they were uncorrected for multiple comparisons (with a significance level for voxels of $p<0.01$). This analysis revealed, indeed, greater

connectivity of the PAG to the cerebellum and the left putamen during the preparatory phase following trials of successful compared to unsuccessful avoidance attempts (fig. 18c). I decided to discuss this finding in the following section while trying to draw conclusions with caution. Although I trust that these results may be meaningful, it is important to note that future studies will have to confirm this final finding that failed to reach significance in my experiment.

6.3 Discussion and conclusions

With this study, I demonstrated that participants showed increased pain avoidance behavior, reflected in increased reaction speed, with increasing task difficulty using an adaptation of the incentive delay task (Gandhi et al., 2013; Knutson et al., 2000). Replicating our previous finding (see chapter 5), pain avoidance behavior was reduced following unsuccessful attempts to avoid pain on the previous trial. On a neural level, we found that activation of brain areas related to alertness and motor preparation ('preparatory matrix') were increasingly activated when the participants were faced with conditions of increasing difficulty following trials of successful pain avoidance (previous stimulus was non-painful). Following painful stimulation, on the other hand, many areas of the preparatory matrix were significantly less activated. Activation of the PAG predicted subsequent pain avoidance behavior, namely a greater reduction in PAG activation following unsuccessful pain avoidance was positively correlated to a reduction in response speed. We found that the PAG was functionally connected to motor preparation areas as well as attention-related areas within the preparatory matrix following non-painful stimulation. This PAG network seemed to be reduced to the attention areas only following painful stimulation on the previous trial. We conclude that the reduced activation of the PAG and its functional connections is central for the reduction in active coping.

6.3.1 Behavioral correlates of pain avoidance

As discussed above, the experience of unsuccessful pain avoidance in our experiments probably led to a negative appraisal of the current stressor, including a threat to one's own well-being with little ability to cope (Lazarus and Folkman 1987; Smith and Kirby 2009). This might have led to reduced avoidance efforts of our participants when the same or a similar situation re-occurred. Adding to our previous findings, in the current study reaction times in the safe and easy condition were not significantly influenced by previous unsuccessful trials, indicating that the painful electrical shock by itself did not generally reduce attention. While the design of the previous experiment seemed to fail characteristics of a parametric nature (as discussed in chapter 5, section 5.2.1), we did find increasing motivation with increasing task difficulty for this current design. The criterion to reach pain avoidance was set separately for each condition and was not adjusted over time. Therefore, pain avoidance was indeed easier to reach in the easy condition compared to the difficult condition at all times, while pain avoidance in the safe condition was always rewarded. This reflected in the reaction speed of the participants which confirmed the parametric nature of the current design. Consequentially, it seems reasonable to assume that participants perceived the easy and safe condition as more controllable than the difficult condition.

Apparently, the appraisal of the current stressor after an unsuccessful avoidance attempt still allows for appropriate behavioral reactions if the current situation seems controllable (i.e. the safe and easy conditions) – the participant has the ability to cope with the stressor (Lazarus and Folkman 1987). Only when the current environment is

very stressful in itself (i.e. the difficult condition), the lack of control on the previous trial leads to a negative appraisal of the current stressor, resulting in reduced active coping: the participant gives up.

6.3.2 Neural correlates of pain avoidance

On the neural level, linearly increasing activation of bilateral anterior insula, parietal cortex, anterior cingulate cortex (ACC), pre-motor areas, basal ganglia, cerebellum, thalamus and occipital lobe was associated with increasing task difficulty. These brain areas have previously been described to be activated in preparation of cued movement (Deiber et al., 1996) and generally in states of alertness (*for review see* Menon and Uddin 2010), implying a general increase in readiness of the brain to tackle the threat with increasing task difficulty.

The role of the PAG

Our results are in line with animal studies describing the dorsolateral PAG as a key player for active coping with pain (Keay and Bandler 2001; 2002; Lovick and Bandler 2005; Lumb 2002; Vianna et al., 2001). We found less activation of the PAG following pain to be associated with reduced response speed, likely providing the neural basis for reduced active coping following unrewarded coping attempts. The human PAG is approximately 4 mm wide and has been proposed to encompass four subdivisions, namely the ventrolateral, the dorsolateral, the dorsomedial, and the lateral column

(Bandler and Shipley 1994; Dampney et al., 2013). With a 2 mm^3-spatial resolution of my fMRI sequence, the exact location within the PAG cannot be determined. However, the activation we observed – with the peak activation being located dorsally to the aqueduct (MNI coordinates x=2 mm, y=-34 mm, z=-6 mm) – seems compatible with the dorsolateral periaqueductal grey (dlPAG) (Faull et al., 2015).

In humans, the dorsal aspect of the PAG has recently been described to encode aversive prediction errors when participants received worse-than-expected pain stimuli (Roy et al., 2014), implying a central role of the PAG in learning from painful events. Moreover, Roy and colleagues demonstrated functional connectivity between the dorsal PAG and brain areas associated with aversive value coding, namely ventromedial prefrontal cortex and left putamen. The two latter regions showed greater activity with low pain expectancy than with high pain expectancy, but these were not different in their activation to trials with no stimulation (Roy et al., 2014). This suggests that ventromedial prefrontal cortex and the putamen send a ‘safety signal’ to the PAG predicting low chances for pain to occur, based on the previous experience. Together with the described role of the dorsolateral PAG in preparing the body for active coping (Keay and Bandler 2001; 2002; Lovick and Bandler 2005; Lumb 2002; Vianna et al., 2001), this seems relevant, because in the case of a (relatively) safe environment, there is no need to waste energetic resources to prepare for a fight or flight response. Accordingly, mediated by the ventromedial prefrontal cortex and the putamen, the PAG prepares the body sufficiently (in the case of safety, no fight and flight response needs to be

triggered). The above discussed study by Roy and colleagues (Roy et al., 2014) is of crucial relevance for the present discussion for at least two reasons:

(1) despite the importance of pain avoidance, the underlying neural correlates are still poorly understood. Roy and colleagues added a profound piece of knowledge to the field by providing neurobiological evidence of the PAG's involvement in shaping behavioral strategies towards pain based on previous experiences.

(2) It supports the findings of the current study. With our functional connectivity analysis we found that only following successful previous pain avoidance the dorsolateral PAG was connected to left putamen during the preparatory phase to avoid subsequent pain, but not following unsuccessful previous avoidance attempts. This suggests that the putamen might have sent signals to the PAG encoding that – based on the most recent experience – the previously utilized coping strategy was rewarded (i.e. pressing the response button quickly) and that it will likely result in successful pain avoidance again. So the activation of the dorsolateral PAG increases with this signal, preparing the body for the appropriate response to the next target cue.

However, the connectivity analysis that was used does not allow us to distinguish between efferent and afferent connections of the PAG. Alternatively to the explanation that the PAG might have received input from the putamen, it is equally plausible to assume the opposite, namely that the putamen was a target region of the PAG. The putamen receives input from several brain structures, including the pulvinar and lateral dorsal thalamic nuclei (Parent et al., 1983). Both of these thalamic structures are

anatomically connected to the dorsolateral PAG (Behrens et al., 2003; Cameron et al., 1995; Schmahmann and Pandya 1990), suggesting an indirect connection from the dorsolateral PAG to the putamen via the thalamus. The contralateral putamen is involved in the planning and initiation of movement (e.g. Alexander and Crutcher 1990; Boussaoud and Kermadi 1997) and might have therefore facilitated the rapid response to the target cue presented immediately subsequent to the preparation phase. Considering that we observed the PAG in most participants to be connected to the putamen located contralaterally to the hand that was prepared to carry out the movement, it may be even more plausible to assume that the putamen in fact received input from the PAG, rather than sending signals to it.

Similar to the left putamen, the PAG was also functionally connected to the cerebellum during the preparatory phase following previous avoidance success. The cerebellum receives direct bilateral input from the PAG (Dietrichs 1983). Its activation has been associated with changes in muscle tone (Koutsikou et al., 2014) which probably serves in the preparation to carry out the movement required to avoid the upcoming pain.

We further demonstrated the PAG to be functionally connected to the posterior parietal cortex under these circumstances; the posterior parietal cortex is commonly associated with attention and vigilance (Bushnell et al., 1981; Corbetta et al., 2000; Corbetta and Shulman 2002; Malhotra et al., 2009) and possibly receives input from the PAG via the anterior pulvinar and lateral posterior nuclei of the thalamus (Behrens et al., 2003; Cameron et al., 1995; Ezra et al., 2015; Schmahmann and Pandya 1990). Increased vigilance towards external cues was necessary for successful pain avoidance in the

threat delay task in order to minimize the risk of missing the shortly presented target cue.

Following unsuccessful pain avoidance attempts, I observed the PAG to be still connected to attention-related areas, while functional connections to motor-preparatory areas seemed reduced. This fits the above mentioned idea that motor responses are delayed under these circumstances, and may thus provide the neural substrate for the observed reduction in active coping following unrewarded coping attempts. However, since the direct comparison of the PAG networks following successful versus unsuccessful avoidance attempts was no longer significant after correcting for multiple comparisons, more research will be needed to confirm this interpretation.

This current study is the first in humans, to my knowledge, to provide evidence of the neural correlates of active coping in the presence of physical threats indicating upcoming acute pain. A previous study by Roy and colleagues (see above, Roy et al., 2014) focused on prediction errors during the experience of a worse-than-expected painful stimulus and their implied consequences on choice behavior in subsequent trials. Here they described the central and integrating role of the PAG for this behavior. With my results I contribute additional novel knowledge. I am able to demonstrate how the dorsolateral PAG is reduced in its activation during threats following previous unsuccessful pain avoidance attempts, predicting less effort to avoid subsequent pain, and thus providing a neural substrate for ‘giving up’ when the most recently used coping strategy did not lead to success. We provide evidence for a network of brain regions

involved in the preparation to actively cope with upcoming pain and further showed how this network is reduced when avoidance attempts remained unrewarded on the former trial. The neurobiology we describe in this study likely depends on the signals reported for aversive prediction errors by Roy and colleagues, as they probably shape the neural responses to future pain.

6.3.3 Adaptive versus maladaptive coping

Considering the proposed role of the PAG in concert with the putamen and ventromedial prefrontal cortex in learning from painful experiences (Roy et al., 2014), it seems plausible that the reduction in active pain coping may, in fact, be adaptive. If a certain active coping strategy has proven itself unsuccessful, repeated attempts to apply this very same strategy contains the risk to waste energy and stamina (Gandhi et al., *in review*). Under these circumstances, it appears more beneficial to rather choose a passive coping style, or in other words, remain quiet and endure the acute pain until it has passed. While passive coping may be adaptive for acute episodes of short-lasting pain, it can lead to maladaptive coping strategies when pain becomes chronic. In the instance of chronic pain the organism may turn to a strategy of learned helplessness when active coping attempts remain repeatedly unsuccessful (Abramson et al., 1978). In this case, passivity is rather harmful and even associated with negative clinical consequences such as poorer treatment outcome and reduced life quality (Camacho et al., 2013; Keefe et al., 2004). Since pain can often not be overcome in many instances

of chronic pain, an adaptive coping strategy could rather consist in the continued pursuit of valued activities and life goals (Van Damme et al., 2008a).

6.4 Limitations

Throughout the paragraphs of the section above, I highlighted difficulties I encountered during the analysis of this study. Here, I will summarize the main limitations of my methods and portrait the solutions I tried to find to overcome the discussed issues.

6.4.1 The spatial resolution of the fMRI scan does not allow for the exact identification of small brain structures and nuclei.

I based parts of my interpretation on a recent fMRI study (Roy et al., 2014), which suggests that ventromedial prefrontal cortex and the putamen send a ‘safety signal’ to the PAG and thus encode the prediction of low chances of upcoming pain based on the previous experience. However, since the spatial resolution of fMRI scans do not allow for exact localization of small brain stem structures, an alternative explanation may have to be considered.

In rats, the medial portion of the prefrontal cortex has been identified to suppress activity in the dorsal raphe nucleus when stimuli are perceived to be controllable (Amat et al., 2005). Similar to the results by Roy and colleagues, this finding suggests that a ‘safety signal’ seems to be conveyed by structures of the prefrontal cortex to a midbrain region. However, the described midbrain regions receiving this signal seem to differ between the studies. The anatomical location of the raphe nuclei is in immediate proximity to the PAG; the raphe nuclei are in fact located slightly dorsal to the

substantia nigra and ventral to the PAG in humans. Due to a resolution of 2 mm^3 and a brainstem cluster of 322 voxels, I cannot exclude the possibility that the activation in the brainstem that predicted active coping in my sample might have been actually caused by the dorsal raphe nucleus. However, because the peak activation of my cluster is located dorsally to the aqueduct and seems to be compatible to the dorsolateral subdivision of the PAG as identified in humans using 7T MRI (Faull et al., 2015), I concluded that it may be more plausible that indeed the dlPAG is the brain structure mediating active coping in my participants. This interpretation is further supported by a study using deep brain stimulation in humans. Activating the dorsolateral PAG increases blood pressure (Green et al., 2005), a symptom that typically accompanies active coping strategies. In addition to the plethora of animal studies identifying the dlPAG as the mediator for active coping, the finding of the cited study suggests a role of the dlPAG in active coping also in humans.

6.4.2 fMRI scans of the brainstem can be heavily affected by noise

The brainstem is located in close proximity to major arteries and the cerebrospinal-filled aqueduct which tends to pulsate. Its location makes it difficult to obtain reliable fMRI data from the brainstem (Brooks et al., 2013). In fact, the physiological noise is likely to completely disguise the actual signal of interest from this region.

In order to overcome this problem, I attempted to remove physiological noise carefully. In order to do so, I undertook an independent component analysis (ICA) as part of the

preprocessing of my data and thus followed suggestions I found in the recent literature (Brooks et al., 2013).

ICA is a method to decompose data into its underlying components. In fMRI data, it has been demonstrated that ICA decompositions successfully separate between physiological noise, scanner artifacts, and actual brain activation (Beckmann and Smith 2004). The components identified by the ICA can be visually inspected and – if identified as noise – removed from the data before further analysis is carried out. Accordingly, I have inspected each dataset and its independent components carefully and removed those components that appeared to be noise or were not correlated to the time course of my task regressors (as identified by a post-hoc analysis carried out subsequent to the actual ICA). Following the latest suggestions for the correction of physiological noise (Brooks et al., 2013), I feel confident that the PAG activation observed in my study were caused by actual brain activation, whilst physiological noise had mostly been removed.

6.4.2 PPI analyses are likely to reveal false positives

As discussed in detail above (see section 6.2.2), PPI analyses is considered to be a conservative statistical approach, often leading to false negatives.

In summary, this caveat is mainly caused by the nature of this approach. In order to avoid confounds, the GLM of PPI analyses include all regressors of the basic GLM, in

addition to a physical regressor (i.e. the time course of the seed region) and the PPI regressors. The PPI regressors are generated by finding the scalar product of the task regressors and the time course of the seed region. The resulting design typically lacks power, because physiological, psychological, and interaction variables are typically highly correlated. Accordingly, a high signal change is needed to obtain significant results. This implies a high chance of false negatives.

As mentioned above, I decided to report findings for my PPI contrast comparing correlation of the PAG with other brain regions for trials following successful versus unsuccessful pain avoidance, although they were uncorrected for multiple comparisons. While I tried to interpret the findings with caution, it is important to note that future studies are needed to confirm my results with regard to reduced PAG connectivity to motor-related areas following unsuccessful pain avoidance.

6.5 Figures and tables

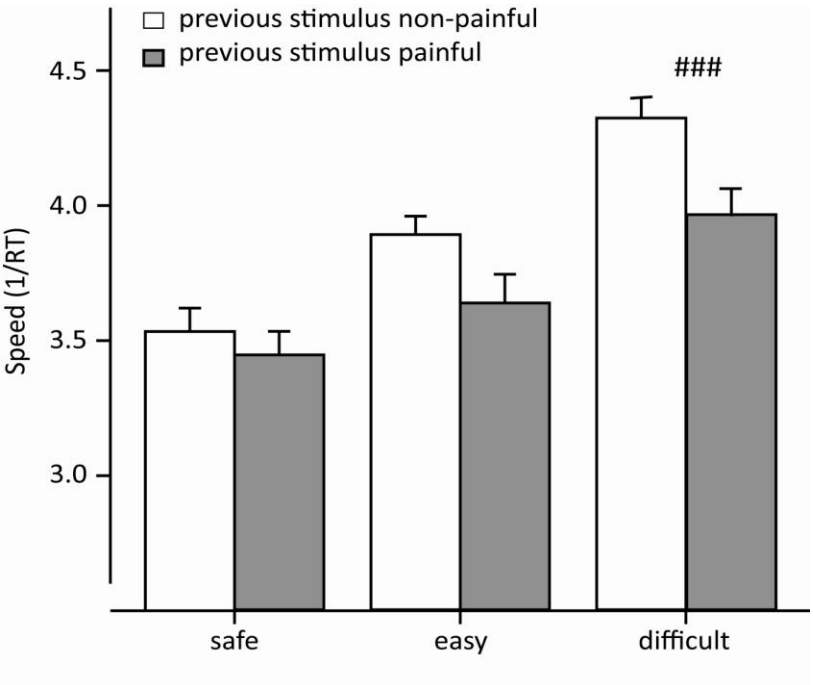

Fig. 15 Reduced motivation to avoid pain following unsuccessful avoidance attempts The response speed was generally reduced in trials that came subsequent to unsuccessful previous pain avoidance attempts (main effect of previous outcome, p=0.024); post-hoc tests revealed a significant differences only for the difficult condition. (### p=0.001).

Table 2 Linearly increasing brain activation during the preparatory phase with increasing task difficulty following trials of a) successful and b) unsuccessful pain avoidance; c) significantly greater activation during the preparatory phase following successful than unsuccessful pain avoidance. For illustration purposes, a more conservative voxel-based threshold of z = 4 was administered.

Brain region	p value of cluster	Peak Z value	Coordinates of the peak activation (x/y/z)	Cluster size (number of voxels)
a) preparatory matrix following successful pain avoidance (difficult>easy>safe)				
Left cerebellum	<0.001	5.05	-32 / -54 / -54	219
Left cerebellum	0.004	4.70	-30 / -62 / -22	53
Right cerebellum	<0.001	4.98	32 / -48 / -52	169
Right cerebellum	0.017	5.23	28 / -30 / -30	36
Right cerebellum	0.017	4.45	2 / -60 / -30	36
Left thalamus	<0.001	4.93	-16 / -22 / 16	138
Right thalamus	0.007	4.62	2 / -16 / 14	47
Visual cortex	<0.001	6.15	-32 / -84 / -14	4378
Visual cortex	0.032	4.86	28 / -76 / -2	28
Left posterior parietal cortex (anterior intra-parietal sulcus)	<0.001	4.95	-16 / -58 / 40	92
Left posterior parietal cortex (inferior parietal lobule)	<0.001	5.00	-56 / -26 / 26	156
Left posterior parietal cortex (inferior parietal lobule)	0.001	4.71	-52 / -36 / 40	70
Left posterior parietal cortex (superior parietal lobule)	0.002	4.57	-2 / -76 / 52	63
Right posterior parietal cortex (inferior parietal lobule)	0.035	4.47	48 / -34 / 32	27
Posterior cingulate cortex	0.003	4.89	0 / -28 / 24	59
Posterior cingulate cortex	0.017	4.82	-12 / -22 / 34	40
Posterior cingulate cortex	0.022	4.51	10 / -18 / 38	33
Left primary motor cortex	<0.001	5.03	-10 / -38 / 60	345
Left premotor cortex	<0.001	6.03	-14 / -14 / 70	2279
Left premotor cortex	<0.001	4.92	-44 / -10 / 52	178
Right premotor cortex	<0.001	5.50	40 / -2 / 46	286
Left pallidum	0.025	4.60	-20 / -6 / 2	28
Left anterior inuslar cortex	<0.001	5.36	-44 / 10 / 2	371
Right anterior insular cortex	<0.001	5.52	34 / 16 / 8	766
Right dorsolateral prefrontal cortex	0.046	4.96	34 / 48 / 26	24
b) preparatory matrix following unsuccessful pain avoidance(difficult>easy>safe)				
Left thalamus	0.001	4.92	-16 / -20 / 12	254
Visual cortex	<0.001	5.28	-10 / -90 / 8	1482
Left premotor cortex	<0.001	4.92	-8 / -4 / 62	623
Right pallidum	<0.001	3.99	20 / -2 / 2	316
Left putamen	0.003	4.23	-30 / -10 / 4	221
c) preparatory matrix following successful > following unsuccessful pain avoidance				
Left cerebellum	0.043	3.64	-12 / -56 / -10	131
Right cerebellum	0.040	4.06	30 / -40 / -34	133
Visual cortex	<0.001	3.90	8 / -68 / 22	686
Left parietal operculum	<0.001	4.65	-62 / -12 / 24	783
Right parietal operculum	<0.001	4.73	62 / -14 / 28	4612
Left primary motor cortex	<0.001	4.67	-44 / -20 / 50	298
Left premotor cortex	0.017	3.75	-20 / -14 / 56	160
Right premotor cortex	0.014	4.15	20 / 10 / 56	168
Left anterior insular cortex	0.002	4.43	-46 / 10 / 2	234
Anterior cingulate cortex	0.008	3.71	14 / 10 / 36	187

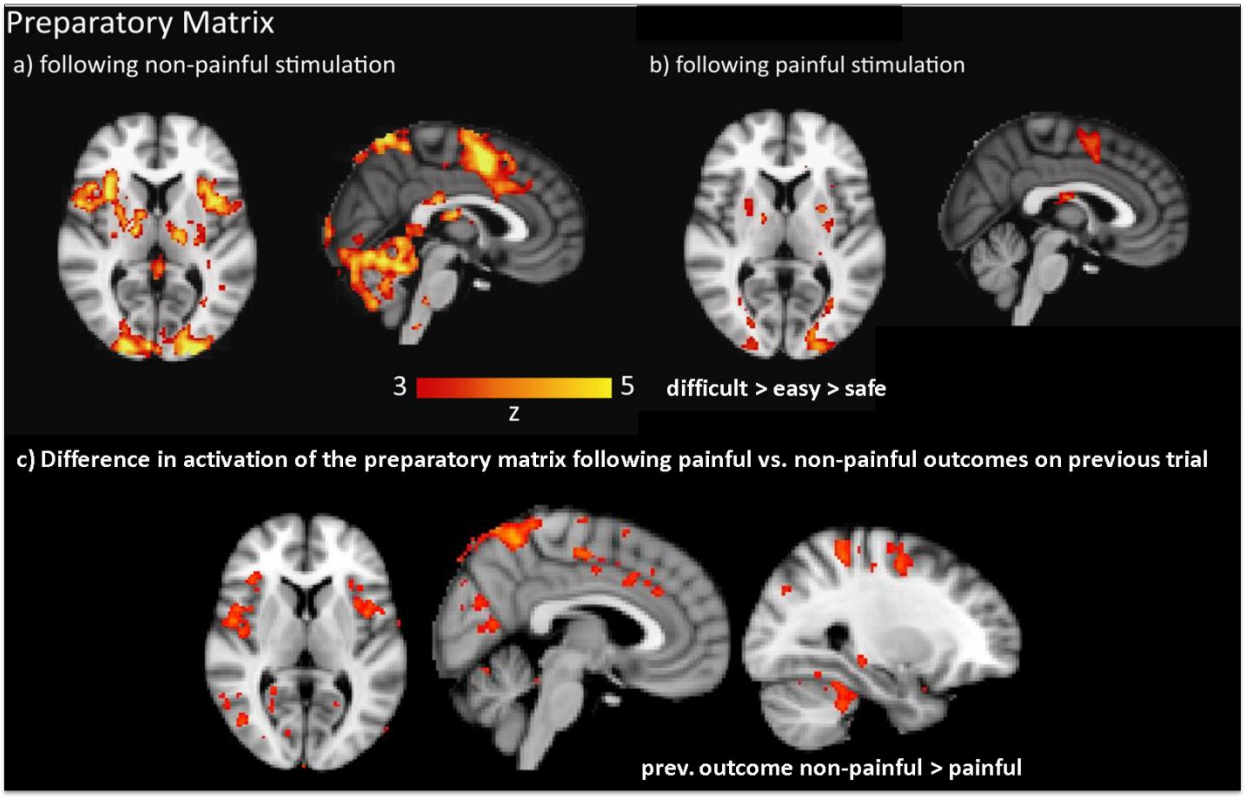

Fig. 16 Activation of the preparatory matrix following trials of (a) rewarded pain avoidance, and (b) unrewarded pain avoidance; and (c) the significant difference between the two matrices.

a) Following successful pain avoidance on the previous trials, a large network of brain areas was increasingly activated during the preparatory phase with increasing difficulty. This matrix encompassed brain areas associated with attention, such as the anterior insula, and the posterior parietal cortex. Further, it included motion-preparation areas such as the cerebellum, dorsal striatum and pre-motor areas.

b) Following unsuccessful pain avoidance on the previous trials, the preparatory matrix is reduced to mainly motor-preparation areas such as the dorsal striatum and pre-motor areas.

c) Following successful pain avoidance on the previous trials, the preparatory matrix is significantly more activated than following unsuccessful pain avoidance on the previous trial in many brain regions, including posterior parietal cortex and insular cortex, cerebellum and the pre-motor areas

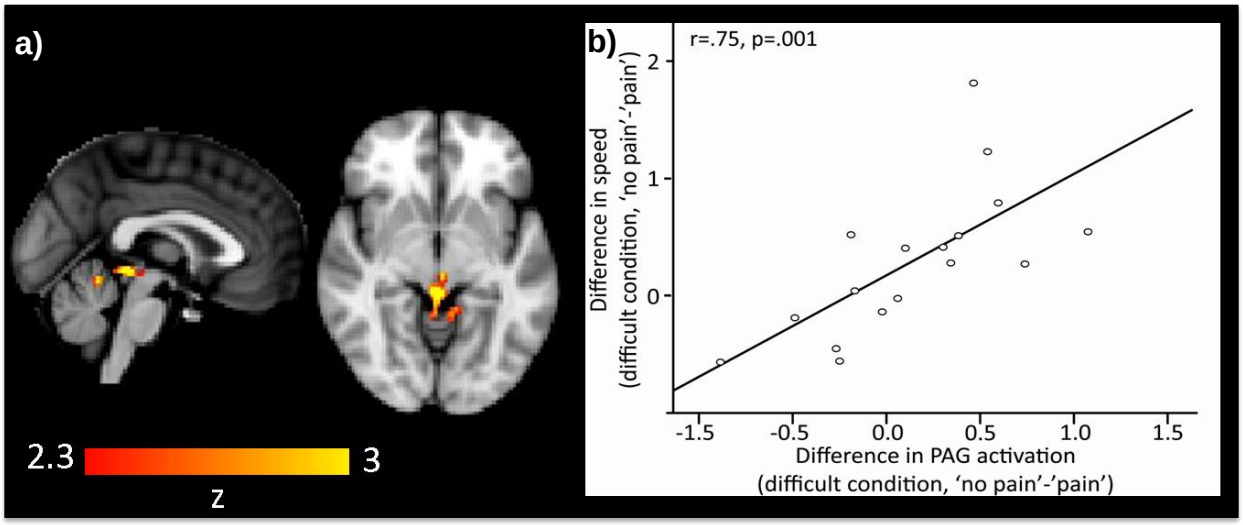

Fig. 17 Activation of the periaqueductal grey predicts pain avoidance behavior. Greater pain-induced changes in response speed were predicted by greater pain-induced reductions in PAG activation, with (a) an activation peak in the dorsolateral aspect of the PAG (MNI coordinates for peak activation: x=2, y=-34, z=-6) and a cluster encompassing 322 voxels (z=3.6, p=0.018). (b) The individual data points of this correlation are depicted in a scatter plot.

Table 3 The brain network associated with the PAG following successful and unsuccessful pain avoidance on the previous trial

Brain region	p	Z	Coordinates of peak the activation (x/y/z)	Number of voxels
a) PAG network following *successful* pain avoidance				
Left posterior parietal cortex	<.001	4.24	-50 / -36 / 42	671
Right posterior parietal cortex	<.001	3.91	54 / -36 / 36	566
Left putamen	.032	3.75	-32 / -6 / 10	208
Cerebellum	<.001	4.73	-2 / -46 / -10	626
Visual cortex	<.001	4.33	8 / -82 / 20	1754
b) PAG network following *unsuccessful* pain avoidance				
Left posterior parietal cortex	<.001	3.76	-44 / -32 / 46	401
Right posterior parietal cortex	<.001	3.90	36 / -42 / 38	313

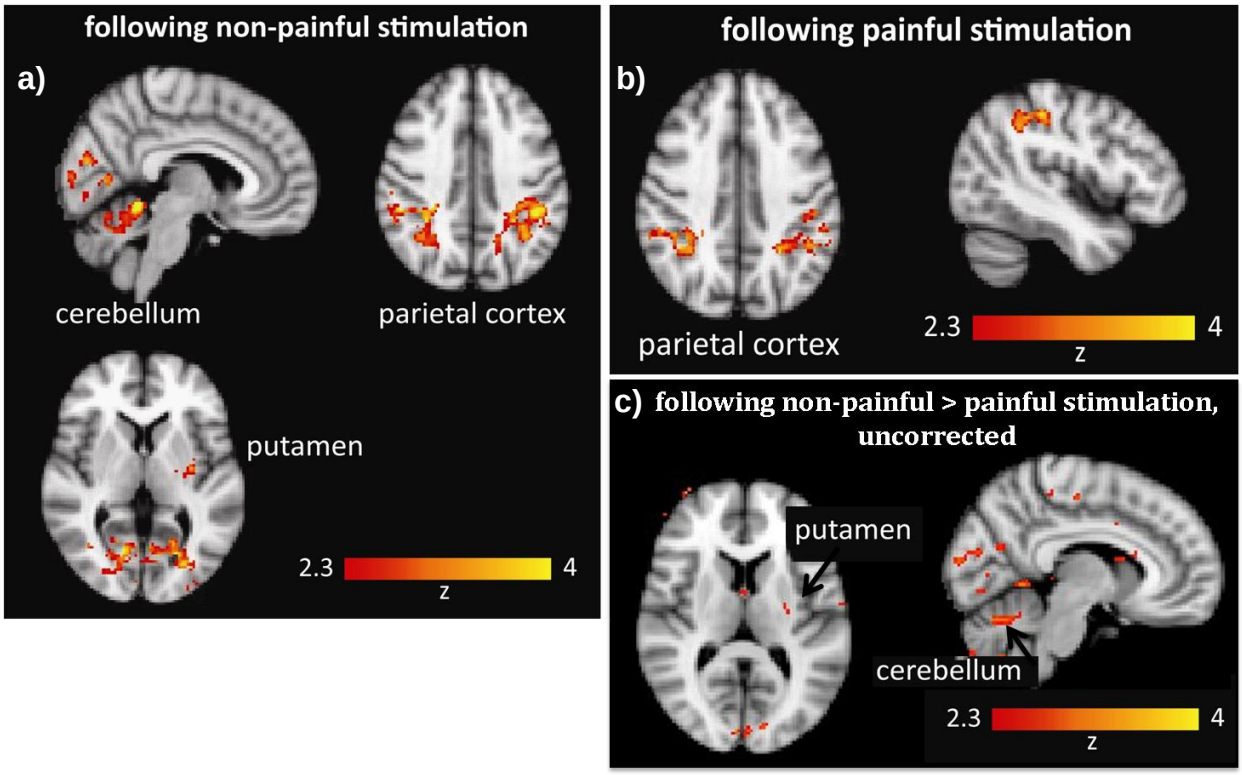

Fig. 18 The functional network of the dorsolateral PAG (a) following trials of successful pain avoidance and (b) following trials of unsuccessful pain avoidance

(a) A network associated with the PAG was observed in trials subsequent to successful pain avoidance including brain areas related to attention (i.e. bilateral posterior parietal cortex), and areas related to motor preparation (i.e. cerebellum, and left/contralateral putamen). Depicted results are cluster corrected.

(b) A smaller functional PAG network was observed following unsuccessful pain avoidance on the previous trial. The network was now reduced to bilateral posterior parietal cortex. Depicted results are cluster corrected.

(c) The direct comparison between the PAG networks following successful versus unsuccessful pain avoidance confirmed stronger connectivity of the PAG to the cerebellum and the left putamen after successful avoidance attempts. However, the effect is only observed before correcting for multiple comparisons.

Chapter 7:

Pain avoidance in patients with a history of unavoidable pain – behavioral, neural, and clinical correlates

7.1 Rationale

The motivation to avoid pain can be disrupted when an organism is repeatedly exposed to inescapable pain; a phenomenon termed ‘learned helplessness’ (Maier and Seligman 1976). As discussed previously in this thesis, learned helplessness has been conceptualized as a maladaptive coping strategy, encompassing lowered expectations towards one’s own ability to avoid stress, resulting in reduced avoidance behavior (Abramson et al., 1978). Based on the assumption that experiencing an inability to avoid an aversive event will cause a generalized tendency to omit any attempts to avoid subsequent stressors (Alloy et al., 1984; Hiroto 1974; Hiroto and Seligman 1975; Klein and Seligman 1976; Thornton and Jacobs 1971), it seems reasonable to assume that patients with a history of frequent unavoidable pain are more vulnerable to show reduced pain avoidance motivation subsequent to unrewarded avoidance attempts than healthy people.

Supporting this reasoning, patients suffering from lower back pain or chronic headaches describe themselves as more helplessness than healthy controls (Matatko et al., 2009; Siniatchkin et al., 1999). This implies that pain patients may resort to learned helplessness as coping strategy when dealing with pain, in situations where active coping would probably be more adaptive. However, despite its known negative consequences for patients (discussed in chapter 1, section 1.2.1.1), I am not aware of any studies investigating the influence of perceived helplessness on behavioral and neurobiological correlates of pain avoidance in pain patients.

In this chapter of my thesis, I present the investigation of episodic migraine as a model of frequent unavoidable pain. Migraineurs were specifically chosen for this study, because the condition is characterized by up to 14 attacks of pulsating headache per month, often accompanied by nausea and vomiting (International Headache Society classification ICHD-II), as well as high self reports of help- and hopelessness (Matatko et al., 2009; Siniatchkin et al., 1999). More specifically, 17 episodic migraineurs underwent the same fMRI experiment as presented above (see chapter 6) and were compared in their behavioral and neural results to the 17 healthy participants from the previous chapter. Further, we linked the behavioral and neural correlates of pain avoidance to clinical characteristics described by the included migraine patients. Here, we focused on self-reported helplessness scores and different measures of disease severity (i.e. the number of migraine attacks per month, and the length of a typical migraine attack).

In accordance with our behavioral hypothesis that pain avoidance behavior will be more influenced by a previous lack of rewarded avoidance attempts in migraineurs, we further hypothesized that the underlying neural correlates will also show a greater difference between trials that follow successful versus unsuccessful pain avoidance attempts. More specifically, based on our previous findings in healthy people, we anticipated the difference in dorsolateral PAG activation during the preparation to avoid the next upcoming painful stimulus to be greater between previously rewarded and unrewarded avoidance attempts in migraineurs than in healthy people.

Before comparing neural correlates between episodic migraine patients and healthy controls, however, we conducted an experiment to compare the generation of the hemodynamic response function in both groups in response to a non-incentive motor-visual control task. This seemed important, because migraine is considered a neurological disorder (Burstein et al., 2015) – including alterations in central processes such as increased blood flow in the primary somatosensory cortex (Hodkinson et al., 2015), altered brain excitability, intracranial arterial dilation, and sensitization of the trigeminovascular pathway (Noseda and Burstein 2013; Vecchia and Pietrobon 2012). This suggests the possibility that the neurovascular coupling may also be affected in migraineurs compared to healthy people. However, to the best of my knowledge, this is still unknown.

Alterations of the neurovascular coupling in migraineurs would imply changes in the hemodynamic response function (see chapter 4, section 4.1.2). This, in turn, means that potential differences between the two groups seen in the read out of our pain avoidance task – i.e. the BOLD response – could be caused by basic physiological differences rather than by changes in the neural correlates of pain avoidance.

To be able to dismiss this alternative explanation, we tested with experiment 1 of this study whether the hemodynamic response function in two cortical and one sub-cortical brain region (i.e. the primary visual cortex, the hand area of the contralateral primary motor cortex, and putamen) differed between migraineurs and healthy controls using a non-incentive control task with visual and motor stimuli.

7.2 Results

7.2.1 Experiment 1: Migraineurs and healthy controls have comparable hemodynamic response functions (HRF) in response to non-incentive visual and motor stimuli.

The hemodynamic response function between migraineurs and healthy controls did not differ significantly in any of the tested brain regions (fig. 19 a-c). The repeated measure ANOVA that estimated the influence of time point as within-subject measure and group as between-subject factor on the hemodynamic response function measured in primary visual cortex in response to the visual cue, revealed no effect of group ($F_{1,33}$=0.76, p=.390), and no interaction between time point and group ($F_{39,33}$=2.29, p=.07). Similarly, the hemodynamic response functions of neither the primary motor cortex (M1) nor the putamen differed between groups (main effect of group for M1: $F_{1,32}$=0.42, p=.523; main effect of group for putamen: $F_{1,32}$=0.01, p=.945); no interaction between time and group was found (interaction of group and time for M1: $F_{39,32}$=1.27, p=.126; interaction of group and time for putamen: $F_{39,32}$=0.82, p=.496).

7.2.2 Experiment 2: The vicious circle of helplessness – how behavioral and neural correlates of pain avoidance are altered with perceived helplessness

7.2.2.1 Self-reported helplessness

Migraine patients reported more help- and hopelessness as assessed by the KPI-AEQ than healthy controls (mean difference 12.01, p=0.007, Cohen's *d*=-1.0, Table 1). The helplessness score of migraineurs was positively correlated to the length of a typical migraine attack (r=0.59, p=0.021, fig. 20), meaning that patients who experience typically longer attacks also report higher helplessness.
Further, helplessness score of migraineurs seemed positively correlated to the attack frequency (i.e. number of attacks experienced per month, r=0.52, p=0.046). However, this correlation was driven by one patient identified as an outlier (with 14 attacks per months which was higher than group mean±2SD, i.e. 4.6 + (2*3.6) = 11.8). Taking this outlier out, the correlation no longer remained significant (r=0.19, p=0.510).
Helplessness was not correlated to disease duration (r=-0.06; p=0.823).

7.2.2.2 The comparison of stimulation intensities between groups

The average intensity applied across all participants was 6.9±3.1 mA for the painful stimulus and 1.1±1.0 mA for the non-painful stimulus; the two groups did not differ for either the painful stimulus (controls 6.5±2.8 mA; patients 7.3±3.5 mA; p=0.46) nor the non-painful stimulus (controls 1.1±1.0 mA; patients 1.1±1.0 mA; p=0.94). All

participants confirmed before and after the task that the painful stimulus was highly unpleasant and aversive, while the non-painful one was perceived as not painful.

7.2.2.3 Pain Avoidance Behavior

Pain avoidance behavior across the time course of the experiment

As a first step, we were interested in differences between migraineurs and healthy people with respect to their changes of reaction speed over the time course of the threat delay task, independent of condition or previous outcome. This analysis tested general differences of learning or – rather the opposite – 'giving up' over time between the groups.

The analysis revealed comparable reaction speeds over time for healthy people and migraineurs (fig. 21) with no significant main effect of group ($F_{1,219}$=0.02, p=.884) and no significant interaction of group and time point on reaction speed ($F_{1,139}$=1.43, p=.075).

Pain avoidance following painful stimuli

Reaction speed in the threat delay task was influenced by the difficulty level, the outcome of the previous trial, and the factor 'group', in an interacting fashion (interaction effect of 'group' by 'difficulty level' by 'outcome on previous trial' on reaction speed: $F_{6,399}$=2.16, p=0.046).

Similar to the control group, the reaction speed of migraine patients was decreased when they perceived a painful shock on the previous trial (main effect of 'outcome on previous trial' $F_{1,281}$=4.64, p=0.032). The post-hoc pairwise comparison for the difference between reaction speed depending on the previous outcome was statistically significant for the difficult condition (mean difference -39.48 ms, p=0.001, Cohen's *d*=0.87), but not for safe and easy (Fig. 22a). Contrary to the control group, however, migraine patients showed an interaction of 'difficulty level' and 'outcome on previous trial' ($F_{2,196}$=4.07, p=0.019). Similar to the healthy controls, migraineurs showed a linear increase in reaction speed with increasing difficulty following successful pain avoidance on the previous trial (univariate effect of 'difficulty level' for previous outcome=non-painful: $F_{2,168}$=21.40, p<0.001). In contrast to healthy controls, however, migraineurs showed similar reaction speed across all three difficulty levels when the pain avoidance attempt of the previous trial had been unsuccessful (univariate effect of 'difficulty level' for previous outcome= painful: $F_{2,123}$=2.04, p=0.135; fig. 22).

Comparing migraineurs and healthy controls directly, there was neither an influence of group on reaction speed (main effect of 'group' $F_{1,215}$=1.34, p=0.249), nor an interaction effect of 'group' and 'difficulty level' on reaction speed ($F_{2,253}$=1.84, p=0.162) following successful pain avoidance on the previous trial. Following *painful* stimulation, however, migraine patients were slower in their reaction speed than the group of healthy controls (main effect of 'group' $F_{1,88}$=9.45, p=0.003). Post-hoc pairwise comparisons revealed a significant difference between the groups for the difficult condition (mean difference -

32.65 ms, p=0.007, Cohen's *d*=0.59), but not for easy and safe. We did not observe an interaction effect for group and difficulty level ($F_{2,132}$=1.33, p=0. 269).

7.2.2.4 Brain networks underlying pain avoidance

Similar to healthy controls, increasing activation of the 'preparatory matrix' of migraineurs was associated with increasing difficulty of the task following non-painful trials (difficult > easy > safe for previous stimulation 'non-painful'; linear GLM, fig. 23). Modeling the outcome of the previous trial (i.e. painful vs. non-painful), we found the activation of the alertness-related brain areas to be reduced following trials of unsuccessful pain avoidance compared to successful trials (fig. 23, table 4). In either condition (previous stimulation 'pain' and 'non-painful') no differences between the groups were found for the activation of the preparatory matrix.

Effective connectivity of the PAG following painful and non-painful stimulation

In the next step we tested whether the PAG network following painful and non-painful stimulations would also be comparable to the one observed in healthy controls. The PPI showed significant functional connectivity of the PAG with the right posterior parietal cortex following non-painful stimulation in migraineurs (fig. 24). The direct comparison between healthy controls and migraineurs (contrasts: patients > controls, and controls > patients) did not reveal any brain areas that differed significantly in their functional connectivity to PAG between migraineurs and healthy people. Exploring the differences between the groups before correcting for multiple comparisons (with a

significance level for voxels of $p<0.01$) revealed no group differences for any of the brain regions shown to be functionally connected to the PAG in healthy controls, i.e. posterior parietal cortex, left putamen, and cerebellum. Following painful stimulation, PAG no longer showed significant connections to brain areas of the preparatory matrix in migraineurs. However, comparing the contrast 'previous outcome non-painful > painful' for migraineurs revealed no differences between the conditions, even when results were uncorrected for multiple comparisons (with a significance level for voxels of $p<0.01$). Further, the direct comparison between healthy controls and migraineurs did not reveal significant differences between migraineurs and healthy people. However, comparing the groups before correcting for multiple comparisons (with a significance level for voxels of $p<0.01$), revealed stronger functional connectivity between the PAG and the contralateral cerebellum in healthy controls (fig. 25). For the reasons discussed in the previous chapter (chapter 6, section 6.2.2), this result might be meaningful, but has to be interpreted with caution. The results imply that the networks underlying pain avoidance are comparable between migraineurs and non-migraineurs following non-painful stimulation. Following unsuccessful pain avoidance on the previous trial, however, the functional connectivity of the PAG to one of the key brain areas involved in motor preparation, i.e. the cerebellum (Ballanger et al., 2008; Horwitz et al., 2000; Thobois et al., 2007), seems lower in migraineurs compared to healthy people.

The role of the periaqueductal grey

Using the PAG region identified to predict pain avoidance in healthy people (*see* chapter 6) as a region of interest, I found a positive correlation between pain-induced changes in PAG activation and pain-induced changes in pain avoidance behavior (r=.53, p=.05, fig 26) for migraineurs – a result that replicates what we already found in healthy people. Note that we had to exclude one outlier for this analysis, because her change in avoidance behavior was -1.5/s (an equivalent of 667 ms) which differed more than 2 standard deviations from the group mean (mean=0.35; SD=0.63).

7.2.2.5 Linking clinical measures with behavioral and neural correlates of pain avoidance

The pain-induced change in PAG is correlated to self-reported helplessness.

The reported decrease in PAG activation following painful stimuli was positively correlated to self-reported helplessness in migraineurs (r=.67, p=.015, fig. 27a). No correlation was found between changes in PAG activation and helplessness scores for healthy people (r=-.31, p=.251).

This means that patients with a history of unavoidable pain who perceive greater helplessness with regard to their clinical pain, show a greater decrease in PAG activation following unsuccessful pain avoidance attempts compared to successful ones.

Further, taking an explorative approach based on the result that helplessness scores are associated with the pain-induced change in PAG activation, we were curious how patients with higher and lower helplessness scores compare to each other and to healthy controls. Splitting the patients into two groups using the median helplessness score of 17 as cut off, three groups resulted:

Healthy controls (n=17),

Low helplessness migraineurs (n=8),

High helplessness migraineurs (n=6, after one patient was excluded from this analysis, because her pain-induced signal change in PAG activation of -.30 % differed more than 2 standard deviations from her group's mean (mean=.27; SD=.28).

Although the helplessness scores of my migraineur sample were normally distributed, I decided to apply a median split to separate the group in 'high helplessness' and 'low helplessness' for two reasons. First, no clinical criterion is published for the applied helplessness scale that would classify patients as high or low in their helplessness. Second, while my migraineur sub-groups were similar in number, one was comparable in their helplessness scores to healthy controls ('low helplessness group', one-tailed t test, $p=0.242$) and the other was significantly higher ('high helplessness', one-tailed t test, $p<0.001$). Therefore, at least in comparison to my own sample of healthy people, one migraineur sub-group seem 'normal' with regard to their helplessness scores, while the other one is higher in helplessness.

The univariate ANOVA showed a trend for group on the pain-induced signal change of the PAG ($F_{2,28}$=1.8 p=.190). The post-hoc t-test for independent samples revealed that patients with high self-reported helplessness showed a greater pain-induced signal change of PAG activation than patients with low helplessness scores (mean difference 0.42 %, $T1_2$=-3.08, p=0.011, Cohen's *d*=1.58; fig. 27b). Further, patients with high helplessness scores showed a trend for a greater pain-induced signal change of PAG activation compared to healthy controls (mean difference 0.23 %, $T2_1$=-1.72, p=0.100, Cohen's *d*=.64), whereas healthy controls and patients with low helplessness scores did not differ in their change of pain activation due to previous pain (mean difference 0.19 %, $T2_3$=-0.97, p=0.340, Cohen's *d*=.44).

7.3 Discussion and conclusions

The results of experiment 1 demonstrate that the hemodynamic response function between healthy people and migraineurs is comparable in a non-incentive, motor-visual control task. This implies that any group differences seen hereafter – in response to the pain avoidance task – is likely not to be attributable to a generally altered BOLD signal in migraineurs, but it can be interpreted as a change to the neural system underlying pain avoidance.

With experiment 2 of the final study of my thesis, I was able to show that migraineurs are comparable to healthy controls in many aspects. Under ‘normal conditions’, they show equal pain avoidance behavior, as well as similar brain activation while preparing for pain avoidance. However, when migraineurs experience an uncontrollable stressful event, differences occur. Compared to healthy controls, migraineurs show greater passivity as a consequence of situations where they previously failed to avoid pain. We interpret this as an increased vulnerability to helplessness. In fact, we were able to demonstrate significant correlations between self-reported helplessness and behavioral and neural measures of our task, as well as characteristics of disease severity.

Our results in migraine patients confirm our previous findings in healthy people. Unrewarded pain avoidance attempts lead to a subsequent reduction in pain avoidance behavior. This finding is in line with recent reports that participants are more likely to switch from one response option to another more frequently when the last response

resulted in a painful outcome (Roy et al., 2014). This implies that learning takes place rapidly and coping strategies are being adjusted after every unrewarded pain avoidance attempt. While we confirmed this finding in healthy controls and migraineurs, migraineurs were even more strongly affected by previous unsuccessful avoidance attempts. In particular, the parametric modulation of pain avoidance behavior by increasing task difficulty was lost in migraineurs after unsuccessful avoidance attempts. This suggests that migraineurs were no longer able to increase their motivation to avoid pain with increasing difficulty. Because the appraisal of a situation not only depends on the most recent experience, it is further influenced by general experiences with stressful situations (Marsella and Gratch 2009); we conclude that patients who experience frequent unavoidable migraine attacks react with more negative appraisals of stressful situations following a perceived lack of control. This ultimately leads to a reduced motivation to avoid an upcoming painful stimulus. While this response might be adaptive over a short time in order to conserve energy when aversive stimuli have proven themselves to be unavoidable (Peterson et al., 1993), it is considered maladaptive in patients who are chronically experiencing unavoidable physical stress. Indeed, passive coping in chronic pain patients is associated with poorer treatment outcomes when compared to active coping strategies (Brown and Nicassio 1987; Snow-Turek et al., 1996).

Despite the behavioral differences between migraine patients and healthy people, we could demonstrate that the underlying neural correlates of pain avoidance were comparable between the groups. Similar to healthy people, we found that migraine

patients showed increasing activation of brain areas related to alertness and motor preparation (‘preparatory matrix’) with increasing difficulty following trials of successful pain avoidance. Following painful stimulation, most areas of the preparatory matrix demonstrated less activation. Further replicating our previous results in healthy controls, we showed that activation of the periaqueductal grey (PAG) predicted subsequent pain avoidance behavior also in migraineurs. The PAG was functionally connected to attention-related areas within the preparatory matrix following non-painful stimulation in migraineurs. Following painful stimulation on the previous trial, we no longer found any brain areas significantly connected to the PAG in migraine patients. Although the functional connectivity analysis suggests a smaller network of brain areas connected to the PAG in migraineurs, no statistical differences were found between migraineurs and healthy controls following successful pain avoidance. I conclude that migraineurs generally employ the same neural networks for pain avoidance as healthy controls, as long as previous avoidance attempts were successful. During the preparatory phase subsequent to *unsuccessful* avoidance attempts, however, the PAG in healthy controls seems to be more strongly connected to the left cerebellum in healthy controls than to that of migraineurs. Activation of the cerebellum has been associated with changes in muscle tone (Koutsikou et al., 2014) which probably served the preparation to carry out the movement required to avoid the upcoming pain in my experiment. Specifically the cerebellar hemisphere contralateral to the movement has been proposed to mediate an increase in movement velocity in situations that require a movement urgently (Ballanger et al., 2008; Thobois et al., 2007). Accordingly, I speculate that the decreased functional connectivity of the PAG to the contralateral

cerebellum following unsuccessful avoidance attempts in migraineurs might have contributed to the stronger pain-induced behavioral impairment of subsequent avoidance behavior in my patient sample. Because these results did not reach significance after correcting for multiple comparisons, more research is needed to confirm this finding.

Interestingly, we have observed that patients who reported high helplessness with regard to their clinical pain had a greater pain-induced reduction of PAG activity during the subsequent preparatory phase than the one observed in patients with low helplessness scores. Further, migraine patients who did *not* perceive themselves as helpless were comparable in their PAG activation to healthy controls. This is in line with a recent structural brain imaging study providing evidence for individual differences in brain anatomy and connectivity of chronic pain patients dependent on their self-reported helplessness (Salomons et al., 2012). We suggest that the responsiveness of the dorsolateral PAG in the presence of a physical threat depends on the person's level of resistance to learned helplessness, despite a frequent exposure to unavoidable pain. Previous studies support the idea that resistance to learned helplessness generally exists. Up to half of all study subjects exposed to uncontrollable stress have been identified to not show the reported behavioral signs of helplessness (Hiroto 1974; Minor et al., 1994).

Further, our correlation analyses suggest strong associations between the individually reported helplessness and the PAG activation, as well as observed pain avoidance behavior and clinical measures. Therefore, we are proposing a 'vicious circle' of helplessness in migraineurs (fig. 28). Migraineurs who perceive themselves as helpless

show a greater reduction of PAG activation in trials subsequent to unrewarded avoidance attempts compared to trials following successful pain avoidance. This change in PAG activation is the neural substrate underlying the increased vulnerability to give up and to no longer show active coping following unsuccessful pain avoidance attempts. Patients who show a greater tendency to abandon active coping following previous unsuccessful attempts also typically report a longer duration of migraine attacks. This, in turn, is associated with a higher perception of helplessness. Interrupting this vicious circle provides a promising avenue to reduce suffering and promote well-being in pain patients. It highlights the importance to focus on active coping strategies when treating pain patients: a specific cognitive behavioral training with the aim to reduce perceived helplessness could possibly lead to higher activation of the PAG even following unsuccessful coping attempts. An increased PAG activation prepares the body for active coping and would ultimately decrease the disease severity of migraineurs. It could be proposed that patients should be reaching out for positive means as an active coping strategy in instances when pain itself is unavoidable. Although this strategy may not eliminate pain, it could help to re-balance the hedonic homeostasis and increase life quality.

7.4 Limitations

The same limitations as discussed for the previous chapter apply (see chapter 6, section 6.4).

Further, certain limitations have to be considered for the comparison between migraineurs and healthy controls. The frequent intake of certain medications, including non-steroidal anti-inflammatory drugs (e.g. aspirin), could potentially have an influence on the BOLD signal (D'Esposito et al., 2003). However, experiment 1 of this chapter revealed no differences of the HRF between healthy people and migraineurs, which we estimated for two cortical and one sub-cortical region in response to non-incented motor and visual stimuli. This result suggests that the frequent intake of medication in the present migraine group did not seem to alter their BOLD signal. Further factors that could interfere with the BOLD response are age and potential comorbidities, such as depression. The two groups in my study were therefore matched for age. In addition, healthy people and migraineurs were comparable in their depressive symptoms.

7.5 Figures and tables

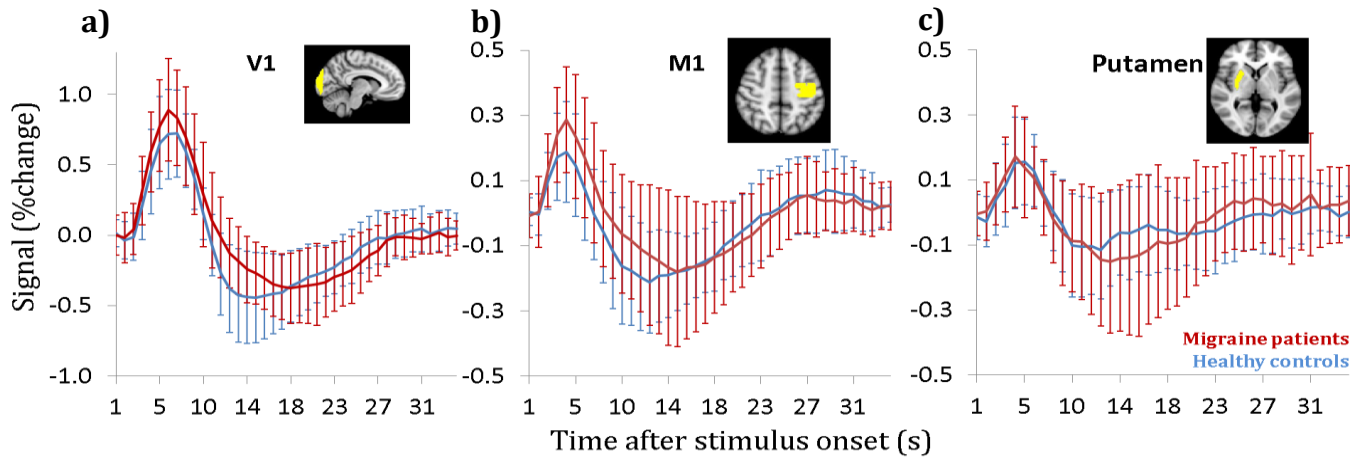

Fig. 19 Estimation of the hemodynamic response function (HRF)
We did not observe any differences between migraine patients (red line) and healthy controls (blue line) w.r.t. their HRF in response to (a) the visual cue assessed in the visual cortex, or in response to the finger tab in (b) contralateral primary motor cortex, and (c) putamen. (Mean±SD)

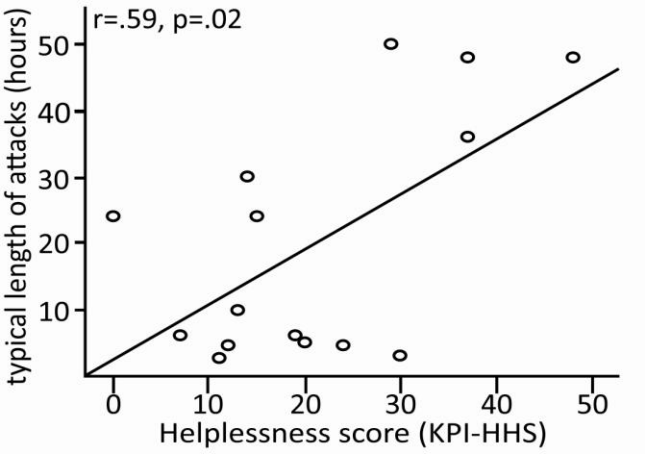

Fig 20 Higher helplessness is related to longer durations of migraine attacks.
We observed a high positive correlation between self-reported helplessness scores and the length of typical migraine attacks, meaning that more helpless patients take longer to overcome their migraine attacks.

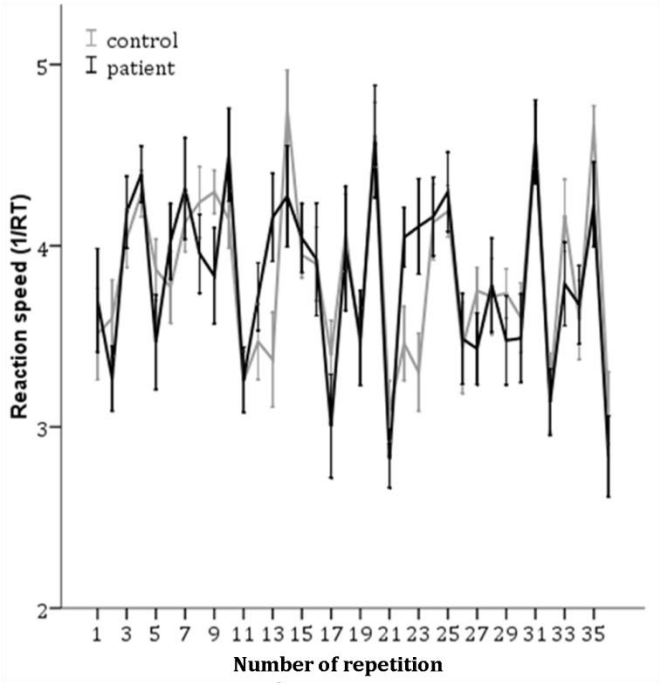

Fig. 21 Reaction speed across the course of the experiment per group
Migraine patients (black line) and healthy controls (grey line) do not show different general trends in their reaction speed over time, meaning that both groups kept their attention up to comparable degrees across the course of the experiment. (Mean±SEM)

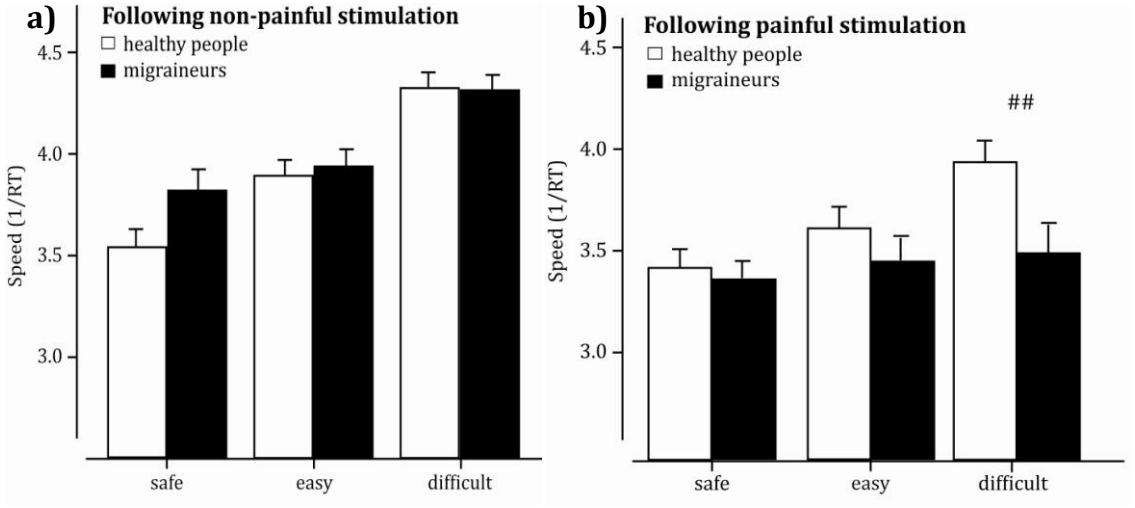

Fig. 22 Patients' pain avoidance behavior is more affected by previous pain Following rewarded pain avoidance attempts on the previous trial (a) migraine patients (black bars) and healthy controls (white bars) do not differ in their motivation to avoid the subsequent painful stimulus; both groups show a linear modulation of response speed with increasing difficulty. Following unrewarded avoidance attempts on the previous trial (b), however, patients show greater impairment of their motivation to avoid subsequent pain than healthy controls with a significant difference between the groups for the difficult condition. Interestingly, while healthy controls still show the linear modulation of reaction speed by difficulty, this effect is lost for patients when they received a painful outcome on the previous trial. (mean±sem, ## $p<0.01$)

Table 4 Linearly increasing brain activation during the preparatory phase with increasing task difficulty in migraineurs following trials of a) successful and b) unsuccessful pain avoidance; c) significantly greater activation during the preparatory phase following successful than unsuccessful pain avoidance. For illustration purposes, a more conservative voxel-based threshold of z = 3 was administered.

Brain region	p value of	Peak Z value	Coordinates of the peak activation (x/y/z)	Cluster size (number of voxels)
a) preparatory matrix following successful pain avoidance (difficult>easy>safe)				
Mesencephalon, substantia nigra	0.002	4.48	10 / -24 / -14	415
Visual cortex	<0.001	5.24	-12 / -92 / -8	12996
Left posterior parietal cortex (inferior parietal lobule)	0.018	3.97	-52 / -42 / 34	293
Right posterior parietal cortex (inferior parietal lobule)	0.001	4.15	-50 / -30 / 34	504
Left parietal operculum	0.005	3.90	-66 / -20 / 16	369
Left premotor cortex	<0.001	5.05	-12 / 8 / 40	4238
Right premotor cortex	<0.001	4.85	48 / -2 / 42	532
Right anterior insular cortex	<0.001	5.46	36 / 14 / 6	5472
b) preparatory matrix following unsuccessful pain avoidance(difficult>easy>safe)				
Left premotor cortex	0.002	2.67	-8 / -12 / 58	661
Left anterior inuslar cortex	0.002	2.65	-32 / 18 / 8	656
Right anterior insular cortex	<0.001	4.57	44 / 18 / -2	1107
c) preparatory matrix following successful > following unsuccessful pain avoidance				
Left posterior parietal cortex (superior parietal lobule)	<0.001	4.00	-12 / -42 / 46	1180
Right premotor cortex	0.030	3.88	14 / 10 / 38	423

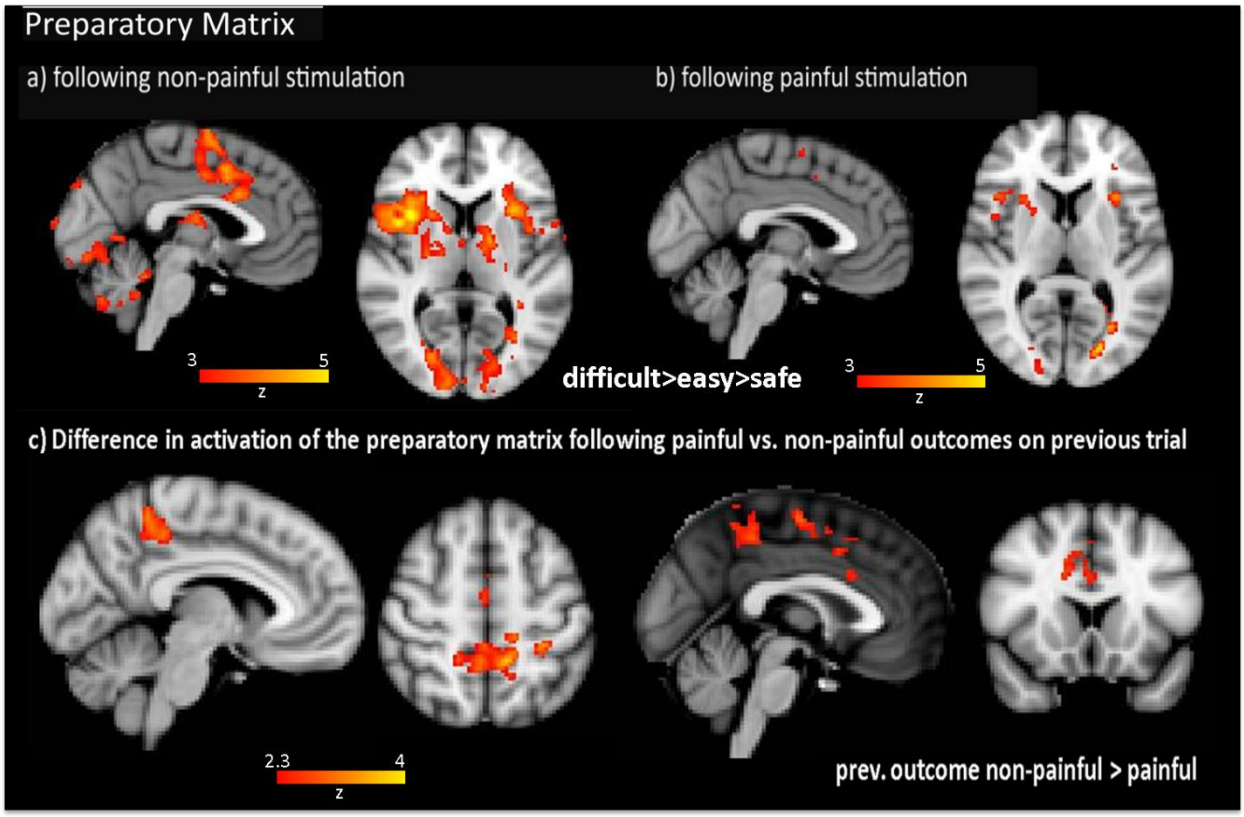

Fig. 23 Activation of the preparatory matrix in migraine patients following trials of (a) rewarded pain avoidance, and (b) unrewarded pain avoidance; and (c) the significant difference between the two matrices.

a) Following successful pain avoidance on the previous trials, a large network of brain areas was increasingly activated during the preparatory phase with increasing difficulty. This matrix encompassed brain areas associated with attention, such as the anterior insular cortex. Further, it included motion-preparation areas such as the cerebellum, dorsal striatum and pre-motor areas.

b) Following unsuccessful pain avoidance on the previous trials, the preparatory matrix is reduced to smaller clusters within the described areas

c) Following successful pain avoidance on the previous trials, the preparatory matrix is significantly more activated than following unsuccessful pain avoidance on the previous trial in brain regions related to attention, such as the parietal cortex (i.e. precuneous cortex), and motor-preparation areas, such as the mid-cingulate cortex and pre-motor areas

No significant difference for any of these matrices were found between migraineurs and healthy controls

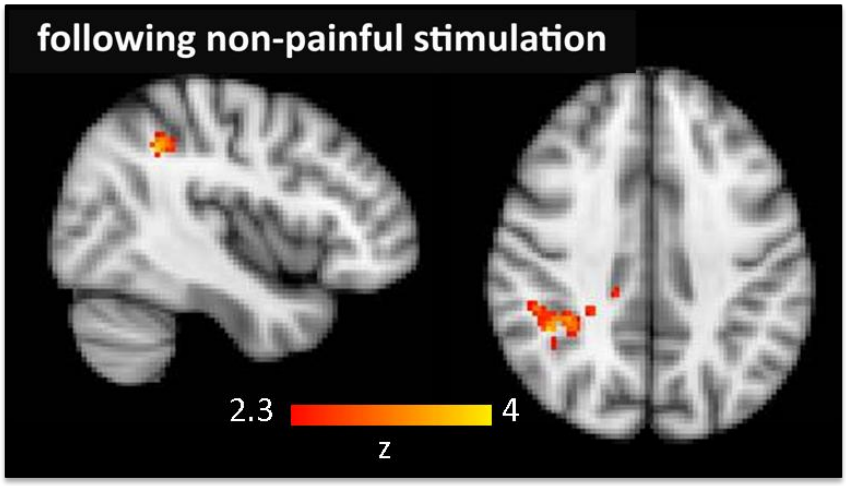

Fig. 24 The functional network of the dorsolateral periaqueductal grey in migraine patients
Functional connectivity of the dorsolateral PAG was observed by the PPI analysis in trials subsequent to successful pain avoidance with the right posterior parietal cortex – an attention-related brain region (MNI coordinates for peak activation: x=42, y=-46, z=38). Following unsuccessful pain avoidance on the previous trial, however, no significant functional connections of the PAG were observed in migraine patients any more. The direct comparison to healthy controls did not reveal any significant differences for the functional networks of the PAG between groups for either condition.

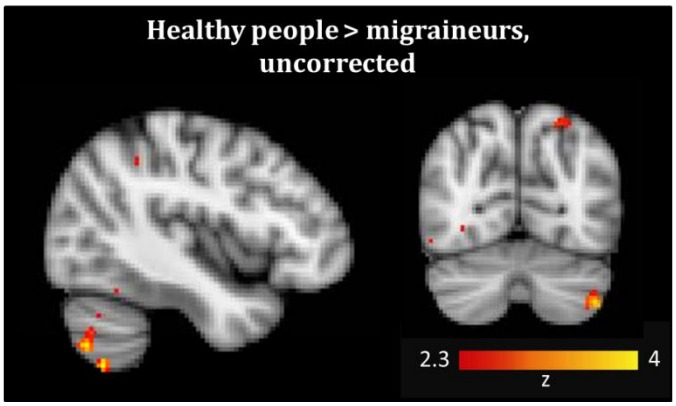

Fig. 25 Comparing the functional network of the PAG following unsuccessful pain avoidance between migraine patients and healthy controls
The direct comparison of the PAG network following unsuccessful pain avoidance between the groups showed reduced connectivity of the PAG to the cerebellum in migraineurs. However, the effect is only observed before correcting for multiple comparisons.

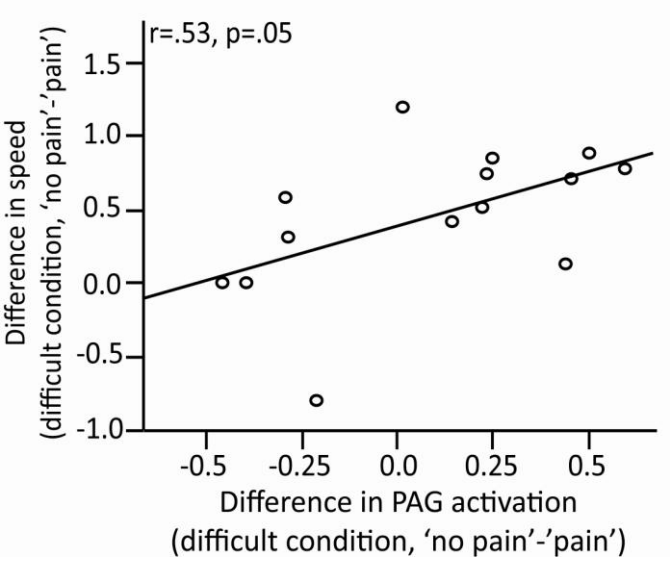

Fig. 26 The PAG predicts pain avoidance behavior also in migraine patients.
Similar to healthy people, an increasing pain-induced change in response speed was predicted by a greater pain-induced difference in PAG activation.

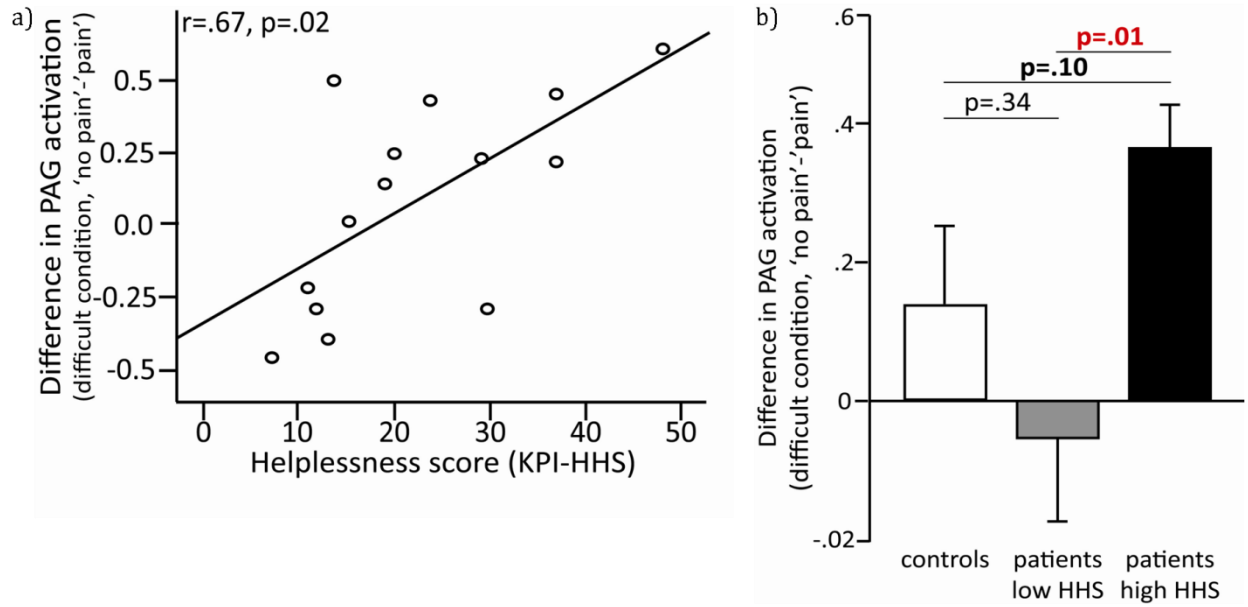

Fig. 27 The central role of helplessness in pain-induced changes of PAG activation

a) Self-reported helplessness in migraine patients is positively correlated with the pain-induced reduction in PAG activation following unsuccessful pain avoidance attempts.

b) In an exploratory approach we compared migraine patients with low and high scores of self-reported helplessness (using median split) to each other and to healthy controls. Interestingly, migraineurs with low self-reports of helplessness show a significantly lower pain-induced reduction in PAG activation than migraineurs with high reports of helplessness. While the latter group shows a trend of a greater pain-induced reduction in PAG activation than healthy controls, there is no difference between healthy controls and patients with low scores of helplessness. This suggests that some patients may learn coping strategies preventing the PAG to reduce in activation following the experience of pain; ultimately they prepare the body for active coping (mediated by the dorsolateral PAG) even if previous attempts were unsuccessful.

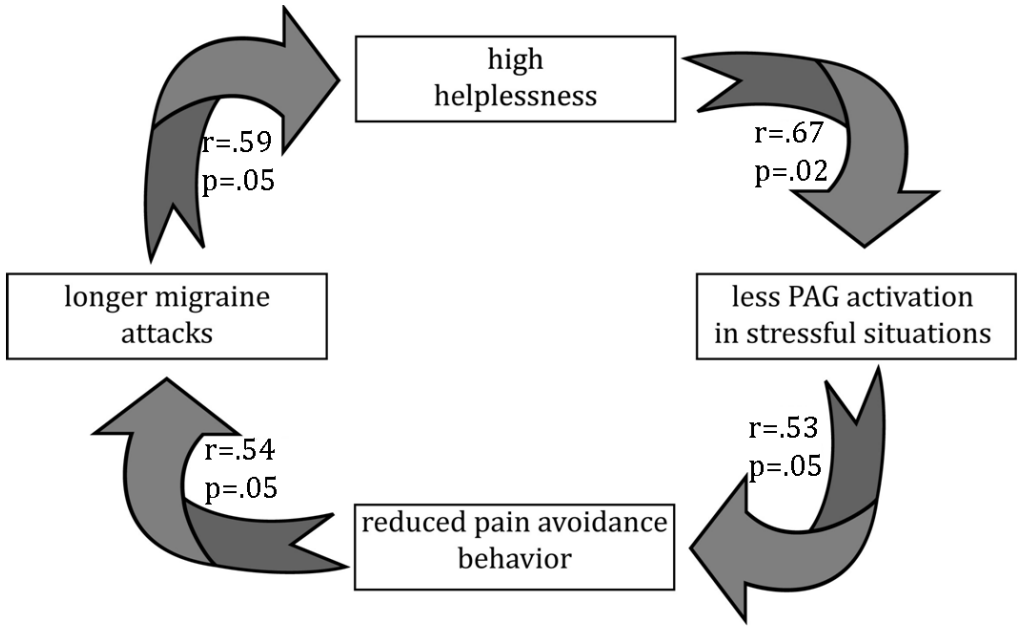

Fig. 28 The vicious circle of helplessness in migraine patients
Helpless patients have altered neurobiology underlying active coping: higher helplessness scores in migraineurs were associated with a greater pain-induced reduction of PAG activation. The dorsolateral PAG is known to be key player preparing the body for active coping. We confirm with our data, that a stronger pain-induced reduction in PAG activation led to a greater reduction in subsequent pain avoidance behavior. Migraineurs who showed greater disturbances of pain avoidance behavior due to previous pain also report longer migraine attacks – a clinical feature related to a greater perception of helplessness. To interrupt the vicious circle of helplessness in migraineurs may reduce suffering in these patients and promote well-being and life quality.

Chapter 8:

General Discussion

8.1 Central findings of this thesis

With the studies of my thesis I investigated the influence of acute pain on reward processing. Exploring both the desire to receive pleasurable outcomes and to avoid aversive events, I demonstrated three central findings for altered reward behavior as a consequence of pain:

1) Acute unavoidable pain increases the motivation to obtain reward (chapter 3).
2) Acute pain as the result of an unsuccessful avoidance attempt reduces the motivation to avoid subsequent pain (chapters 5, 6).
3) Migraineurs who have a clinical history of frequent unavoidable pain are even more affected than healthy people in their motivation to avoid acute pain following previous unrewarded avoidance attempts (chapter 7).

Further, in investigating the neural correlates of the motivation to avoid pain, I was able to demonstrate a central role of the PAG:

1) The relative reduction of PAG activation following unsuccessful compared to successful pain avoidance predicted the subsequent pain avoidance behavior in healthy people (chapter 6) and in migraineurs (chapter 7).
2) During the preparation to avoid pain, the PAG is functionally connected to a network of brain areas associated with motor preparation and attention following trials of successful avoidance attempts; this network seems to be reduced to the attention areas only following trials of unsuccessful avoidance attempts (chapter 6).

3) Patients with higher self-reported helplessness scores show a greater pain-induced reduction in PAG activation following trials of unsuccessful avoidance attempts than patients with lower helplessness scores (chapter 7), suggesting a link of clinical characteristics to the underlying neurobiology of pain avoidance.

I will discuss my results within the broader scope of pain coping. Acute avoidable pain triggers active coping, i.e. avoiding or escaping the harmful source. This motivation, however, can be disrupted quite easily when pain avoidance attempts remain unrewarded. While this reduced motivation might be adaptive in situations of acute short-term pain in order to avoid wasting energy, passivity and learned helplessness are considered to be maladaptive in chronic pain (see chapter 1, section 1.2.1.1). In the search for an adaptive coping style, reaching out for positive means could be proposed as a more desirable strategy when pain itself is unavoidable (chapter 3). While this strategy may not eliminate pain, it does help to re-balance the hedonic homeostasis and may even have some analgesic benefits.

In the following sections, I will discuss these ideas in more detail, focusing on behavioral and neural findings that underlie the described coping mechanisms.

8.2 Pain initiates coping: behavioral and neural correlates of dealing with avoidable and unavoidable pain

8.2.1 Behavioral correlates

8.2.1.1 Adaptive coping styles to deal with acute pain

Coping is defined as the measures taken ‘to solve personal and interpersonal problems, and seeking to master, minimize or tolerate stress or conflict’ (Cram101 Textbook Reviews 2016). The motivation to cope with pain is obviously of paramount importance to prevent injury. In a situation of avoidable pain, the organism shows a (conscious or unconscious) effort to avoid or escape the harmful stimulus with the aim to eliminate or reduce pain. This has been referred to as ‘active coping’. In the face of a physical threat, the organism switches to an alert state, and blood pressure and heart rate increase (Bandler et al., 2000; Keay and Bandler 2001; Lumb 2002), helping the body to face the threat and be prepared for fight or flight. The contrary would be major passive coping strategies, such as quiescence, surrender, and learned helplessness. Coping styles can be adaptive in different ways, depending on whether the pain is avoidable/escapable or not. For acute escapable pain, active coping strategies are most likely to be adaptive (Gandhi et al., *in review*). Escape and avoidance behaviors

encompass a wide repertoire of actions, ranging from withdrawal reflexes to complex nocifensive behavior (Morrison et al., 2013).

In the experiments of this thesis, we confirmed that healthy people as well as migraine patients are highly motivated to avoid an aversive electric shock by showing the required avoidance responses rapidly (chapters 5, 6, 7). Under normal conditions, all participants were able to even increase their response speed with increasing task difficulty (chapters 6, 7). We further showed, however, that this motivation can easily be disrupted when the previous pain avoidance attempt was unrewarded. While this was true for healthy people (chapters 5, 6), we saw an even stronger effect after previous unsuccessful avoidance attempts on the subsequent pain avoidance behavior of migraine patients (chapter 7). A similar change in behavior following unsuccessful pain avoidance has previously been reported (Roy et al., 2014). Contrary to the cited study though, where participants could switch to a different response option when the previous one was not successful, our participants only had one type of behavioral action that led to successful pain avoidance. While participants in the study by Roy and colleagues had the opportunity to learn from the punishing experiences and, in fact did adapt their avoidance behavior successfully, our participants had a tendency to give up and showed less motivation to avoid subsequent pain. This might have important clinical implications. If chronic pain patients are unable to avoid pain although they have tried to do so, it might be important to suggest behavioral alternatives to cope – different actions they can turn towards if their initial behavior remained unrewarded. This may counteract the tendency to give up and avoid the development of learned

helplessness. I will further discuss the clinical implications of unrewarded coping attempts in pain patients in more detail below.

Contrary to chronic pain, in situations of acute short-term pain it can be considered adaptive to refrain from active coping in situations where previous pain avoidance was unsuccessful. In this instance, persistent active escape and avoidance may even constitute a waste of energy and stamina (Gandhi et al., in review), because, based on the previous experience, this strategy is unlikely to lead to the desired reduction of pain. In this situation it might be best to rather stay passive, endure the pain, and save energy.

8.2.1.2 Adaptive active coping when pain itself is unavoidable

In many acute pain situations, escape or avoidance of the pain-provoking stimulus is not possible: an inflamed wound, toothache, or visceral pain are examples of acute pain situations that we are unable to escape from. Under these circumstances, it seems advantageous to engage in a passive coping style. Often, the body is immobilized, and blood pressure and heart rate decrease (Bandler et al., 2000; Keay and Bandler 2001; Lumb 2002), helping the body to rest and heal.

While passive coping can promote the healing process itself, it provides no immediate solution to re-establish the hedonic homeostasis that was disturbed by the unpleasant experience of pain (IASP Taxonomy Working Group, 2011). With the results presented

in chapter 3 of this thesis, I could demonstrate that healthy individuals show increased motivation to obtain reward when in pain, presumably to compensate for the negative emotional state caused by pain, and to re-establish the hedonic homeostasis. In my study, participants showed increased efforts to obtain monetary reward with higher incentives when in pain compared to when they were pain-free. I conclude that vigilance for environmental cues with the potential to improve the hedonic state is increased by the ongoing pain. Thereby, people are able to react faster when an incentive promises a high reward while in pain; obtaining this reward would ultimately improve their hedonic state. This phenomenon is not restricted to humans and comparable results have been found in rodents (Low and Fitzgerald 2012).

The fact that humans perform better when in pain is remarkable, given that pain demands attention and has been described as reducing the availability of cognitive resources (e.g. Buhle and Wager 2010; Eccleston and Crombez 1999; Keogh et al., 2014). To resolve this apparent contradiction, it is important to take a closer look at the tasks people are engaged in while in pain, and – probably even more important – whether the outcome of the task is of relevance to the participant's state. In general, individuals are more sensitive to information that is pertinent to reach a certain goal; goal-irrelevant information, in contrast, is likely to be ignored (reviewed in Van Damme et al., 2010). In analogy, while in pain, the sensitivity towards incentives associated with rewarding outcomes – as well as towards negative cues threatening to further worsen the homoeostatic imbalance – would be increased, because it assists in achieving the goal to re-establish hedonic homeostasis. Conversely, during goal-irrelevant tasks that

do not impact the homeostatic balance while in pain, such as mental arithmetic, memory or discrimination tasks, the performance is worse compared to a pain-free state, as shown in many experimental studies (e.g. (Buhle and Wager 2010; Eccleston 1994; Van Damme et al., 2008b; Van Ryckeghem et al., 2012). Supporting the notion that ongoing pain makes individuals more reward sensitive, are observations in chronic pain patients engaged in a reward task. Pain patients preferably choose options associated with high immediate reward whilst ignoring the fact that this choice is associated with higher risk (Apkarian et al., 2004b; Tamburin et al., 2014; Verdejo-Garcia et al., 2009). This phenomenon does not seem to be restricted to humans; a study in rodents showed that rats with persistent monoarthritic inflammatory pain chose a lever associated with higher, but less frequent rewards (i.e. the risky option) over a safer option that was associated with smaller immediate rewards (Pais-Vieira et al., 2009). I propose that individuals with ongoing pain focus on environmental cues that offer an opportunity to immediately improve their hedonic imbalance (i.e. high incentives) while the higher-order processing of odds and potential risks is diminished. Interestingly, the experience of winning is in itself analgesic (Becker et al., 2013; Becker et al., 2015). Thus, reaching out for positive means – i.e. showing an increased effort to obtain reward – constitutes an active coping attempt with a two-fold benefit when pain itself cannot be avoided or escaped: obtaining reward re-establishes, or at least improves, the hedonic homeostatic balance and it reduces the perception of the pain. It is conceivable that such active compensatory coping might even occur when the rest of the body is in passive coping mode. That is, the affected body site or the whole body is kept at rest while the mind

stays alert, screening the environment for incentives signaling the potential of immediate reward.

8.2.2 Neural correlates of coping with pain

Studies on the neurobiology underlying pain coping have often used escapable and inescapable stimuli to investigate coping responses. As expected, the former are typically associated with active escape responses while the latter are related to passive strategies (Keay and Bandler 2001). In the following sections, I will discuss the central role of the PAG in mediating these different coping strategies in responses to physical threat or actual pain.

The different columns of the PAG receive distinct peripheral and supraspinal input (An et al., 1998; Bandler et al., 2000; Ezra et al., 2015; Keay and Bandler 2001; 2002; Lumb 2004; Parry et al., 2008). The exact PAG area where the input is received matters because the different areas are associated with opposed coping responses (Carrive 1993; Lovick and Bandler 2005; Lumb 2002). The behavioral coping responses are accompanied by changes in autonomic function, namely changes in blood pressure, heart rate, respiration, and muscle tone (Lovick and Bandler 2005), suggesting that the PAG is central for the preparation of the body to cope with pain.

8.2.2.1 Neural correlates of active coping: the central role of the PAG

Rodent studies have identified that active coping is mediated by the dorsolateral PAG, (Bandler et al., 2000; Keay and Bandler 2001; Lumb 2004). In humans, deep brain stimulation has revealed that activating the dorsolateral PAG increases blood pressure (Green et al., 2005), a symptom that typically accompanies active coping strategies. This evidence hints at the involvement of the human dorsolateral PAG in the preparation for active coping. The results of my thesis are in accordance with the animal literature and complement the cited human study. During the preparation to avoid pain, a relative reduction of PAG activation following trials of unsuccessful avoidance attempts significantly predicted the pain-induced reduction in subsequent avoidance behavior (chapters 6, 7). This confirms a central role of the dorsolateral PAG for active pain coping behavior in humans.

In our paradigm, we studied the activation of the PAG in response to a physical threat. While this threat signaled the risk of upcoming pain, no actual nociceptive input from the periphery was being received at that time point. In this situation, it is reasonable to speculate that the dorsolateral PAG might have received its input from cortical structures involved in memory and decision making. Here, the medial prefrontal cortex is a likely candidate. Studies in macaques identified this structure to provide prominent anatomical projections to the dorsolateral PAG (An et al., 1998). The function of the medial prefrontal cortex has been described to form and store schemata which integrate context, events, and appropriate action (reviewed in Euston et al., 2012). The purpose of these schemata is to initiate the most suitable emotional and motor

response to a given event based on past experiences. Accordingly, if the appraisal of a situation in our experiment resulted in the interpretation that the upcoming pain stimulus could be avoided, the dorsolateral PAG possibly received input from the medial prefrontal cortex and prepared the body for active coping.

During the preparation for active coping, we demonstrated functional connection of the PAG to a network including attention-related areas (bilateral posterior parietal cortex) and areas involved in motor-preparation (bilateral cerebellum, contralateral putamen). The identified network is supported by anatomical connections of the PAG which are described in the human and animal literature. Prominent connections between the human parietal cortex and the dorsolateral PAG have been revealed using diffusion MRI (Ezra et al., 2015). This connection might result from an indirect anatomical pathway via the anterior pulvinar and lateral posterior nuclei of the thalamus (Behrens et al., 2003; Cameron et al., 1995; Schmahmann and Pandya 1990). The cerebellum receives direct bilateral input from the PAG (Dietrichs 1983). Its activation has been associated with changes in muscle tone (Koutsikou et al., 2014) which probably serves the preparation to carry out the movement required to avoid the upcoming pain. The putamen receives input from several brain structures, including the pulvinar and lateral dorsal thalamic nuclei (Parent et al., 1983). Both of these thalamic structures are anatomically connected to the dorsolateral PAG (Behrens et al., 2003; Cameron et al., 1995; Schmahmann and Pandya 1990), suggesting an indirect connection from the dorsolateral PAG to the putamen via the thalamus. The contralateral putamen is involved in the planning and initiation of movement (e.g. Alexander and Crutcher 1990;

Boussaoud and Kermadi 1997) and may facilitate the rapid response to the target cue presented immediately subsequent to the preparation phase.

Albeit not reaching statistical significance, the qualitative differences we described for the functional network of the PAG following unsuccessful pain avoidance attempts were interesting and might be behaviorally meaningful. Following unsuccessful pain avoidance attempts, I observed the PAG to be still connected to attention-related areas, while functional connections to motor-preparatory areas were no longer significant. This fits the above mentioned idea that motor responses are delayed under these circumstances, and may thus provide the neural substrate for the observed surrender following unrewarded coping attempts. However, more research will be needed to confirm this hypothesis.

8.2.2.2 Neural correlates of passive coping: how the PAG may mediate a state of physical quiescence while simultaneously reaching out for reward.

Unavoidable acute pain, such as deep somatic or visceral pain, triggers passive coping behaviors and down-regulation of the sympathetic nervous system via C-fiber input to the ventrolateral PAG (Bandler et al., 2000; Keay and Bandler 2001).

The efferent connections of the ventrolateral PAG form a wide network including structures such as the thalamus, hypothalamus, ventral tegmental area (VTA), and substantia nigra pars compacta (Cameron et al., 1995), providing the anatomical

substrate for its central role in orchestrating behavioral, autonomic, and analgesic responses to threats and aversive events. Of particular interest here are the efferent connections of the ventrolateral PAG to the dopaminergic structures VTA and substantia nigra (Cameron et al., 1995; Geisler et al., 2007; Omelchenko and Sesack 2010). The PAG input to the nigrostriatal dopamine system via the substantia nigra pars compacta is conveyed mainly by the ventral bundle (Cameron et al., 1995). Considering the central role of the nigrostriatal dopamine system in initiating and preparing motor responses (Amalric and Koob 1993), this may be the substrate for increased motor performance in response to reward-associated stimuli whilst experiencing inescapable pain. Similar to the substantia nigra, the VTA also receives afferent input from the ventrolateral columns of the PAG (Omelchenko and Sesack 2010). Within the VTA, these PAG efferents target dopaminergic neurons in the paranigral and the parabrachial subregions (Omelchenko and Sesack 2010), providing a circuitry via which nociceptive input could trigger the mesolimbic dopaminergic system. Based on the role of this system in reward processing (Cagniard et al., 2005; Cooper and Knutson 2008; Pecina et al., 2003; Smith et al., 2011; Yin et al., 2006; Zink et al., 2004), this may be the substrate for increased salience of appetitive stimuli, i.e. increased reward sensitivity, when experiencing unavoidable/inescapable pain (see Chapter 3).

I focus specifically on dopamine and its role in coping with pain at this point of the discussion, because it provides a reasonable explanation of the neural substrates possibly underlying my behavioral findings that pain increases the motivational drive to

obtain reward. However, other neurotransmitter systems play a role in the mediation of behavioral responses to different types of stressors. Specifically, the serotoninergic system, in particular the dorsal raphe nucleus and serotoninergic cells in the dorsal PAG (Amat et al., 1998), has been implicated in differential responses to escapable and inescapable nociceptive stimuli (Amat et al., 2014; Amat et al., 1998). Serotonin is important for psychological states such as fear and depression (reviewed in Bocchio et al., 2016; Kohler et al., 2016) and might therefore contribute to the initiation or maintenance of the homeostatic imbalance associated with inescapable stressors.

8.3 Clinical implications

While quiescence has been described as an adaptive coping strategy for acute unavoidable pain, it is considered maladaptive in most chronic pain situations (Gandhi et al., *in review*). In the case of chronic pain, passivity and helplessness does not contribute to the termination of the problem and further reduces well being and treatment success (Brown and Nicassio 1987; Keefe et al., 2004; Nicassio et al., 1999; Snow-Turek et al., 1996).

The results of my thesis demonstrate that pain patients who perceive themselves as helpless with regard to their clinical pain show alterations of the brain activity underlying active pain coping. The activation of their dorsolateral PAG during the preparation to avoid subsequent pain is more profoundly reduced following previous unsuccessful avoidance attempts than with patients who report low scores of helplessness (chapter

7). This pain-induced change in PAG activation predicted the subsequent pain avoidance behavior in my study sample. A greater reduction in PAG activation following previous unsuccessful avoidance attempts was associated with a greater reduction in the motivation to avoid subsequent pain. Further, this pain-induced passivity, as observed by our behavioral measure, correlated positively with the average length of a typical migraine attack. This supports the above argument that passivity is maladaptive in chronic pain; patients who show more passivity when previous coping attempts remained unrewarded seem to take longer to overcome their episodes of clinical pain. However, since correlations do not imply causality, it is equally reasonable to conclude the reverse, i.e. that patients with longer migraine attacks become more passive. Unreliable or poor efficacy of acute migraine treatments (reviewed in Silberstein 2010) may be the reason for prolonged migraine attacks. Leaving the patient with the feeling of uncontrollability over their pain may consequently lead to surrender and passive coping styles. I speculate that a reciprocal influence between the length of migraine attacks and passivity is, in fact, very likely.

Completing the vicious circle, longer migraine attacks were further associated with higher self-reports of helplessness in migraineurs.

To improve well-being in pain patients, it seems important to interrupt this vicious circle by decreasing perceived helplessness and encourage active coping even if it does not have immediate effects on the pain itself. As briefly discussed above, it may be important for patients who perceive themselves as helpless to learn alternative actions to cope with their pain. Consequently, they could switch to these alternative coping

strategies when their initial attempts to reduce pain failed. Therefore, their surrender could be avoided.

Reaching out for positive means and actively pursue rewarding activities could be one of these alternative strategies. As discussed above, this strategy does not only help to re-balance the hedonic homeostasis, but it could also have analgesic effects (Becker et al., 2013; Becker et al., 2015). Considering the relative lack of pharmaceutical options, embracing lifestyle adaptations and substantial self-management have, in fact, been described as key components for successful treatment of chronic pain (Garver et al., 2015).

Cognitive behavioral training aiming to counteract helplessness may rely on powerful top-down mechanisms originating in brain areas such as the medial prefrontal cortex and the hippocampus. These areas have been recently shown to mediate activation of the PAG as a consequence of learning (Roy et al., 2014). Thus, they may provide a neural substrate via which PAG activation could be targeted by psychological interventions.

8.4 Summary and significance

In conclusion, the findings of this thesis contribute significantly to our understanding of the interaction between pain and reward. Throughout the diffferent chapters I identified that pain influences reward in various manners. The main finding of part 1 revealed that

acute unavoidable pain increases the motivation to reach out for positive means. I interpreted this result as an adaptive strategy to re-balance the hedonic homeostasis when pain itself cannot be escaped. Screening the environment for incentives that promise to improve one's situation may accompany quiescence of the body or the affected body limb. Whilst allowing the body to rest and heal, an active approach can be taken to improve the hedonic state. I suggested the involvement of the ventrolater PAG in tight connection to the ventral and dorsal striatum to be the neural correlate of the increased motivation to obtain reward whilst experiencing unavoidable pain. Future research will have to confirm this hypothesis.

While I focused on active compensatory coping when pain itself was unavoidable in part 1 of this thesis, in part 2, I addressed active coping in situation where acute pain was, in fact, avoidable. Here, I demonstrated repeatedly that the motivation to actively cope, and avoid pain can be easily disrupted when a previous effort to avoid pain remained unrewarded. While this was true for healthy people, the effect was even stronger in migraineurs. Investigating the neural correlates of pain avoidance behavior, I identified the dorsolateral PAG as the central structure mediating active coping in humans. I argued that it is adaptive in situations of acute pain to abandon active coping when previous attempts remained unsuccessful, because it avoids wasting energetic resources. In the case of chronic pain, however, passivity has been associated with negative consequences and lower treatment success.

Further, I proposed a vicious circle of helplessness in migraineurs. This circle described how high helplessness in pain patients is associated with a stronger reduction in PAG activation following unsuccessful avoidance attempts. This, in turn, predicted a

reduction in pain avoidance behavior on the subsequent trial. Patients who reacted with more passivity following unrewarded coping attempts also reported longer average durations of their migraine attacks. Finally, longer migraine attacks were associated with higher self-reports of helplessness and, thus, completing the circle.

I argue that the results of my thesis may have important clinical implications. To improve well-being in chronic pain patients, it seems important to interrupt this vicious circle. Here, it seems central to decrease perceived helplessness and encourage active coping even if it does not eliminate the pain. Reaching out for positive means and actively pursue rewarding activities could be one of these active strategies – it supports a re-balancing of the hedonic homeostasis, and has even shown to have analgesic effects.

Lastly, I hypothesized that a cognitive behavioral training aiming to counteract helplessness could be centrally mediated by top-down mechanisms, which may originate in brain areas such as the medial prefrontal cortex and the hippocampus and finally target the PAG. While more research is required to confirm this assumption, it is an intriguing hypothesis which potential provides a novel avenue to reduce suffering in pain patients and enhance life quality.

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Appendices

Appendix A

McGill

Faculty of Medicine
3655 Promenade Sir William Osler
Montreal, QC H3G 1Y6

Faculté de médecine
3655, Promenade Sir William Osler
Montréal, QC, H3G 1Y6

Fax/Télécopieur: (514) 398-3595

16 August 2011

Dr. Petra Schweinhardt
Faculty of Dentistry
Strathcona Anatomy and Dentistry Building
3640 University, Room 2/38F

RE: IRB Study Number A05-M53-11B
Tonic pain and Neurocognitive processing in healthy volunteers

Dear Dr. Schweinhardt,

Thank you for responding to the IRB's correspondence in reference to the May 30, 2011 full Board review of the above-referenced study.

The submitted response and revisions are acceptable. Final ethics approval for this study and the following documents is provided on 16 August 2011:

- Study Protocol, Version 2, 11/07/11;
- Study Assessments: PASS, Fear of Pain Questionnaire – III, BIS/BAS, TCI;
- Recruitment Advertisement Texts (IRB dated May 2011);
- Psychophysical Consent Form, Version 2, July 11, 2011;
- MRI Study Consent Form, Version 2, July 11, 2011.

The ethics approval for this study is valid until **May 2012.** The Certificate of Ethical Acceptability is enclosed.

All research involving human subjects is required to undergo an annual ethics review as stipulated in Federal and Provincial documents guiding and regulating research involving human subjects. This annual review is scheduled according to the date of initial approval and it is the responsibility of the investigator to submit a completed application form for Continuing Ethics Review to the IRB prior to the expiration of the study's ethics approval. A copy of the Continuing Review form is available on the IRB website at: http://www.mcgill.ca/medresearch/ethics/.

Any modifications or unanticipated developments that may occur to the study prior to the annual review must be reported to the IRB promptly. Study modifications cannot be implemented prior to ethics review and approval of the change.

In addition to the continuing review requirements, it is the Investigator's responsibility for ensuring that all documents approved by this IRB are reported to and meet the standards in effect at the institution where subject recruitment occurs and/or where study data is collected. There is a risk that

the study's data may be invalidated and research funds frozen for failing to comply. *This study cannot be initiated until the Research Ethics Board or Office provides administrative approval for the study.*

The IRB has assigned this study the following **IRB Study Number: A05-M53-11B.** Please reference this number for all correspondence with our office.

Regards,

Serge Gauthier, MD
Chair
Institutional Review Board

Cc: Ms. L. Zegarelli - MNI/REB
A05-M53-11B

TONIC PAIN AND NEUROCOGNITIVE PROCESSING IN HEALTHY VOLUNTEERS

MRI STUDY

Official title of project Tonic pain and neurocognitive processing in healthy volunteers

Investigators Petra Schweinhardt, MD, PhD; Wiebke Gandhi, PhD candidate, Susanne Becker, PhD; Laura Stone PhD; Juan Francisco Asenjo MD

Location Alan Edwards Centre for Research on Pain, McGill University; Brain Imaging Centre, Montreal Neurological Institute

Funding Source CIHR operating grant

Reason for the study

Cognitive processing is typically altered in patients with chronic pain. At this point it is not clear whether this is a direct consequence of the activation of pain-processing pathways or caused by other changes that are associated with chronic pain, for example emotional disturbances. Also, cognitive processing in pain patients could be influenced by pain medication. Regions in the brain involved in cognition and pain perception are hugely overlapping. With this study we want to investigate the effect of pain itself on different cognitive tasks, and the brain regions involved in these effects. Since we are testing healthy participants who do not suffer from chronic pain, emotional disturbances and who are free of any pain medication we are asking whether you are interested in participating in this study.

Procedures

Your participation in this study will involve two visits on separate days, each taking approximately 90 minutes.

Before consenting we will provide you with further information on the phone or via email, and you will have the opportunity to ask questions. Please take your time to consider your participation carefully. If you decide to participate one of the investigators will schedule an appointment with you. At the beginning of the first session, the study procedure will be explained to you in detail and you will have the opportunity to ask any remaining question. If your questions were answered in a satisfactory manner, you will be asked to give written consent by signing this form. It will also be signed by the investigator. When you have consented to participate in the study, we will explain to you the thermal stimulation, the different tasks, the rating scales you will be using and the course of the Magnetic Resonance Imaging (MRI) scanning. Throughout the actual experiment, you will be receiving thermal stimulation while performing the tasks described below. The experiments will be performed when you are in the MRI scanner.

TONIC PAIN AND NEUROCOGNITIVE PROCESSING IN HEALTHY VOLUNTEERS

Official title of project Tonic pain and neurocognitive processing in healthy volunteers

Investigators Petra Schweinhardt, MD, PhD; Wiebke Gandhi, PhD candidate, Susanne Becker, PhD; Laura Stone PhD; Juan Francisco Asenjo MD

Location Alan Edwards Centre for Research on Pain, McGill University

Funding Source CIHR operating grant

Reason for the study

Cognitive processing is typically altered in patients with chronic pain. At this point it is not clear whether this is a direct consequence of the activation of pain-processing pathways or caused by other changes that are associated with chronic pain, for example emotional disturbances. Also, cognitive processing in pain patients could be influenced by pain medication. With this study we want to investigate the effect of pain itself on different cognitive tasks. Since we are testing healthy participants who do not suffer from chronic pain, emotional disturbances and who are free of any pain medication we are asking whether you are interested in participating in this study.

Procedures

Your participation in this study will involve two visits on separate days, each taking approximately 90 minutes.

Before consenting we will provide you with further information on the phone or via email, and you will have the opportunity to ask questions. Please take your time to consider your participation carefully. If you decide to participate one of the investigators will schedule an appointment with you. At the beginning of the first session, the study procedure will be explained to you in detail and you will have the opportunity to ask any remaining question. If your questions were answered in a satisfactory manner, you will be asked to give written consent by signing this form. It will also be signed by the investigator. When you have consented to participate in the study, we will explain to you the thermal stimulation, the different tasks, and the rating scales you will be using. Throughout the actual experiment, you will be receiving thermal stimulation while performing the tasks described below.

In one of the two sessions, an area of approximately 10 cm by 10 cm on your leg will be treated with capsaicin cream. Capsaicin is the active ingredient in chilli peppers. The cream will sensitize your skin which means that your skin is more sensitive than normally. We will apply warm stimuli to the capsaicin-treated skin using a heating pad. This stimulation might be painful on the sensitive skin.

In the other session we will treat a similar skin area with a cream that does not contain any active ingredient. In this session, applied warm temperatures might be perceived as not

TONIC PAIN AND NEUROCOGNITIVE PROCESSING IN HEALTHY VOLUNTEERS

STUDY PROTOCOL

1. **a) Official Titel:** Tonic pain and neurocognitive processing in healthy volunteers
   b) Does this protocol involve any patient population? No
   c) Does it involve the administration of therapy? No
   d) Is this an imaging study? Yes - MRI

2a Principal Investigators: P Schweinhardt MD PhD, The Alan Edwards Centre for Research on Pain, McGill University Strathcona Anatomy and Dentistry Building,
Rm. 2/38F; tel. #: 514-398-7203 ext. 0420

a) **Associate investigator(s) at the MNI/MNH**: N/A
b) **Full names, titles and affiliations of other associate investigators:**
W Gandhi PhD(c), The Alan Edwards Centre for Research on Pain, McGill University
S Becker PhD, The Alan Edwards Centre for Research on Pain, McGill University
L Stone PhD, The Alan Edwards Centre for Research on Pain, McGill University
JF Asenjo MD, The Alan Edwards Pain Management Clinic, Montreal General Hospital, McGill University Hospital Centre

2b Location: The Alan Edwards Centre for Research on Pain, McGill University
McConnell Brain Imaging Center, Montreal Neurological Institute

3. Is the PI the author of the protocol? No, Wiebke Gandhi is

4. Physicians, if any, to be involved in this project: JF Asenjo MD

5. Letters of agreement and support from individuals or departments whose facilities are to be used:

5.a. MUHC/ MNH/ MNI departments or facilities (eg. Director of professional Services (DPS), Neurological Services Operations Committee, etc)

Bruce Pike, Magnetic Resonance Research Committee. Montreal Neurological Institute (*to be handed in later*)

5.b Regulatory Compliance

A clinical trial involving human subjects planned for conduct in Canada must comply with the regulations stipulated by the Food and Drugs Act including the Food and Drug Regulations, and be authorized by Health Canada (HC) via a No Objection Letter (NOL). **N/A**

Add for psychophysical study

We are seeking healthy volunteers for a research project.

The Alan Edwards Centre for Research on Pain is conducting a study that involves pain testing and cognitive tasks. Participation involves 2 testing sessions (approximately 90 minutes each) and taking blood and saliva samples. You will be compensated for your time and inconvenience.

If you are interested, please send us an email at xxx@xxxxxx with your name and phone number.

The principal investigator is Dr. Schweinhardt, Alan Edwards Centre for Research on Pain, McGill University.

Add for MRI study

We are seeking healthy volunteers for a research project.

The Alan Edwards Centre for Research on Pain is conducting a study that involves pain testing, cognitive tasks, and Magnetic Resonance Imaging of your brain. Participation involves 2 testing sessions that will take approximately 90 minutes each. You will be compensated for your time and inconvenience.

If you are interested, please send us an email at xxx@xxxxxxx with your name and phone number.

The principal investigator is Dr. Schweinhardt, Alan Edwards Centre for Research on Pain, McGill University.

Version May 2011

PASS

Individuals who experience pain develop different ways to respond to that pain. We would like to know what you do and what you think about when in pain. Please use the rating scale below to indicate how often you engage in each of the following thoughts or activities. Circle any number from 0 (NEVER) to 5 (ALWAYS) for each item.

		NEVER					ALWAYS
1.	I think that if my pain gets too severe, it will never decrease	0	1	2	3	4	5
2.	When I feel pain I am afraid that something terrible will happen	0	1	2	3	4	5
3.	I go immediately to bed when I feel severe pain	0	1	2	3	4	5
4.	I begin trembling when engaged in activity that increases pain	0	1	2	3	4	5
5.	I can't think straight when I am in pain	0	1	2	3	4	5
6.	I will stop any activity as soon as I sense pain coming on	0	1	2	3	4	5
7.	Pain seems to cause my heart to pound or race	0	1	2	3	4	5
8.	As soon as pain comes on I take medication to reduce it	0	1	2	3	4	5
9.	When I feel pain I think that I may be seriously ill	0	1	2	3	4	5
10.	During painful episodes it is difficult for me to think of anything else besides the pain	0	1	2	3	4	5
11.	I avoid important activities when I hurt	0	1	2	3	4	5
12.	When I sense pain I feel dizzy or faint	0	1	2	3	4	5
13.	Pain sensations are terrifying	0	1	2	3	4	5
14.	When I hurt I think about the pain constantly	0	1	2	3	4	5
15.	Pain makes me nauseous (feel sick)	0	1	2	3	4	5
16.	When pain comes on strong I think I might become paralyzed or more disabled	0	1	2	3	4	5
17.	I find it hard to concentrate when I hurt	0	1	2	3	4	5
18.	I find it difficult to calm my body down after periods of pain	0	1	2	3	4	5
19.	I worry when I am in pain	0	1	2	3	4	5
20.	I try to avoid activities that cause pain	0	1	2	3	4	5

Fear of Pain Questionnaire—III

Name: _____ Date: _____

INSTRUCTIONS: The items listed below describe painful experiences. Please look at each item and think about how FEARFUL you are of experiencing the PAIN associated with each item. If you have never experienced the PAIN of a particular item, please answer on the basis of how FEARFUL you expect you would be if you had such an experience. Circle one rating per item to rate your FEAR OF PAIN in relation to each event.

AMOUNT OF FEAR					
Not at All	A little	A Fair Amount	Very Much	Extreme	
1	2	3	4	5	1. Being in an automobile accident
1	2	3	4	5	2. Biting your tongue while eating
1	2	3	4	5	3. Breaking your arm
1	2	3	4	5	4. Cutting your tongue licking an envelope
1	2	3	4	5	5. Having a heavy object hit you in the head
1	2	3	4	5	6. Breaking your leg
1	2	3	4	5	7. Hitting a sensitive bone in your elbow-your "funny bone"
1	2	3	4	5	8. Having a blood sample drawn with a hypodermic needle
1	2	3	4	5	9. Having someone slam a heavy car door on your hand
1	2	3	4	5	10. Falling down a flight of concrete stairs
1	2	3	4	5	11. Receiving an injection in your arm
1	2	3	4	5	12. Burning your fingers with a match
1	2	3	4	5	13. Breaking your neck
1	2	3	4	5	14. Receiving an injection in your hip/buttocks
1	2	3	4	5	15. Having a deep splinter in the sole of your foot probed and removed with tweezers
1	2	3	4	5	16. Having an eye doctor remove a foreign particle stuck in your eye
1	2	3	4	5	17. Receiving an injection in your mouth
1	2	3	4	5	18. Being burned on your face by a lit cigarette
1	2	3	4	5	19. Getting a paper-cut on your finger
1	2	3	4	5	20. Receiving stitches in your lip
1	2	3	4	5	21. Having a foot doctor remove a wart from your foot with a sharp instrument
1	2	3	4	5	22. Cutting yourself while shaving with a sharp razor
1	2	3	4	5	23. Gulping a hot drink before it has cooled
1	2	3	4	5	24. Getting strong soap in both your eyes while bathing or showering
1	2	3	4	5	25. Having a terminal illness that causes you daily pain
1	2	3	4	5	26. Having a tooth pulled
1	2	3	4	5	27. Vomiting repeatedly because of food poisoning
1	2	3	4	5	28. Having sand or dust blow into your eyes
1	2	3	4	5	29. Having one of your teeth drilled
1	2	3	4	5	30. Having a muscle cramp

BIS/BAS

Each item of this questionnaire is a statement that a person may either agree with or disagree with. For each item, indicate how much you agree or disagree with what the item says. Please respond to all the items; do not leave any blank. Choose only one response to each statement. Please be as accurate and honest as you can be. Respond to each item as it were the only item. That is, don't worry about being "consistent" in your responses. Choose from the following four response options:

1 = very true for me
2 = somewhat true for me
3 = somewhat false for me
4 = very false for me

1. A person's family is the most important thing in life. ____
2. Even if something bad is about to happen to me, I rarely experience fear or nervousness. ____
3. I go out of my way to get things I want. ____
4. When I'm doing well at something I love to keep at it. ____
5. I'm always willing to try something new if I think it will be fun. ____
6. How I dress is important to me. ____
7. When I get something I want, I feel excited and energized. ____
8. Criticism or scolding hurts me quite a bit. ____
9. When I want something I usually go all-out to get it. ____
10. I will often do things for no other reason than that they might be fun. ____
11. It's hard for me to find the time to do things such as get a haircut. ____
12. If I see a chance to get something I want I move on it right away. ____
13. I feel pretty worried or upset when I think or know somebody is angry at me. ____
14. When I see an opportunity for something I like I get excited right away. ____
15. I often act on the spur of the moment. ____
16. If I think something unpleasant is going to happen I usually get pretty "worked up". ____
17. I often wonder why people act the way they do. ____
18. When good things happen to me, it affects me strongly. ____
19. I feel worried when I think I have done poorly at something important. ____
20. I crave excitement and new sensations. ____
21. When I go after something I use a "no holds barred" approach. ____
22. I have very few fears compared to my friends. ____
23. It would excite me to win a contest. ____
24. I worry about making mistakes. ____

Instructions:
To answer you only need to circle either "T" or "F" after each question.
Read each statement carefully, but don't spend too much time deciding on the answer.
Please answer every statement, even if you are not completely sure of the answer.
Remember that there are no right or wrong answers- just describe you own personal opinions and feelings.

Number	Question	TRUE	FALSE
1	I often try new things just for fun or thrills, even if most people think it is a waste of time.	T	F
2	I usually am confident that everything will go well, even in situations that worry most people.	T	F
3	I am often moved deeply by a fine speech or poetry.	T	F
4	I often feel that I am the victim of circumstances.	T	F
5	I can usually accept other people as they are, even when they are very different from me.	T	F
6	I believe that miracles happen.	T	F
7	I enjoy getting revenge on people who hurt me.	T	F
8	Often when I am concentrating on something, I lose awareness of the passage of time.	T	F
9	Often I feel that my life has little purpose or meaning.	T	F
10	I like to help find a solution to problems so that everyone comes out ahead.	T	F
11	I could probably accomplish more than I do, but I don't see the point in pushing myself harder than is necessary to get by.	T	F
12	I often feel tense and worried in unfamiliar situations, even when others feel there is little to worry about.	T	F
13	I often do things based on how I feel at the moment without thinking about how they were done in the past.	T	F
14	I usually do things my own way - rather than giving in to the wishes of other people.	T	F
15	I often feel so connected to the people around me that it is like there is no separation between us.	T	F
16	I generally don't like people who have different ideas from me.	T	F
17	In most situations my natural responses are based on good habits that I have developed.	T	F
18	I would do almost anything legal in order to become rich and famous, even if I would lose the trust of many old friends.	T	F
19	I am much more reserved and controlled than most people.	T	F
20	I often have to stop what I am doing because I start worrying about what might go wrong.	T	F
21	I like to discuss my experiences and feelings openly with friends instead of keeping them to myself.	T	F
22	I have less energy and get tired more quickly than most people.	T	F
23	I am often called "absent—minded" because I get so wrapped up in what I am doing that I lose track of everything else.	T	F
24	I seldom feel free to choose what I want to do.	T	F
25	I often consider another person's feelings as much as my own.	T	F
26	Most of the time I would prefer to do some thin a little risky (like riding in a automobile over steep hills and sharp turns) - rather than having to stay quiet and inactive for a few hours.	T	F
27	I often avoid meeting strangers because I lack confidence with people I do not know.	T	F
28	I like to please other people as much as I can.	T	F
29	I like old "tried and true" ways of doing things much better than trying "new and improved" ways.	T	F
30	Usually I am not able to do things according to their priority of importance to me because of lack of time.	T	F
31	I often do things to help protect animals and plants from extinction.	T	F
32	I often wish that I was smarter than everyone else.	T	F
33	It gives me pleasure to see my enemies suffer.	T	F
34	I like to be very organized and set up rules for people whenever I can.	T	F
35	It is difficult for me to keep the same interests for a long time because my attention often shifts to something else.	T	F
36	Repeated practice has given me good habits that are stronger than most momentary impulses or persuasion.	T	F
37	I am usually so determined that I continued to work long after other people have given up.	T	F
38	I am fascinated by the many things in life that cannot be scientifically explained.	T	F
39	I have many bad habits that I wish I could break.	T	F
40	I often wait for someone else to provide a solution to my problems.	T	F
41	I often spend money until I run out of cash or get into debt from using too much credit.	T	F
42	I think I will have very good luck in the future.	T	F
43	I recover more slowly than most people from minor illnesses or stress.	T	F

McGill

Faculty of Medicine
3655 Promenade Sir William Osler
Montreal, QC H3G 1Y6

Faculté de médecine
3655, Promenade Sir William Osler
Montréal, QC, H3G 1Y6

Fax/Télécopieur: (514) 398-3595

CERTIFICATION OF ETHICAL ACCEPTABILITY FOR RESEARCH INVOLVING HUMAN SUBJECTS

The Faculty of Medicine Institutional Review Board (IRB) is a registered University IRB working under the published guidelines of the Tri-Council Policy Statement, in compliance with the Plan d'action ministériel en éthique de la recherche et en intégrité scientifique, (MSSS, 1998) and the Food and Drugs Act (17 June 2001); and acts in accordance with the U.S. Code of Federal Regulations that govern research on human subjects. The IRB working procedures are consistent with internationally accepted principles of good clinical practice.

At a full Board meeting on May 30, 2011, the Faculty of Medicine Institutional Review Board, consisting of:

THIERRY ALCINDOR, MD	EVGENIA GAROUFALIS, MD
VINCENT GRACCO, PHD	MARLYNNE GURSKY, BN, M.ED.
PATRICIA HAMILTON, BN	MARIGOLD HYDE, B.SC.
ADRIAN LANGLEBEN, MD	DAVID PARRY, BA
DANIEL SAUMIER, PHD	MAIDA SEWITCH, PHD
HARVEY SIGMAN, MD	JONATHAN WAN, MD

Examined the research project **A05-M53-11B** titled, *Tonic pain and Neurocognitive processing in healthy volunteers*

As proposed by: Dr. Petra Schweinhardt (Applicant) to _____ (Granting Agency, if any)

And consider the experimental procedures to be acceptable on ethical grounds for research involving human subjects.

16 August 2011
Date

Chair, IRB

Dean of Faculty

Institutional Review Board Assurance Number: FWA 00004545

Appendix B

Montréal, le 22 mai 2014

Docteure Petra Schweinhardt, MD, Ph.D.
a/s de Madame Wiebke Gandhi, M.Sc
McGill University, M/19
Strathcona Anatomy and Dentistry Building
3640 University Street
Montreal (Québec), H3A 0C7

Objet: CMER RNQ 13-14-026 : Approbation finale

Behavioral and neural correlates of pain avoidance.

Docteure,

Le Comité mixte d'éthique de la recherche du RNQ a évalué votre projet de recherche à sa réunion du 7 avril 2014, tenue à l'IUGM. Lors de cette réunion, les documents suivants ont été examinés :

- Lettre de présentation datée du 12 février 2014.
- Formulaire de demande d'évaluation d'un projet de recherche.
- Protocole de recherche intitulé : Behavioral and neural correlates of pain avoidance, daté du 12 février 2013.
- Formulaire d'information et de consentement, daté du 26 janvier 2014.
- Informed consent form, daté du 26 janvier 2014.
- Formulaire de dépistage pour étude en IRM.
- Form screening for MRI Study.
- AEQ PER.
- AEQ PCR.
- AEQ PBR.
- KPI-AE PER.
- KPI-AEM PCR.
- KPI-AEM PCopR.
- Échelle de Beck (BDI : Beck Depression Inventory).
- BDI.
- BIS/BAS, version française.
- BIS/BAS, version anglaise.
- Auto-efficacité Généralisée, (2000).
- The general Self-Efficacy Scale (GSE), (1995).
- PCS.
- Pain Catastrophizing Scale, (1995).
- Affiche de recrutement, versions française et anglaise
- Copie de l'octroi de fonds des IRSC, portant sur « The importance of dopamine, dopamine receptors, and domaminergic pathways for analgesia and pain modulation in humans », No. 200909MOP-209983-BSC-CFAA-167698, datée du 12 février 2010.

Suite à cette réunion, une approbation conditionnelle vous a été émise en date du 14 avril 2014. Vous nous avez soumis en date du 8 mai 2014, les documents suivants :

- Formulaire d'information et de consentement, daté du 29 avril 2014 – mode révision.
- Informed consent form, daté du 29 avril 2014 – mode révision.
- Affiche de recrutement, versions française et anglaise – mode révision.

Vos réponses et les modifications apportées à votre projet de recherche ont fait l'objet d'une évaluation. Le tout ayant été jugé satisfaisant, nous avons le plaisir de vous informer que votre projet de recherche a été approuvé à l'unanimité par le Comité mixte d'éthique de la recherche du RNQ.

Les documents que le Comité mixte d'éthique de la recherche du RNQ a approuvés et que vous pouvez utiliser pour la réalisation de votre projet sont les suivants :

- Protocole de recherche intitulé : Behavioral and neural correlates of pain avoidance, daté du 12 février 2013.
- Formulaire d'information et de consentement, daté du 22 mai 2014.
- Informed consent form, daté du 22 mai 2014.
- Formulaire de dépistage pour étude en IRM.
- Form screening for MRI Study.
- AEQ PER.
- AEQ PCR.
- AEQ PBR.
- KPI-AE PER.
- KPI-AEM PCR.
- KPI-AEM PCopR.
- Échelle de Beck (BDI : Beck Depression Inventory).
- BDI.
- BIS/BAS, version française.
- BIS/BAS, version anglaise.
- Auto-efficacité Généralisée, (2000).
- The general Self-Efficacy Scale (GSE), (1995).
- PCS.
- Pain Catastrophizing Scale, (1995).
- Affiche de recrutement, versions française et anglaise, datée du 22 mai 2014.

Cette approbation éthique est valide pour un an à compter du 22 mai 2014. Un mois avant la date d'échéance, vous devrez faire une demande de renouvellement auprès du Comité mixte d'éthique de la recherche du RNQ, en utilisant le formulaire du Comité prévu à cet effet.

Dans le cadre du suivi continu, le Comité vous demande de vous conformer aux exigences suivantes en utilisant les formulaires du Comité prévus à cet effet :

- De soumettre, pour approbation préalable au Comité, toute demande de modification au projet de recherche ou à tout document approuvé par le Comité pour la réalisation de votre projet.
- De soumettre, dès que cela est porté à votre connaissance, les incidents thérapeutiques graves, les réactions indésirables graves, les réactions indésirables et inattendues et les accidents observés en cours de recherche.
- De soumettre, dès que cela est porté à votre connaissance, tout nouveau renseignement sur des éléments susceptibles d'affecter l'intégrité ou l'éthicité du projet de recherche ou d'accroître les risques et les inconvénients des sujets, de nuire au bon déroulement du projet ou d'avoir une incidence sur le désir d'un sujet de recherche.
- De soumettre, dès que cela est porté à votre connaissance, toute modification constatée au chapitre de l'équilibre clinique à la lumière des données recueillies.
- De soumettre, dès que cela est porté à votre connaissance, la cessation prématurée du projet de recherche, qu'elle soit temporaire ou permanente.
- De soumettre, dès que cela est porté à votre connaissance, tout problème identifié par un tiers, lors d'une enquête, d'une surveillance ou d'une vérification interne ou externe.
- De soumettre, dès que cela est porté à votre connaissance, toute suspension ou annulation de l'approbation octroyée par un organisme de subvention ou de réglementation.
- De soumettre, dès que cela est porté à votre connaissance, toute procédure en cours de traitement d'une plainte ou d'une allégation de manquement à l'intégrité ou à l'éthique ainsi que des résultats de la procédure.

Vous pouvez obtenir les formulaires du Comité téléchargeables à partir du site web de l'UNF : http://www.unf-montreal.ca/siteweb/Home_fr.html, sous l'onglet : Planifiez votre étude – Suivi des projets.

De plus, nous vous rappelons que vous devez conserver pour une période d'au moins un an suivant la fin du projet, un répertoire distinct comprenant les noms, prénoms, coordonnées, date du début et de fin de la participation de chaque sujet de recherche.

Finalement, nous vous rappelons que la présente décision vaut pour une année et pourra être suspendue ou

révoquée en cas de non-respect de ces exigences.

Le Comité mixte d'éthique de la recherche du RNQ est désigné par le ministère de la Santé et des Services sociaux, en vertu de l'application de l'article 21 du Code civil du Québec et suit les règles émises par l'Énoncé de politique des trois conseils et les Bonnes pratiques cliniques.

Avec l'expression de nos sentiments les meilleurs.

Johane de Champlain
Présidente du CMER RNQ

JdeC/kb

p. j. Formulaires d'information et de consentement approuvés.
Affiches pour le recrutement approuvées.

Comité mixte d'éthique de la recherche du RNQ
4565, Chemin Queen Mary, local R-1738
Montréal (Québec) H3W 1W5
Téléphone : 514- 340-2800, poste 3250
Courriel : karima.bekhiti.iugm@ssss.gouv.qc.ca
Site du Comité : www.unf-montreal.cal