PAIN SYMPTOMS IN DEPRESSED OUTPATIENTS

by

DR. AHMAD QABIL BIN KHALIB

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LIST OF ABBREVIATIONS

BPI:	Brief Pain Inventory
CCEI:	Crown-Crisp Experiential Index
DEP:	Depression
DSM-IV:	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
E.g.:	For example
FFA:	Free floating anxiety
HAM-D:	Hamilton Rating Scale for Depression
HYS:	Hysterical
MDD:	Major depressive disorder
OBS:	Obsessionality
PHO:	Phobic anxiety
SCID-CV:	Structured Clinical Interview for DSM-IV Axis I Disorders, Clinician Version
SOM:	Somatic concomitants of anxiety
STAR*D:	Sequenced Treatment Alternatives to Relieve Depression
WHO:	World Health Organization

ABSTRAK

Latar belakang: Kemurungan "major depressive disorder" adalah suatu masalah kesihatan yang penting dan penyebab ketidakupayaan di serata dunia. Terdapat kaitan yang rapat antara kemurungan dan simptom kesakitan, yang dipengaruhi oleh pelbagai faktor biologi dan mekanisme psikososial. Kewujudan bersama simptom kesakitan kronik serta kemurungan dikaitkan dengan ketidakupayaan, kekurangan sosioekonomi, penggunaan perkhidmatan kesihatan yang tinggi, serta kadar kematian yang ketara.

Objektif: (a) Mengenalpasti kadar kekerapan simptom kesakitan di antara pesakit dewasa yang mengalami kemurungan di klinik psikiatri, (b) untuk mengenalpasti ciri-ciri personaliti para peserta, (c) untuk mengenalpasti kaitan antara ciri-ciri personaliti para peserta dengan simptom kesakitan, dan (d) untuk mengenalpasti kaitan antara ciri kemurungan para peserta dengan simptom kemurungan.

Kaedah: Satu soal-selidik telah dijalankan terhadap pesakit-pesakit berumur 18 tahun dan ke atas yang mengidap kemurungan "major depressive disorder" mengikut klasifikasi "Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition" (DSM-IV), dan menghadiri klinik psikiatri di Hospital Universiti Sains Malaysia. Pengambilan sampel secara "convenience sampling" telah dijalankan dalam tempoh kajian antara Februari 2008 dan Jun 2009. Borang soal-selidik yang digunakan adalah borang maklumat sosiodemografi, Skala Kemurungan Hamilton (HAM-D), Inventori Ringkas Kesakitan (BPI) Versi Bahasa Malaysia, dan Indeks Eksperiential Crown-Crisp (CCEI) Versi Bahasa Malaysia; semuanya diisi setelah mendapat kebenaran bertulis daripada peserta kajian. Pesakit yang enggan memberi kebenaran, mereka yang mengalami penyakit psikiatri selain kemurungan, serta mereka yang mengidap penyakit fizikal atau surgikal yang

menyebabkan simptom kesakitan; telah dikecualikan daripada mengambil bahagian dalam kajian ini.

Keputusan: 51 orang peserta telah diambilkira dalam kajian ini. Secara keseluruhannya, para peserta dalam kajian ini mengalami paras kemurungan yang ringan, dan kira-kira separuh daripada mereka mengalami neurosis. 80.4% daripada para peserta mengalami simptom kesakitan, tetapi secara keseluruhannya paras kesakitan para peserta adalah ringan. Apabila dibandingkan dengan kewujudan simptom kesakitan, tiada perbezaan ditemui untuk ciri-ciri sosiodemografi. Walau bagaimanapun, ujian "Fisher's chi-square test" menunjukkan terdapat perbezaan ketara dalam status kemurungan (masih murung berbanding kemurungan yang telah reda) dan ciri "kemurungan yang resah", di mana peserta yang masih murung ($p < 0.05$) dan mereka yang mengalami "kemurungan yang resah" ($p < 0.05$) adalah lebih berkemungkinan mengalami simptom kesakitan. Analisis "logistic regression" terhadap ciri-ciri sosiodemografi dan klinikal tidak menunjukkan sebarang penemuan ketara apabila disabitkan dengan status kewujudan simptom kesakitan. Terdapat korelasi positif antara faktor-faktor "Free floating anxiety" (FFA) ($r = 0.363$, $p = 0.009$), "Somatic concomitants of anxiety" (SOM) ($r = 0.394$, $p = 0.004$), dan "Depression" (DEP) ($r = 0.478$, $p < 0.001$) serta jumlah markah Indeks Eksperiential Crown-Crisp (CCEI) ($r = 0.415$, $p = 0.002$) dengan tahap kesakitan yang dialami. Jumlah markah Indeks Eksperiential Crown-Crisp menyumbangkan 17.2% daripada varians jumlah markah Inventori Ringkas Kesakitan (BPI). Dua belas perkara daripada Skala Kemurungan Hamilton (HAM-D) yang berkait dengan perasaan murung, jenis-jenis keresahan (termasuk "perasaan murung", "kerja & minat", "keresahan psikik", "keresahan somatik" dan "simptom genital") serta jumlah markah Skala Kemurungan Hamilton ($r = 0.608$, $p < 0.001$) didapati mempunyai korelasi positif dengan tahap kesakitan yang dialami. Jumlah

markah Skala Kemurungan Hamilton menyumbangkan 33.2% daripada varians jumlah markah Inventori Ringkas Kesakitan.

Kesimpulan: Kadar kewujudan simptom kesakitan di kalangan pesakit dewasa yang mengalami kemurungan adalah 80.4 peratus. Kajian ini menunjukkan wujudnya kaitan antara keresahan, ciri-ciri personaliti dan tahap kemurungan dengan tahap kesakitan yang dialami oleh pesakit kemurungan.

ABSTRACT

Background: Major depressive disorder is an important health problem and a major cause of disability worldwide. There is a strong association between depression and pain, which is influenced by various biological and psychosocial mechanisms. The combination of chronic pain and depression is associated with high rates of disability, socioeconomic disadvantage, greater utilization of health care resources, as well as a considerable mortality rate.

Objectives: (a) To determine the proportion of adult depressed patients attending the psychiatric clinic who have pain symptoms, (b) to assess the characteristic of personality traits in the respondents, (c) to determine the association between specific personality traits and pain symptoms in the respondents, and (d) to determine the association between depression and pain symptoms in the respondents.

Methods: A survey was carried out on patients aged 18 years and above with a diagnosis of major depressive disorder according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), who attended the psychiatric clinic in Hospital Universiti Sains Malaysia. Convenience sampling was carried out during the study period between February 2008 and June 2009. The questionnaires utilized were the sociodemographic data form, Hamilton Rating Scale for Depression (HAM-D), Brief Pain Inventory (BPI) - Malay version, and Crown-Crisp Experiential Index (CCEI) - Malay version, which were filled after obtaining written informed consent. Patients who refused to give consent, those with co-morbid psychiatric diagnosis and those with medical or surgical conditions associated with pain symptoms were excluded from the study.

Results: 51 respondents were included in this study. Overall, the respondents in this study had mild levels of depression, and about half had neurotic traits. 80.4% of respondents experienced pain, but overall the severity of pain in the group was mild. When compared by the presence of pain, there was no difference in the sociodemographic characteristic. However, Fisher's chi-square test revealed statistically significant difference in the status of depression (depressed versus remitted) and "anxious depression" characteristic, whereby those who were still depressed ($p < 0.05$) and those with "anxious depression" ($p < 0.05$) were more likely to experience pain. Logistic regression analysis of sociodemographic and clinical variables did not show any statistically significant finding with regard to their status of pain presence or absence. There was positive correlation between the Free floating anxiety (FFA) ($r = 0.363$, $p = 0.009$), Somatic concomitants of anxiety (SOM) ($r = 0.394$, $p = 0.004$), and Depression (DEP) ($r = 0.478$, $p < 0.001$) sub-scales of CCEI as well as CCEI total score ($r = 0.415$, $p = 0.002$) with the severity of pain. The CCEI total score accounts for 17.2% of the variance of BPI total score. Twelve items from the HAM-D pertaining to depressed mood and various types of anxiety (including "depressed mood", "work & interests", "psychic anxiety", "somatic anxiety", "general somatic" and "genital symptoms"), as well as HAM-D total score ($r = 0.608$, $p < 0.001$) were positively correlated with severity of pain. The HAM-D total score accounts for 33.2% of the variance of BPI total score.

Conclusions: The proportion of adults with major depressive disorder having pain is 80.4 per cent. This study shows there is association between anxiety, personality traits and severity of depression with the severity of pain experienced by depressed patients.

CHAPTER 1 - INTRODUCTION

Major depressive disorder is an important health problem and a major cause of disability worldwide. It was ranked fourth according to disability-adjusted life years for year 2000 (World Health Organization, 2001). Moreover, major depression is predicted to rise to second by rank in 2020, second only to ischaemic heart disease (Murray and Lopez, 1996). Depression is also responsible for the greatest proportion of disease burden attributable to non-fatal health outcomes, accounting for almost 12% of total years lived with disability worldwide (Ustun and Chatterji, 2001). In a prospective population-based cohort study with 23 years of follow-up involving 3481 subjects (Eaton *et al.*, 2008), it was found that about 50% of those with first episode of depression recovered and had no future episodes, while major depressive disorder was unremitting in 15% of cases and recurrent in 35%. Unfortunately some researchers have shown that primary care physicians fail to accurately diagnose at least 50% of patients with major depression (Bair *et al.*, 2003), which may perpetuate the illness further.

Research has shown strong association between depression and chronic pain such as in rheumatoid arthritis, fibromyalgia and chronic back pain (Fishbain *et al.*, 1997). Depressed patients have also been found to be more vulnerable to complaints of pain (Bar *et al.*, 2005). In the Text Revision of Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) (American Psychiatric Association, 2000), it is stated that the associated features of major depressive episodes include excessive worry over physical health, and complaints of pain such as headaches or joint, abdominal, or other pains. Research have shown that pain is also strongly associated with anxiety as with depressive disorders (Von Korff and Simon, 1996). Furthermore, it is now a well established fact that having chronic

pain predisposes someone to develop depressive symptoms. For instance, data analysis from the World Health Organization World Health Survey involving 245,404 participants in 60 countries (Moussavi *et al.*, 2007) revealed that those with one or more chronic physical disease had significantly higher likelihood of having depression ($p<0.0001$) compared to participants without a chronic physical disease. Furthermore, after controlling for other factors such as socioeconomic and health conditions, depression had the largest effect on worsening mean health scores, in comparison to other chronic conditions. In addition, depressed patients with one or more comorbid chronic disease had the worst health scores compared to all the disease states. The results of the World Mental Health Surveys also show that chronic pain problems are common world-wide, and that the association of chronic pain with mood disorders extends to non-Western countries (Gureje *et al.*, 2008).

However, the interplay between depression and pain symptoms is influenced by various biological and psychosocial mechanisms: from factors such as the type, location, duration and severity of pain, self-efficacy, to maladaptive coping responses such as cognitive distortions. Additionally, treatment outcome of depression is also adversely affected by the presence of neuroticism (Mulder, 2002), which is a biologically determined personality trait. With robust evidence showing the association between neuroticism and depression, the personality trait of neuroticism has been proposed to be a vulnerability factor in the development of major depressive disorder (Kercher *et al.*, 2009).

It is important to note that the comorbidity of chronic pain and depression, which affects around 2% of the general population, represents an important health problem, as it is associated with greater socioeconomic disadvantage, disability, and utilization of health care resources (Currie and Wang, 2004). Furthermore, individuals with depression have a

considerable associated mortality rate, with up to 15% of depressed inpatients eventually dying by suicide (Andreasen and Black, 1995). A large analysis of 100 suicide studies carried out in the past 30 years found that overall suicide rate for patients with depression is 2 to 9 percent (Bostwick and Pankratz, 2000). On the other hand, chronic pain is also an important independent risk factor for self-harm and suicide (Peveler *et al.*, 2006). With pain being an important factor in health and in illness, both the Joint Commission on Accreditation of Healthcare Organizations and the Veterans Health Administration emphasize pain as the "fifth vital sign" (Bair *et al.*, 2004). In terms of biological treatment, tricyclic antidepressants and dual (serotonin and noradrenalin) reuptake inhibitors have been shown to relieve pain (Angst *et al.*, 2008). However, apart from medications, exercise and psychological and behavioural treatments both address pain and depression simultaneously (McWilliams *et al.*, 2004).

Many people believe that the Asian populations with depression have a tendency to present with predominantly somatic symptoms such as aches and pains, rather than presenting with a complaint of low mood or anhedonia. This is one of the reasons which contribute to delayed diagnosis and treatment of depression in these populations. Many will resort to seeking traditional treatments for many months or even years before eventually coming to see their doctor for their symptoms. In clinical practice, clinicians often come across depressed patients who have multiple pain symptoms, which can prove to be quite a challenge to the clinician. Unfortunately in our local Malaysian setting, there is lack of robust evidence on the prevalence of pain symptoms amongst this group of patients.

Therefore, this study aims to determine the prevalence of pain symptoms and its associated factors in depressed adult outpatients in our local population. The specific

objectives of this study are (a) to determine the proportion of adult depressed patients attending the psychiatric clinic who have pain symptoms, (b) to assess the characteristic of personality traits in the respondents, (c) to determine the association between specific personality traits and pain symptoms in the respondents, and (d) to determine the association between depression and pain symptoms in the respondents. The null hypothesis is that there is no association between characteristics of personality traits and depression with pain symptoms.

CHAPTER 2 - LITERATURE REVIEW

2.1 Historical background

The interest in the relation between personality and depression has been present for a long time. Since the olden days, melancholic temperament was associated with individuals who were moody, pessimistic, and vulnerable to episodic depression. An excess of black bile was even offered as a neurobiological explanation for this phenomenon (Mulder, 2008). Some researchers suggested that personality traits and disorders represent an "inflexible, unchangeable" set of characteristics that may predispose one to develop chronic pain (Engel, 1959). On the other hand, the underlying genetic and early-life predispositions to personality disorders may become expressed under the stress of a chronic pain disorder (Weisberg and Keef, 1997). Some believed that psychotic depression and neurotic depression were related to the underlying personality traits of psychoticism and neuroticism respectively (Eysenck, 1970); while Paykel (Paykel, 1972) put forward four categories of depressive typology: anxious depressives, hostile depressives, young depressives with personality disorder, and psychotic depressives. From the psychoanalytical point of view, it was believed that depressed patients had undue interpersonal dependency, obsessionality, and labile self-esteem (Hirschfeld *et al.*, 1983). Furthermore, Freud (Breuer and Freud, 1895) had put forward the theory that pain may represent a "conversion" from unpleasant affect to bodily pain. Over years of research, scientific advances have improved the understanding of depression and personality, although none can claim to have full understanding of the relation between the two. However, the idea that personality is intimately tied up with psychopathology has persisted up to today, and will continue to be studied.

2.2 Prevalence of depression and pain

Kessler and colleagues (Kessler *et al.*, 2003) reported the results from the National Comorbidity Survey Replication (NCS-R), which was a face-to-face household survey in the United States with 9090 responders. In this study, using World Health Organization's Composite International Diagnostic Interview, the lifetime prevalence of major depressive disorder was determined at 16.2%, while the 12-month prevalence was 6.6%. Of the latter group, 10.4% were found to have mild depression, 38.6% moderate, 38.0% severe and 12.9% very severe; and the mean duration of depressive episodes was 16 weeks. Whereas in Europe, The European Study of Epidemiology of Mental Disorders (ESEMeD) reported an overall annual prevalence of 3.9% for major depression and a lifetime prevalence of 12.8% (Garcia-Cebrian *et al.*, 2008). In terms of the clinical characteristics of depressed patients, findings from the Vantaa Depression Study (Vuorilehto *et al.*, 2007) was that psychotic subtype and severity of depression were highest among inpatients, but otherwise there were few clinical differences between psychiatric and primary care patients.

In a large cross-sectional telephone survey involving 18,980 subjects in Europe (Ohayon and Schatzberg, 2003), it was found that chronic painful physical conditions was strongly associated with major depressive disorder, whereby those with depression were 4 times more likely to have a painful condition. On the other hand, Bair (Bair *et al.*, 2007) analyzed the Medical Outcomes Study, a 4-year prospective observational study of adult outpatients from 1986-1990 carried out via telephone interviews. The authors used the National Institute of Mental Health (NIMH) Diagnostic Interview Schedule (DIS) and had found a prevalence of major depression of 23.4% from the whole sample. Furthermore, the researchers assessed pain using the 36-item Short Form Bodily Pain scale, a two-item scale that assesses pain severity and pain interference in the last 4 weeks. Overall, 50.6% of the

sample experienced pain. However, in the subset of subjects having major depression (N=503), the prevalence of pain was remarkably high: 41% reported having mild pain, 28% reported moderate pain, and 14% had severe pain; giving rise to a prevalence of pain of 83% in this group.

Similarly, a survey of 5,808 Kaiser Permanente patients found that 66% of patients with major depressive disorder reported chronic pain, compared to 43% in those without depression (Arnow *et al.*, 2006). Furthermore, disabling chronic pain was present in 41% of those with major depressive disorder versus 10% in those without depression. In a large review of 70 studies to investigate the association between depression and painful physical symptoms (Garcia-Cebrian *et al.*, 2006), data from 46 of the studies showed a positive association between painful physical symptoms and depression, and this association was observed in all 3 types of population studied i.e., general populations, patients presenting to their general practitioners, and patients treated at specialist pain clinics or psychiatric clinics.

In a study carried out by Mathew (Mathew *et al.*, 1981), prevalence of pain in depressed persons was similar for patients seen in primary care or psychiatric settings. More recently, the prevalence of painful physical symptoms in depressive patients in the psychiatric setting was found to be 50-69% (Ierodiakonou and Iacovides, 1987), with musculoskeletal complaint and headache being the most common symptoms, reported by 68.3% and 60.4% of patients with depression, respectively. Meanwhile, in a study of depressed patients being admitted to hospital, pain complaints were present in 92% of subjects upon admission, with 76% of patients reporting several pain complaints (Corruble and Guelfi, 2000). On the other hand, an assessment of 97 psychiatric outpatients in Malaysia found that 39% of new psychiatric outpatients had pain, associated chiefly with

the diagnosis of depression and anxiety neurosis (Ramli and Ariff, 1994). In this study, female sex was significantly associated with pain in depressed patients.

In terms of gender differences, a study carried out by Statistics Canada involving 131,535 participants (Munce and Stewart, 2007) revealed a prevalence of depression in women at 9.1%, which was almost twice that of men at 5%. Of all the participants, 32.8% had a chronic pain condition. Depression was prevalent in 11.3% of those with a chronic pain condition, compared to 5.3% in those without pain. In the cohort of 2541 outpatients in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study (Marcus *et al.*, 2008), the researchers observed that women had greater symptom severity, but men had more episodes of major depression, despite no difference in the length of illness. Furthermore, women had greater rates of an anxiety disorder, somatoform disorder, and pain complaints compared to men. In a study of the prevalence of common pain conditions (headache, back or neck pain, arthritis or joint pain, and other chronic pain) in 10 developed and 7 developing countries involving 42,249 participants (Tsang *et al.*, 2008), the cross-nationally consistent findings were that females exhibited a higher overall prevalence of chronic pain than males, and that there is increased vulnerability to chronic pain with increasing age, especially arthritis or joint pain. In this large prevalence study, age-standardized prevalence of chronic pain conditions in the previous 12 months was found to be 37.3% in developed countries and 41.1% in developing countries, confirming that chronic pain conditions are common in the general population world-wide.

In the older age group, clinically significant depressive symptoms affect nearly one in four adults over the age of 65 (Blazer, 2003). In the local scenario, a screening study using the Geriatric Depression Scale on patients aged 60 years and above in Butterworth, Malaysia revealed that 18% the participants had depression (Mohd Sidik *et al.*, 2003).

Factors associated with depression were females, those without formal education, low total family income and urban residence. In a different study, a meta-analysis of 89 treatment studies of late-life depression (Pinquart *et al.*, 2006) revealed that only 50% of subjects treated with medication or psychotherapy improve considerably by the end of treatment. Furthermore, apart from increasing health-care costs, depressive symptoms amplify risk for morbidity and mortality in the elderly.

2.3 Pathophysiology of depression

Serotonin is widely implicated in the pathophysiology of depression. Serotonin-producing neurons are localized in the raphe nuclei of the brain stem and project to terminal regions throughout the brain including hypothalamus, cortex, hippocampus, and amygdala (Foster and MacQueen, 2008). Serotonin transporters are in the focus of research on the neurobiological correlates of major depressive disorder, because several antidepressant medications alleviate negative mood states by blocking serotonin-reuptake. Using positron emission tomography, Reimold (Reimold *et al.*, 2008) demonstrated that patients with untreated major depressive disorder had reduced serotonin transporter availability in the thalamus, compared to matched healthy control subjects. This lowered serotonin reuptake capacity contributes to the anxiety experienced by patients with depression.

There is general acceptance of the hypothesis that there is stress-like dysregulation of the hypothalamo-pituitary axis during a depressive episode (Foster and MacQueen, 2008). Furthermore, stress can also predispose people to episodes of depression, which includes both stress that is temporally proximate as well as temporally remote, such as early-life abuse (Nemeroff, 2004). The hippocampus, a key region involved in the modulation of stress, is implicated in the pathophysiology of major depressive disorder.

Deficits in the glucocorticoid negative feedback system between the hippocampus and the hypothalamo-pituitary axis may contribute to the altered function of this system observed in depressed patients (Barden, 2004). Furthermore, it has also been shown that the expression of brain derived neurotrophic factor in the hippocampus is decreased following chronic stress (Rasmusson *et al.*, 2002).

In the forebrain and hippocampus, brain derived neurotrophic factor is produced and interacts via trkB receptors (Foster and MacQueen, 2008). While chronic stress results in a reduction of brain derived neurotrophic factor, antidepressant therapies increase its level in the hippocampus. Electroconvulsive therapy has also been demonstrated as a potent inducer of brain derived neurotrophic factor in animal studies (Altar *et al.*, 2003). Consistent with this theory, structural magnetic resonance imaging studies show that structural hippocampal changes occur in people with recurrent depression (Sheline *et al.*, 2003). In terms of cognitive abilities, a meta-analytic study (Zakzanis *et al.*, 1998) suggest that hippocampal-dependent learning and memory are most impaired when depressed patients are compared with controls. Importantly, the cognitive impairments may persist into euthymia (Campbell and Macqueen, 2004).

The anterior cingulate cortex is another region implicated in major depressive disorder, in which it plays a crucial role in emotional processing and the integration of emotional, cognitive, and physiological stimuli (Devinsky *et al.*, 1995). In addition, the amygdale, basal ganglia and secondary visual areas have also been found to show altered responses to emotional stimuli in depression. In their study, Abler and colleagues (Abler *et al.*, 2007) used functional magnetic resonance imaging to study 12 female patients with unipolar depression on stable antidepressant medication and 12 healthy women. When the subjects were presented with positive, negative and neutral pictures (that were announced

by a congruent cue), the depressed patients showed significantly more activation within the left and right ventral amygdale with the expectation of negative stimuli. This finding was interpreted as a possible consequence of altered future thinking in patients with depression.

2.4 Pathophysiology of pain in depression

The International Association for the Study of Pain defines pain as "a subjective and an emotional experience associated with actual or potential tissue damage or expressed in terms of such damage" (Merskey and Bogduk, 1994). In addition to direct activation by the spinothalamic pathway, a corticolimbic pathway may play a role in integrating sensory pain characteristics with information from other sensory systems as well as learning and memory (Wagner *et al.*, 2009). Direct pathways from the thalamus to the amygdala and related structures may also exist. Lautenbacher (Lautenbacher and Krieg, 1994) put forward a hypothesis of a global impairment of the sensory system in depression which includes hypoalgesia to phasic experimental pain due to diminished spinal and brainstem transmission, and hyperalgesia to endogenous painful sensations due to insufficient activation of inhibitory systems. This hypothesis was supported by the experimental findings of Bar (Bar *et al.*, 2005), where hypoalgesia was demonstrated in depressed patients when thermal and electrical pain was applied to the skin ('surface pain'), and hyperalgesia when 'deep somatic' sensations of pain were obtained by inducing ischaemic muscle pain.

In addition to this hypothesis, the experience of pain is believed to be influenced by a complex interplay of biological factors, such as personality traits and gender, and emotional, cognitive and social-cultural factors, such as perception and interpretation of a nociceptive input (Mongini *et al.*, 2009). Experimental evidence shows that emotion