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Stress- and pain (dys-)regulation in Chronic orofacial pain

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STRESS - AND PAIN - (DYS) REGULATION IN CHRONIC OROFACIAL PAIN

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SUMMARY

The aim of this research was to examine patients with chronic orofacial pain with regard to two significant facets of stress and pain regulation – on the one hand the neuroendocrinological system of the hypothalamic-pituitary-adrenal axis and on the other hand subjective illness beliefs, as measured by Leventhal's self-regulation model (SRM) (Leventhal et al., 1998). The significant effect of psychological and psychosocial factors on the chronicity of pain has been proved in numerous empirical studies and although stress has been investigated for some time as one of the most important psychosocial factors of chronic orofacial pain, there are hardly any studies that examine the underlying mechanisms of the hypothalamic-pituitary-adrenal axis. For this reason we conducted two studies at the interdisciplinary orofacial pain consultant service at the Center for Dental and Oral Medicine and Cranio-maxillofacial Surgery of the University of Zurich.

The first study investigated a possible dysregulation of the HPA axis by means of the "low-dose dexamethasone test". Twenty patients (17 females, 3 males) with chronic myogenous facial pain were dentally examined according to the criteria for RDC/TMD. Further, each underwent a personal interview and completed a series of questionnaires (DIAX, HADS-D, Fatigue Scale, VAS Scales of pain intensity and quality of sleep). The control group comprised 20 healthy subjects, matched by gender, age and BMI. Salivary cortisol was measured on two consecutive days (awakening and daytime profile). 0,5 mg of dexamethasone was administered on the first evening.

Results: in comparison to controls, chronic myogenous facial pain patients showed enhanced and prolonged suppression of cortisol following the administration of 0,5 mg of dexamethasone. Unstimulated cortisol response to awakening and daytime cortisol levels did not differ between the groups. Dysregulation in terms of enhanced negative feedback suppression exists in chronic myogenous facial pain.

The second study investigated the predictive value of illness beliefs on therapy outcome in patients with chronic orofacial pain, as measured by the *SRM*. Relations

could be found between subjective illness beliefs and physical as well as psychological adjustment in various chronic illnesses. No research is available to date with regard to chronic orofacial pain. 152 consecutive patients referred to the interdisciplinary orofacial pain consultant service at the Center for Dental and Oral Medicine and Cranio-maxillofacial Surgery, University of Zurich received questionnaires to assess pain and pain related disability, anxiety, depression as well as physical and mental quality of life at three time points: prior to treatment, three and six months after beginning of treatment. Results: Significant improvement over time was found for all outcome measures except mental quality of life. Results of the regression analysis indicated that believing pain could have serious consequences on one's life (IPQ subscale consequences) is one of the most important predictors for treatment outcome regarding pain as well as mood in patients with chronic orofacial pain. The belief in low personal control and in a chronic timeline are shown to be predictive for outcome as well, explaining however a smaller proportion of variance. These results provided evidence that even when controlled for pain and mood, beliefs about pain are important predictors for treatment outcome and need to be considered in in the management of patients with chronic orofacial pain. Asking patients about their view of illness can provide essential information about these important predictors.

Taken together both studies are in line with a multifactorial etiology of chronic facial pain, shifting the perspective away from a local towards a more central etiology with dysregulations in the stress and pain modulating system and pain related beliefs as important psychological determinants of adjustment to chronic pain.

Contents

FIGURES AND TABLES

1 Introduction:

Orofacial pain comprises a heterogeneous group of pain syndromes in the facial and oral areas (including teeth), which affect the temporomandibular joint, the masticatory muscles and teeth, as well as neuropathies and neuralgias of the nerves supplying this area (N. Trigeminus). Patients with chronic orofacial pain are similar to patients with other chronic pain conditions in terms of gender differences, pain intensity, pain related psychosocial dysfunction, psychological distress and comorbid psychiatric disorders (Vonkorff et al., 1988; Dworkin et al., 2002; Suvinen et al., 2005b; Dworkin and Massoth, 1994; Aghabeigi et al., 1992; Dworkin and Massoth, 1994; Mongini et al., 2007). It is important to note that chronic pain is not only defined by time criteria (>three months) but especially by qualitative criteria, such as increasing impairment of various levels of behavior and experiences (Dworkin and Massoth, 1994; Palla, 2006). Furthermore, the impact of pain on life shows only low correlations with objective somatic findings, but is strongly correlated with psychological parameters such as anxiety, depression and somatization, respectively (Yap et al., 2002) as well as pain-related attitudes and beliefs (Turner et al., 2005; Vonkorff et al., 1988) .

Pain perception and pain experience are the result of diverse influences, which are processed in a highly complex neuronal network. From a neuroendocrinological perspective the most important input in this network comes from the stress regulation system of the HPA axis (Lariviere and Melzack, 2000).

Dysregulations of the hypothalamic-pituitary-adrenal (HPA) axis as a physiological substrate of stress have been observed in patients with chronic pain and fatigue disorders, such as chronic fatigue syndrome and fibromyalgia (Parker et al. 2001; Turner et al., 2006) whiplash-associated disorder (Gaab et al. 2005), chronic pelvic pain (Heim et al., 1998; Turner et al., 2006), low back pain (Griep et al., 1998), irritable bowel syndrome (Bohmelt et al. 2005) as well as in persons exposed to chronic or traumatic stress (Meinlschmidt and Heim, 2005; Yehuda et al., 1993). In patients with these chronic pain and fatigue symptoms as well as in traumatized

persons reduced activity and / or enhanced negative feedback sensitivity of the HPA axis was found. In other terms, for patients with these chronic somatic symptoms there is accumulating evidence of a basal hypocortisolism and an altered cortisol response to stress challenge (Parker et al., 2001; Tanriverdi et al., 2007b). To selectively assess the negative feedback sensitivity of the HPA axis on the level of the pituitary gland, the low dose (0.5 mg) dexamethasone suppression test (DST) is frequently used (Yehuda et al., 1993). Dexamethasone mainly suppresses HPA axis functioning via hypophyseal pathways since it does not readily cross the blood-brain-barrier (De Kloet, 1997).

The low dose DST has been shown to be of diagnostic value in depression, post traumatic stress disorders, chronic pain and fatigue syndromes (Gaab et al., 2003; Gaab et al., 2005; Heim et al., 2000; Hunt et al., 1991; Parker et al., 2001; Yehuda et al., 1993). However to date only a few studies investigated the role of HPA hormones in orofacial pain patients under natural and experimental conditions, finding increased daytime cortisol levels (Korszun et al., 2002) and elevated cortisol response to experimental stress (Jones et al., 1997; Yoshihara et al., 2005) compared to controls. Furthermore to our knowledge HPA dysregulations in terms of increased negative feedback sensitivity have not been examined for orofacial pain patients. The aim of the first study was therefore to perform the DST in patients with chronic myogenous facial pain, the hypothesis being that this group of patients has a dysregulation of the HPA axis compared to healthy controls. This could help to clarify the etiology of chronic myogenous facial pain.

The second part of this work is a prospective study investigating the predictive value of illness representations using the self-regulation model (SRM) of health and illness of Leventhal et al. (1980) in patients with chronic orofacial pain. The SRM is one of the most significant models on illness beliefs and perceptions, and has been studied in a wide range of medical conditions (for review see Petrie et al., 2007). The role of patients' illness beliefs, i.e. patients' individual understanding of their illness, has been identified as an important factor influencing both health seeking

behavior and treatment outcome. Several studies showed that changes in pain beliefs and coping strategies are strongly associated with treatment outcomes in pain and functioning (Jensen and Karoly, 1991; Jones et al., 2006; Turner et al,. 2000; Turner et al., 2007).

Illness perceptions significantly predicted patients' lower satisfaction with medical consultations and were strong predictors for high health care use two years later (Frostholm, 2005; Frostholm et al., 2005; Frostholm et al., 2007) or the decision to seek medical care (Sensky, 1996; Leslie et al., 2000). Reassurance by information or by medical testing is considered a central part in medical consultations but is likely to fail when not considering patients' pre-existing illness beliefs (Donkin et al., 2006; Howard and Wessely, 1996). Adjustment to chronic illness and treatment outcome is highly influenced by individual illness perceptions, for example in patients with myocardial infarction (French et al., 2005; French et al., 2006), chronic fatigue syndrome (Edwards et al., 2001), rheumatoid arthritis (Scharloo et al., 1998; Sharpe et al., 2001), low back pain (Foster et al., 2008).

To our knowledge, no study has been conducted to date that examines the predictive value of illness beliefs as measured with the SRM for outcome in patients with chronic orofacial pain.

2 Models of chronic pain

2.1. Definition: chronic v. acute pain

Acute pain has a warning and protective function for the body, in that it indicates danger, overload and illness, simultaneously demanding the removal of the source of pain. It is a symptom of an underlying pathological process. Symptom-oriented therapy generally results in freedom from pain. On the other hand, persistent or chronic pain has lost this warning and protective function and is defined as an independent illness (Flor, 2003). Apart from the traditional time criterion of pain persisting over three or six months, qualitative criteria now increasingly complement the definition in terms of a biopsychosocial pain model.

2.1. Biopsychosocial model of pain

In the differentiation between acute and chronic pain it is clear that chronic pain is more than just the sensory experience of pain. It is understood as a syndrome, which comprises accompanying impairments on a physical, cognitive, emotional and social level (Turk, 1999). Cognitive and emotional aspects of pain such as hopelessness, loss of control, desperation or depression, as well as pain related behavior are not only correlates but also intensifiers of pain. Changes on the level of social and role functioning as well as in capacity to work should also be taken into consideration. All these factors can considerably affect the development of pain and the outcome of therapy (Kröner-Herwig, in Basler et al., 2007). Comprehensive diagnoses and treatment planning must evaluate and take into account all these different aspects.

3 Orofacial pain

3.1. Definition

To date there is no internationally acknowledged standardized definition for the heterogeneous group of orofacial pain. In terms of a most comprehensive definition, facial pain can be understood as conditions of pain in or around the eyes, ears, nose including sinuses, teeth including paradontics, mouth including lips, jaw bone, salivary glands, throat, cheeks and the preauricular area (Hugger et al., 2006).

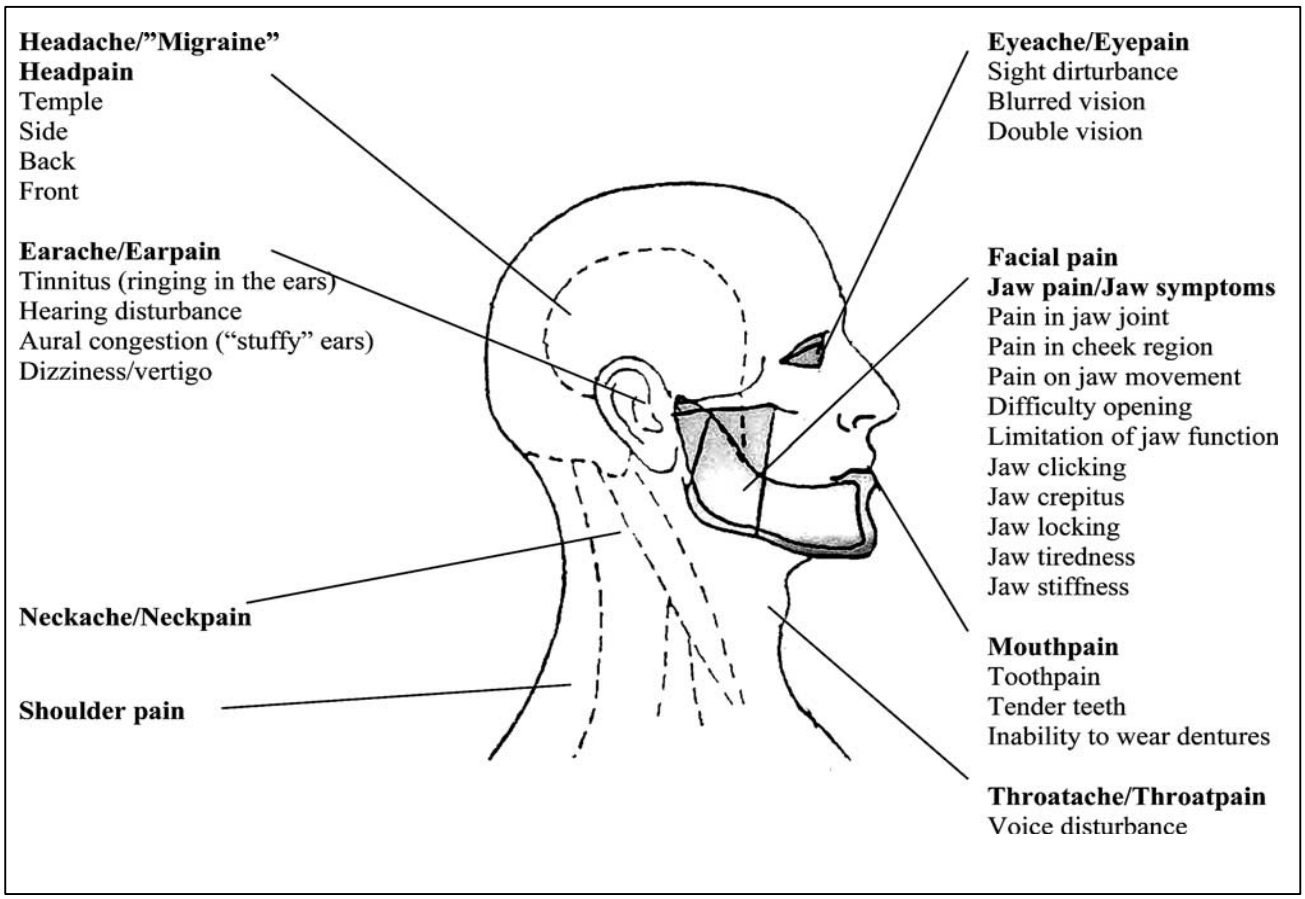


Figure 1. A schematic drawing of some of the various symptoms and signs causing pain and dysfunction in the orofacial region (Suvinen et al. 2005a).

3.2. Diagnostic criteria, classification, differential diagnoses

Not only is there no standardized definition for orofacial pain, but there is also no internationally acknowledged diagnostic and classification system. This is perhaps due to the multitude of medical fields concerned with the facial area and the frequently overlapping symptoms (Hugger et al., 2006).

There are at least four diagnostic classification systems from various associations: the International Headache Society (IHS, 2004), the American Academy of Orofacial Pain (Okeson, 1997), the Diagnostic Research Criteria for Temporomandibular Disorders (RDC/TMD) (Dworkin and LeResche, 1992). A unification of the classification systems could not be achieved to date (Woda et al., 2005). The RDC/TMD are the only classification system which takes into account a standardized recording of psychosocial factors such as pain severity, pain-related impairment, depression und necessity of a two-dimensional diagnostic and therapy of chronic pain covering both somatic and psychological factors (Goulet in Sessle, 2008).

3.2.1. Myoarthropathies of the masticatory system (MAP)

Myoarthropathies of the masticatory system are defined as “disorders of the masticatory system caused by inflammatory or degenerative changes of the masticatory muscles and/or the temporomandibular joint“ and are regarded as the most common cause of non-dentogenic facial pain (Palla, 1998). The conventional international term is temporomandibular disorders (TMD), which will be used in the following. They are characterized by three cardinal symptoms: impairment of movement of the lower jaw, joint sounds and localized pain in the masticatory muscles and/or around the temporomandibular joint. In addition to these cardinal symptoms, various forms of attendant symptoms are specified: toothache, headache, earache/ear noises, neck pain, dizziness, lachrymation/running nose, numbness, formication, other types of headache, sleep disorders. The pain is described as dull and dragging, stabbing or burning with strongly fluctuating intensity which is usually low to medium (Okeson, 1997). The classification system *Research*

Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) differentiates three categories of TMD: tendomyopathies (masticatory muscle disorders), discopathy as well as arthralgia and arthrosis of the temporomandibular joint (Dworkin and LeResche, 1992)

3.2.2. Persistent idiopathic facial pain and persistent idiopathic odontalgia

As a differentiation from typical trigeminal neuralgia, it was previously defined as "atypical facial pain" (Madland and Feinmann, 2001). It is described as deep-rooted, difficult to locate, dragging, burning, continuous pain of varying intensity (low to medium), with possible attacks of more intense pain. Radiations can also appear in the eyes, nose, cheeks, temples and lower jaw. There is frequently a strong affective pain component (IHS, 2004). The pain is commonly accompanied by a subjective, non-objectifiable feeling of swelling or numbness. Although to date no population data exists, there is increasing evidence that a majority of these conditions are neuropathic (LeResche in Sessle, 2008). The diagnosis persistent idiopathic facial pain is an elimination diagnosis and should only be made if other known pain syndromes can be eliminated and there are no clinical findings (IHS, 2004).

3.2.3. Deafferentiation pain / neuropathic pain

The pain picture is very similar to that of persistent idiopathic pain. The burning sensation of the pain is central. Injuries to nerves following traumatic or surgical damage (root canal treatment, tooth extraction, implantations, sinus surgery) are considered to be the probable cause, although there is a higher risk if preoperative pain was present (Jones and Cooney, 2003).

3.2.4. Burning mouth syndrome (BMS)

The main symptom is a persistent burning pain of medium intensity localized in the tongue, the oral mucosa and/or the lips, commonly connected with impairment of the sense of taste, a dry mouth, a prickling sensation and numbness, although the

oral mucosa is without pathological findings. BMS is an elimination diagnosis and should only be made if local, neurological or systemic factors (e.g. diabetes, vitamine B or zinc deficiency) can be eliminated. (Bergdahl and Bergdahl, 1999; Zakrzewska et al., 2005).

3.2.5. Trigeminal neuralgia

Although the prevalence of trigeminal neuralgia (TN) is low, it is one of the most well known cranial neuralgias and a central cause of facial pain. It is characterized by strong unilateral, lightning-like, shooting pains in one or more branches of the N. Trigeminus (Zakrzewska, 2002). Sufferers are free of pain between attacks. Typically, the pain can be activated by specific triggers (gentle contact, speaking, cleaning teeth), but it also occurs spontaneously and can be intensified by emotional stress. Two forms can be distinguished: the classic (idiopathic) and the symptomatic form. Unlike the symptomatic form, which is caused by a distinct brain pathology (e.g. tumor in the cerebellopontine angle, multiple sclerosis), the causes of the idiopathic form are not clearly known. In many cases, a compression of the N. Trigemenalis by a blood vessel at the root entrance by the brain stem is suspected.

3.2.6. Primary headaches: orofacial migraine, tension type headache

Most prevalent forms of primary headaches are migraine, tension type headache and trigemino-autonomous headaches. Headaches can become partially or completely manifest in the facial area, the jaw and/or the tooth area. This phenomenon is called heterotopic pain, e.g. the actual origin of the nociceptive input causing the pain and the region in which the pain is felt by the patient are not identical (IHS, 2004). In orofacial migraine the pain appears without an identifiable trigger and follows no clear time pattern. The headache normally remains for several hours to a few days and is sometimes accompanied by lachrymation, a running nose and reddening of the eyes. As symptoms appear in these “unusual” anatomical areas, these manifestations of headache are frequently not recognized as such. This quite frequently leads to mistreatment such as root canal work and/or tooth extractions as

well as surgical operations in the sinuses, i.e. invasive treatment which itself carries the risk of additional neuropathic pain in the form of deafferentiation pain (Gaul et al., 2007)

3.2.7.Summary

The suggestion of combining the diagnoses “temporomandibular disorders”, “persistent idiopathic facial pain”, “atypical odontalgia” and “burning mouth and tongue” under the category “idiopathic orofacial pain” has not yet been put into practice (Madland and Feinmann, 2001; Woda et al., 2005). In all symptom groups there are frequently large discrepancies between objective findings and subjective feeling, so it is presumed that the same pathophysiological mechanism is responsible and that this becomes manifest in various anatomical regions. The classification of MAP as idiopathic orofacial pain is however disputed, since the former is medically more explicable and less resistant to therapy than other forms of idiopathic pain (Turp, 2001).

3.3. Epidemiology

3.3.1 Prevalence

Orofacial pain is one of the most common pain syndromes apart from headaches and musculoskeletal pain, accounting for 40% of all chronic pain problems. The 12-month prevalence of chronic orofacial pain lies between 7% - 26% percent, dependent on the exact diagnoses (Lipton et al., 1993; Macfarlane et al., 2002; LeResche in Sessle, 2008). Prevalence rates for migraine vary from 20% for women to 7% for men. Tension-type headache is a common condition and prevalence rates are at 60-80% very high. (LeResche in Sessle, 2008). Burning mouth syndrome (BMS) and persistent idiopathic dental / orofacial pain is less common. For BMS only few population based studies exist. Due to differing case definitions and mean age in the population, prevalence varies from 1% to 15% (Lipton et al., 1993; Macfarlane et al., 2002; Tammialasalonen et al., 1993). Prevalence of persistent

idiopathic orofacial or dental pain is between 3% and 12% (Macfarlane et al., 2002; Marbach et al., 1982;,Polycarpou et al., 2005). As trigeminal neuralgia is rare only incidence rates exist. These are about 3 to 27 new cases per 100,000 persons per year (Hall et al., 2006; Katusic et al., 1990; Macfarlane et al., 2002). In summary, due to the non-standardized definition and classification systems there is a considerable research deficit of reliable epidemiological data on prevalence and risk factors for orofacial pain.

3.3.2. Gender distribution, age distribution

In chronic pain consistently higher prevalence rates were found for women than for men. Women report not only more frequent pain but also more severe pain and pain of longer duration than do men (Fillingim 2003). As regards orofacial pain, females are affected twice as frequently as males and the highest prevalence rate is for middle-aged females (Macfarlane et al., 2002; LeResche in Sessle, 2008). The underlying mechanisms of these gender differences are poorly understood. Biological mechanisms as well as psychological factors and social learning, e.g. the socially learned reactions to pain, may play a role in modulating pain experience. For example in a recent study gender accounted for 46% of the variance in willingness to report pain (Fillingim 2003; Macfarlane et al., 2002; Robinson et al., 2001). Orofacial pain of temporomandibular origin mainly occurs between the ages of 18 and 45, although there is a sinking prevalence rate in the higher age categories. The peak age is around 35 to 45 years. Mean age of persons seeking treatment for persistent idiopathic orofacial or dental pain is higher, about 40 to 55 years. The same is true for neuralgias where increased age is a possible risk factor (LeResche in Sessle, 2008).

3.4. Comorbidities

Chronic pain patients show a higher probability of having a comorbid clinically relevant mental disorder in comparison with the general population. The most common disorders found in chronic orofacial pain patients comprise somatoform

pain disorders, depression, generalized anxiety disorders, substance abuse and personality disorders (Kinney et al., 1992; Vonkorff et al., 1988). As mentioned above, for diagnoses of temporomandibular disorders a routine screening for psychosocial factors is recommended and includes measures for depression, somatization and pain related disability (Dworkin and LeResche, 1992). Interestingly, mental disorders were also taken into account in the International Classification of Headache Disorders, 2nd edition (IHS, 2004), and a new chapter was included: "headache attributed to psychiatric disorders". Sufficient evidence exists to include "somatization disorder" and psychotic disorder in the classification, although others were listed in the appendix because they are "believed to be real but for which further scientific evidence must be presented before they can formally be accepted" (cited from: International Classification of Headache Disorders, 2nd edition (IHS, 2004, p. 138). This concerns major depression, undifferentiated somatoform disorder, panic disorder, generalized anxiety disorder, social phobia, separation anxiety and posttraumatic stress disorder.

3.4.1. Functional somatic disorders

Patients with chronic orofacial pain often suffer from pain in other body parts (Turp et al., 1998) and there are significant overlaps with other chronic pain disorders, such as fibromyalgia and tension headaches (Aaron and Buchwald, 2001; Aaron and Buchwald, 2003; Glaros et al., 2007) as well as with stress-related functional somatic disorders such as irritable bowel syndrome, irritable bladder, chronic fatigue and premenstrual syndrome (Kouyanou et al., 1998; Nimnuan et al., 2001); (Macfarlane et al., 2002; Madland and Feinmann, 2001; Vonkorff et al., 1988); (Aaron and Buchwald, 2003; Balasubramaniam et al., 2007; Korszun et al., 1998; Leblebici et al., 2007; Plesh et al., 1996; Yatani et al., 2002). Korszun et al. (1998) examined 92 patients who fulfilled the criteria for CFS or FM or both. They discovered that of these patients 42% reported a former diagnosis of TMD. Furthermore, they found that of these 42%, 46% had a former diagnosis of IBS, 42% of premenstrual syndrome, and 19% of interstitial cystitis. In a study by

Plesch et al. (1996), it became evident that of 60 patients with a diagnosis of FM, 75% fulfill the diagnosis of muscular TMD and that at least 18,4% of TMD patients fulfill the diagnostic criteria for FM. Two recent studies of Balasubramaniam as well as Leblebici found 80% and 71% of TMD respectively in patients with fibromyalgia (Aaron and Buchwald, 2003; Balasubramaniam et al., 2007; Korszun et al., 1998; Leblebici et al., 2007; Plesh et al., 1996; Yatani et al., 2002). Because of these overlaps the recent tendency is to postulate idiopathic orofacial pain as specific functional somatic disorder (Diatchenko et al., 2006; Macfarlane et al,. 2002; Mongini et al., 2007).

3.4.2. Depression and anxiety

Depending on the sample, comorbid depression was found in 25 to 60 percent of chronic orofacial pain patients (Feinman, 1999; Vimpari et al., 1995; Yap et al., 2002). Psychosocial processes which accompany persistent pain, such as helplessness, social withdrawal and loss of recognition generally contribute significantly to the development of depression, although the pain intensity per se is not usually directly related to the magnitude of depressed mood (Feinman, 1999). The conception that orofacial pain without clear biomedical findings could represent a “hidden” depressive disorder has now been disregarded. In a large prospective cohort study on depressive symptoms and orofacial pain (TMD pain), the proportion of depression was significantly higher in subjects with symptoms of TMD compared with asymptomatic subjects, (OR adjusted for marital status, education, and self-rated general health between 1.3–2.3). Of the TMD symptoms, those related to pain had the most significant relations to the depression score. (Sipila et al., 2001). Two reviews addressed possible causal relations between depression and pain. Gallagher & Verma (1999) provided evidence that depression rates of affective disorders in families of patients with depression occurring after the onset of chronic pain are similar to those in the general population and significantly lower than in the families of patients with major depression alone, suggesting that depression is rather a consequence of living with chronic pain, than a personal or

family predisposition (Dohrenwend et al., 1999). The same conclusion was drawn by Fishbain and colleagues who found in a review on 83 studies greater support for the consequence hypothesis than the antecedent hypothesis. (Fishbain et al., 1997). Many patients report stressful life events preceding onset of orofacial pain becoming chronic (Auerbach et al., 2001; Korszun et al., 2002) and the same is documented for the onset of depression (Brugha et al., 1997; Kessing et al., 2003; Arean and Reynolds, 2005; Coyne et al., 2004). These findings fit to a diathesis-stress model explaining why under particular circumstances some subjects are vulnerable to developing depression (Coyne et al., 2004) and both depression and facial pain (Korszun et al., 1996).

Although in pain literature more emphasis was placed on depression, there is a growing body of evidence indicating that anxiety may be even more strongly related to pain than depression (Madland et al., 2000; Manfredini et al., 2004; McWilliams et al., 2004; Suvinen et al., 2005a). In a recent cross-sectional study with 649 patients suffering from different groups of facial pain 15% - 30% of patients had an anxiety disorder, with highest rates in the group with myofacial pain and pain disorder respectively (Mongini et al., 2007). Several studies have been conducted to identify differences in psychosocial profiles between subgroups of orofacial pain patients, with inconsistent results. Whereas some authors found higher prevalences of psychosocial distress in patients with myogenous pain (Auerbach et al., 2001; Mccreary et al., 1991a), recent studies could not find these differences either between diagnostic subgroups of temporomandibular disorder patients (Reissmann et al., 2008) or between patients with TMD and atypical facial pain (List et al., 2007) or between myofacial or TMJ pain patients (Nifosi et al., 2007).

3.5. Pain chronification: risk factors and influencing factors

3.5.1. Psychosocial risk factors

Risk factors for pain chronification are recognized to be prevalently psychosocial such as private and work stress, life-events, maladaptive cognitive and behavioral coping strategies as well as psychiatric comorbidities (de Leeuw et al., 2005a; de Leeuw et al., 2005b). Research on this topic was conducted predominantly on low back pain but there is increasing evidence that these factors are equally important for the chronification of orofacial pain (Macfarlane et al., 2004; Suvinen et al., 2005a). Parallel to the concept of "red flags" as signs of serious disease the term "yellow flags" was introduced to name these psychosocial factors indicating that they are are not mere secondary reactions to pain but serious barriers to recovery which should be discovered as early as possible in order to counteract progressive chronification (Kendall et al., 1998; Turner et al,. 2000).

Evaluative components of pain, e.g. cognitions and cognitive coping strategies such as appraisal have been widely studied in orofacial pain populations, especially TMD. Mainly two aspects of cognitive dimensions are found to be important for pain progression and adaptation to chronic pain. These are perceived control over pain and the use of maladaptive cognitive coping strategies, e.g., catastrophizing v. belief in self-efficacy (Jensen and Karoly, 1991; Turner et al., 2000).

3.5.2. The role of parafunctions

Since the 50s, stress has been discussed as an important etiological factor for the development of chronic orofacial pain (Schwartz, 1955). Enhanced oral parafunctional activity has been suggested to provide an outlet for emotional tension or stress in humans (Bracha et al., 2005). Indeed muscular hyperactivity is frequent in patients with orofacial pain. It consists of bruxism, tongue thrust, nail or lip biting, increased muscle contraction of the pericranial and neck muscles and may play an important role in the development of tension-type headaches (Langemark and Olesen, 1987; Hatch et al., 1992; Jensen et al., 1998) and myogenous pain in the craniofacial-cervical area (Mense, 1993). Increased parafunctions may result in

a mechanical overload and microtraumata in the masticatory systems (Svensson and Graven-Nielsen, 2001). (See also section 2.6.) The etiology of daytime parafunctions is unknown, however stress and anxiety are considered to be risk factors (Lavigne et al., 2008).

For myogenous facial pain, daytime clenching is especially considered to be an important maintaining factor (Chen et al., 2007; Lavigne et al., 2008; Svensson et al., 2008), whereas the role of nighttime grinding is increasingly questioned (Janal et al., 2007). However the exact relations are unclear, as in various therapies aiming to reduce muscular hyperactivity and tooth contact, e.g. habit reversal training, biofeedback, occlusal splints, treatment success is not strongly related to a reduction of these specific parameters. Furthermore a very recent study with a mixed facial pain population showed that the likelihood of higher muscle tenderness scores was increased by the presence of higher rates of depression and anxiety, independent of the diagnostic group. The authors concluded that there might be an interrelationship between muscle hyperactivity and psychological comorbidity, which should be considered in treatment (Mongini et al., 2007).

Another historically important hypothesis - the relationship between occlusional factors and orofacial pain - could not been sustained by more recent studies (Forssell and Kalso, 2004; Gesch et al., 2004).

On the other hand, pain itself can become an important stressor, resulting in increased arousal and reduced capacity to relax. Recent research suggests that nighttime bruxism is part of an sleep related micro-arousal response, which includes increased heart and respiratory rate and increased EMG activity and can be influenced by various stressors as well as by substances like alcohol, caffeine, illicit drugs and a variety of medications. Furthermore there is evidence for an interaction in bruxism between limbic structures such as the amygdala, and motor systems. Diseases, personality characteristics and genetics may also be involved in the etiology. Similarly, nighttime bruxism was not related to stress in general but to anxiety (for details see: (Lavigne et al., 2008; Lavigne and Montplaisir, 1995).

However as already mentioned the evidence of a direct relationship between pain and parafuncional activity, especially those occurring during sleep, is inconsistent. Furthermore, it needs to be noted that criteria used to identify bruxism are not standardized and rather imprecise (Pergamalian et al., 2003). Today's research in fact focuses on central nervous function disorders, examining in particular the interaction between various functional systems, such as the interconnection between the autonomic nervous system with the muscular system (Kato et al., 2003; Lavigne and Kato, 2005; Lavigne et al., 2003;,Lobbezoo and Naeije, 2001;,Roatta et al., 2005).

The above mentioned symptom overlaps of chronic orofacial pain with other chronic complaints, such as fibromyalgia, chronic fatigue syndrome (CFS) and with functional disorders, respectively (Aaron et al., 2000;,Fricton, 2004) indicate alterations in pain processing and perception due to central nervous processes (Bragdon et al., 2002;,Lavigne et al., 2005), as well as neuroendocrinological changes, in particular in the hypothalamic-pituitary-adrenal axis (Gameiro et al., 2006).

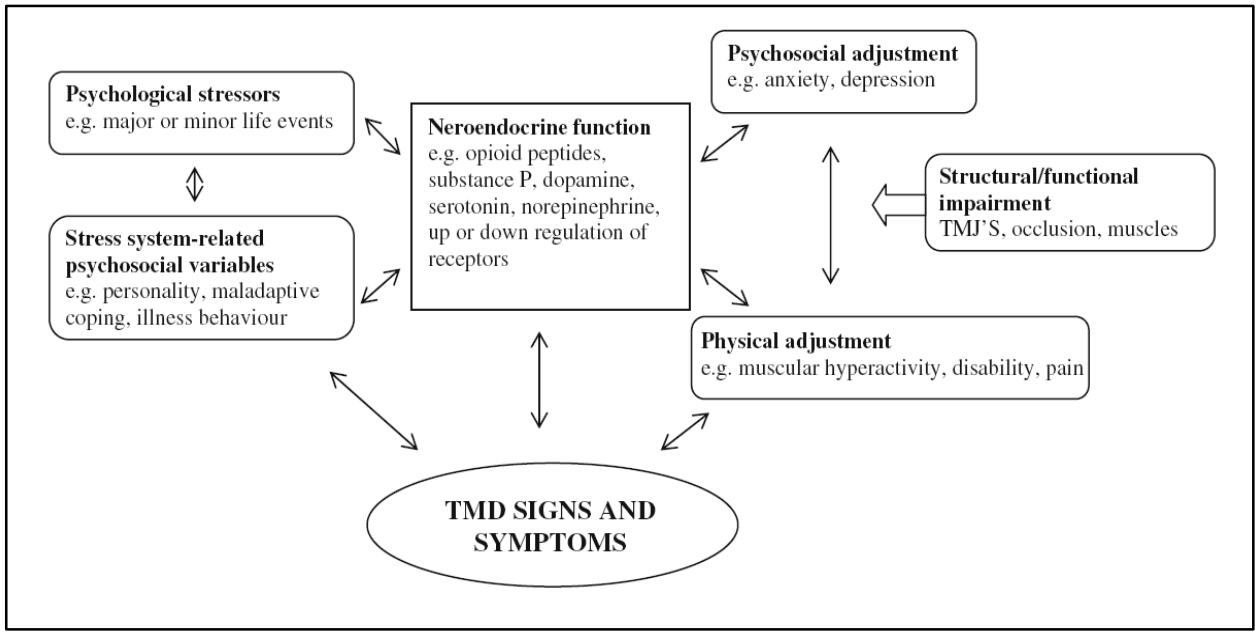


Figure 2: Psychosocial and physical factors potentially modifying and exacerbating the effects of stressors (taken from Gameira, 2006)

3.6. Conclusion

Orofacial pain is one of the most common pains and comprises a variety of different entities and diagnostic groups. There is growing evidence that chronic orofacial pain is similar to other chronic pain syndromes in both etiology and in successful treatment strategies. Modern etiological concepts of chronic orofacial pain adopt a multifactorial view that distinguishes predisposing, initiating, and perpetuating factors and includes neurophysiological, biomechanical, occlusal, psychological, and psychosocial factors. The extent to which the respective factors are involved in the genesis of orofacial pain varies from person to person.

4 Stress

4.1. Development of the psychobiological stress models

The term «stress» goes back to one of the earliest scientists in stress research: Hans Selye, who in 1936 first described the physiological consequences of exposure to nocuous agents. "*if organisms are severely (but not lethally) damaged by acute nonspecific nocuous agents (e.g. exposure to cold, surgical injury, production of spinal shock, excessive muscular exercise, or intoxications with sublethal doses of diverse drugs) a typical syndrome appeared, the symptoms of which are independent of the nature of the damaging agent (...) and represent rather a response to damage as such"* (cited from: Selye, 1998, p. 230). He introduced the term "general adaptation syndrome" (GAS), meaning that stress response is an unspecific reaction to different threats which develops in three successive phases: first the alarm stage, second the resistance and stabilization phase in which the organism is using all its capacity to regain and maintain its inner balance (homeostasis), followed - when threat is ongoing and severe - by the final exhaustion stage, indicated by loss of physical resistance, exhaustion and even death.

Years before, the term "homeostasis" was already introduced by Cannon to describe "the coordinated physiological processes which maintain most of the steady states

in the organism….." he explicites furthermore that "the word does not imply something set and immobile, a stagnation. It means a condition - a condition which may vary, but which is relatively constant" (cited from Cannon W., 1932). Thus the concept of homeostasis essentially means stability of physiological systems to ensure survival. He recognized the importance of both psychological and physiological responses during stress and further postulated that stress responses were specific rather than non-specific (Pacak and Palkovits, 2001).

An important psychological approach to stress was developed by Lazarus who postulated that individual differences in motivational and cognitive variables, e.g. evaluations of a threatening situation, intervene between the stressor and the reaction and explain why similar stressful events elicit a stress reaction in some persons but not in others (Lazarus et al., 1952) (see section 4.2.4.).

One of the most comprehensive current psychobiological models is McEwen's "allostatic load model" (McEwen, 1998), which focuses not only on stress stimuli and stress reaction but also on intra- and interindividual mediators and modulators of the stress response, integrating physiological, psychological, behavioral and social factors (see Figure 2). In his model of allostasis and allostatic load McEwen distinguishes in contrast to the concept of homeostasis two different physiological systems: those which are essential for life maintain homeostasis and the others maintain these systems in balance, i.e. allostasis. In other words, allostasis is the process that keeps the organism alive and functioning, i.e., maintaining homeostasis or "maintaining stability through change" and promoting adaptation and coping, at least in the short run (McEwen, 2000). Chronic exposure to frequent, repeated and long-lasting environmental challenges leads to allostatic load, the so-called "price of adaptation", resulting in a variety of somatic disorders including cardiovascular disease, immune disorders and chronic pain conditions (McEwen and Stellar, 1993).

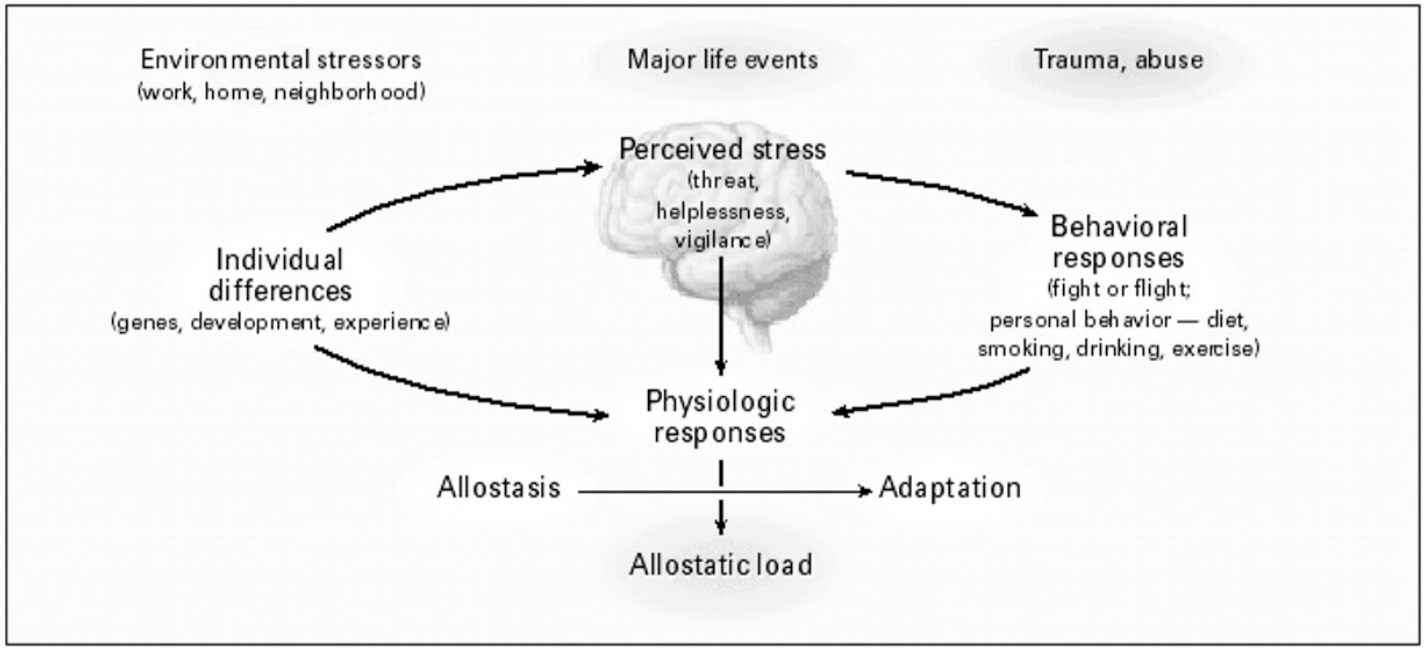


Figure 3: Mediators and modulators of the stress response and development of allostatic load (taken from: McEwen, 1998a)

Two main physiological systems are activated by stress: the hypothalamic-pituitary-adrenal (HPA) axis and the autonomic nervous system, in particular the sympathetic response of the adrenal medulla and sympathetic nerves (the sympathico-adrenal medullar system, SAM) (McEwen, 2000).

Stress-induced activation of the HPA axis and the SAM results in a series of neural and endocrinal adaptations known as the "stress response" or "stress cascade". After the stressor has occurred, the first wave of the stress response occurs immediately, within seconds. It is characterized by sympathetic activation (catecholamine, epinephrine and norepinephrine) as well as hypothalamic release of corticotropine releasing hormone (CRH) which itself stimulates the release of adreno-corticotropine releasing hormone (ACTH) in the pituitary (Sapolsky et al., 2000). The second wave, which occurs over the course of minutes, consists of an increased release of steroid hormones, e.g. cortisol. Under acute stress, energy reserves are mobilized, vegetative processes and reproduction are suppressed, and the body is ready for fight or flight. In the following, this work focuses on the key elements of the HPA system, the SAM system is not described in detail.

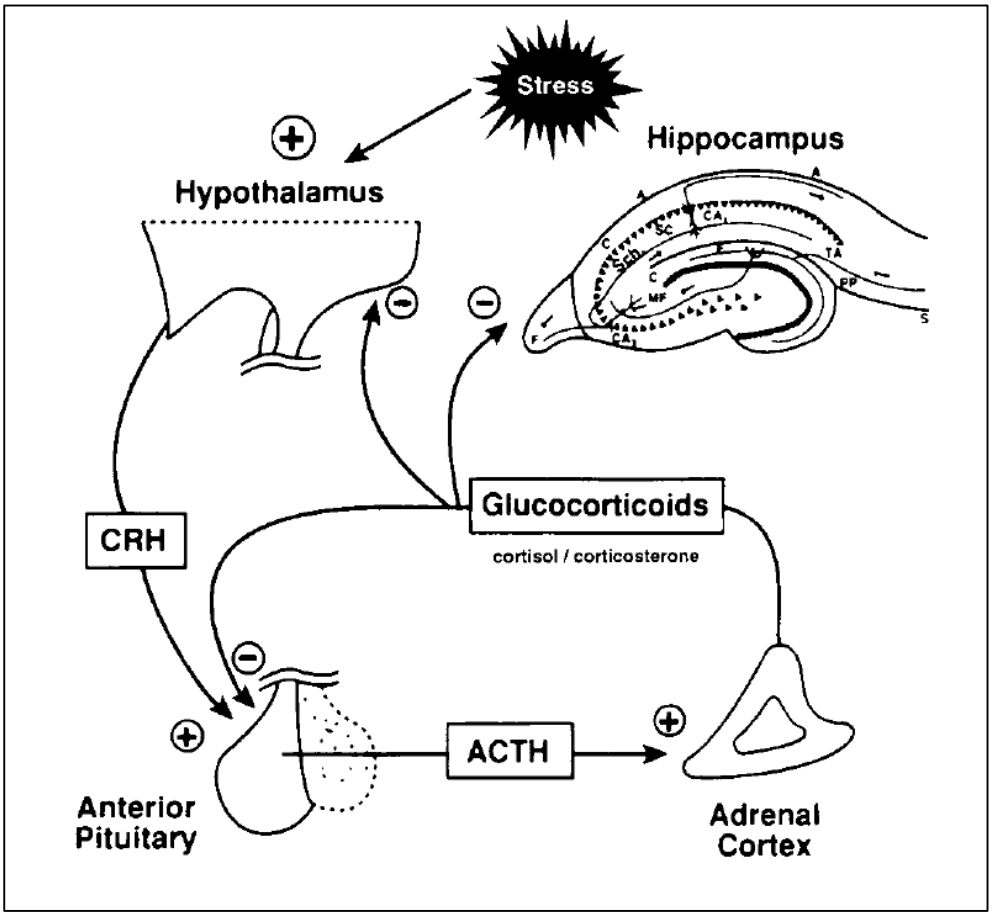


Figure 4: Schematic of the stress cascade (taken from: Miller & O'Callaghan, 2002)

4.2. The role of the hypothalamic-pituitary-adrenal (HPA) axis

Stress provokes the release or synthesis of three key hormones of the HPA axis: corticotrophine releasing hormone (CRH), adreno-corticotropine hormone (ACTH), and a species-specific glucocorticoid, either cortisol (humans and primates) or corticosterone (rodents).

Cortisol level itself is regulated by the release of CRH, which is considered as a major mediator of the effects of stress encompassing initiation, modulation and inhibition of the stress response (Dunn and Berridge, 1990; Miller and O'Callaghan, 2002). (See figure 4). CRH receptors are widely distributed in the brain, mainly in the hypothalamus, hippocampus and amygdala, suggesting an important role of CRH in the regulation of anxiety, learning and memory as well as in the behavioral response to stress. (Miller and O'Callaghan, 2002). Under basal conditions,

glucocorticoid secretion exhibits a 24h circadian profile which is very robust, with the maximal glucocorticoid concentration in the morning (the circadian peak), declining slowly during the day and reaching lowest levels in the evening and nocturnal period. After a few hours of sleep an abrupt elevation emerges. Stress-induced secretion is superimposed on this basal circadian rhythm. The HPA axis is regulated by a negative feedback system at multiple levels of the axis mediated via glucocorticoid receptors within both the brain and the anterior pituitary protecting the system against spillover. By this, cortisol as the end product of the stress-axis inhibits the production of the initiating substance. (Kirschbaum & Hellhammer, 1999b; Miller and O'Callaghan, 2002).

Glucocorticoids are the final effectors of the HPA axis and are important for the regulation of a wide range of bodily functions. Inflammatory responses, cardiovascular responsiveness, cognitive functions such as information processing, learning and memory as well as metabolic processes and immune function are influenced by glucocorticoid levels (Chrousos and Gold,1998; de Kloet et al., 1998; Sapolsky et al., 2000). Dysregulation of this negative feedback is possible in two forms: exaggerated CRH and cortisol secretion, e.g. hypercortisolism and deficient CRH secretion with hypocortisolism. Both are described in the following sections.

4.2.1. HPA axis dysregulation - hypercortisolism

HPA axis dysregulations in terms of exaggerated CRH and cortisol secretion have been described in a number of psychiatric disorders with melancholic depression, anxiety and emotional disturbances (Nemeroff, 1996; Chrousos and Gold, 1998; Holsboer et al., 1982a ;Yehuda, 2000), for summary (Ehlert et al., 2001). Indeed hypercortisolism in depression is one of the most frequent findings in biological psychiatry (Gold et al., 1996). CRH hypersecretion is assumed to be a result of a disinhibition of the negative feedback control of the HPA axis (Young et al., 2003). This disinhibition is considered to be a consequence of longstanding hypersecretion of glucocorticoids. A common endocrine feature of melancholically depressed patients comprises non-suppression to the standard dexamethasone suppression test

(Rush et al., 1996), which was developed to test the integrity of the HPA axis, selectively assessing the negative feedback sensitivity on the level of the pituitary gland (Yehuda et al., 1993). Furthermore normalization of the dysfunctional HPA axis has been shown to precede successful treatment of depression (Holsboer et al., 1982b).

4.2.2. HPA axis dysregulation - hypocortisolism

Reduced activity and / or enhanced negative feedback sensitivity of the HPA axis was found in a number of disorders with mainly somatic or somatoform symptoms such as chronic fatigue syndrome and fibromyalgia (Parker et al., 2001), whiplash-associated disorder (Gaab et al., 2005), chronic pelvic pain (Heim et al., 1998), low back pain (Griep et al., 1998), irritable bowel syndrome (Bohmelt et al., 2005) as well as in persons exposed to chronic or traumatic stress (Yehuda et al., 1993, Goenjian et al., 1996; Meinlschmidt and Heim, 2005), but also in patients with atypical depression (Geracioti et al., 1997). Atypical depression is characterized by reduced energy, a reactive mood, and reversed neurovegetative signs of hyperphagia, hypersomnia, lethargy and weight gain, which are frequent comorbid symptoms in chronic pain patients (Korszun et al., 1996). For patients with these chronic somatic symptoms there is accumulating evidence of a basal hypocortisolism and an altered cortisol response to stress challenge (Parker et al,. 2001; Tanriverdi et al., 2007a). Especially for chronic pain the role of CRH has been extensively examined (see below).

Little is known about how possible HPA axis dysregulations persist. Several risk factors for chronicity of the syndrome have been identified, such as psychiatric illness, a somatic subjective illness model, avoidance of exercise and activity as well as sleep dysregulations (Joyce et al., 1997; Deale et al., 1998; Morriss et al., 1997). However there is ongoing discussion whether the changes in HPA axis functioning are of primary (a consequence of chronic or traumatic stress precipitating the illness symptoms) or secondary (a consequence of individuals' emotional and behavioral coping responses to the illness). In patients with

somatoform disorders, the extent of HPA axis dysregulations was negatively correlated with the duration of the syndrome (Gaab et al., 2004). A prospective study on chronic fatigue syndrome failed to predict fatigue levels by cortisol levels after surgery (Rubin et al., 2005). Both studies provide evidence for a secondary HPA axis dysregulation.

4.2.3. HPA axis dysregulation in chronic pain

There is evidence for generalized hyperalgesia in chronic orofacial pain patients and hormonal as well as neural mechanisms leading to hyperexcitability and amplification of the nociceptive inputs have been discussed (Sarlani and Greenspan, 2003). One possible mechanism leading to enhanced pain sensitivity may be a reduced release of corticotropine releasing hormone (CRH), since CRH seems to be involved in central as well as peripheral pain processing and experimental studies predominantly demonstrate an analgesic effect of CRF especially for prolonged tonic pain. (Lariviere and Melzack, 2000).

Interestingly, the first human study on the CRH analgesic properties was conducted in dentistry, demonstrating that intravenous administration of CRH led to significantly less postoperative dental pain than with a placebo. It is important to note that this effect was significant only on an affective but not on a sensory scale (Hargreaves et al., 1987). Indeed in a study with similar doses of CRH no analgesic effect could be shown on experimental phasic heat pain. (Lautenbacher et al., 1999). The specificity of CRF's effect on tonic pain suggests that CRF may primarily play a role in prolonged clinical pain. In fact, altered CRF release and neurotransmission are likely to be involved in certain chronic pain syndromes in humans that show little or no evidence of pathology in the painful tissue such as FM (Chen and Treede, 1985 from Melzack, 2000).

An interesting recent animal study links stress, behavior (masticatory muscle activity) and HPA axis activity. The authors found that oral parafunctions (i.e. biting on a wooden stick) suppressed the stress-induced expression of CRF in the paraventricular nucleus (PVN) of the hypothalamus (Hori et al., 2004). They

concluded, that enhanced oral parafunctions observed in many TMD patients in stressful situations may represent an effective but maladaptive coping mechanism for preventing noxious influences of acute stress by suppressing the activity of the HPA axis. However this remains speculative and requires further investigation.

Two studies investigated the HPA axis reactivity of TMD patients to experimentally induced psychosocial stress. One reported an elevated cortisol response to a standardized stress paradigm in a subgroup of TMD patients compared to controls (Jones et al., 1997). These results were partly confirmed by a recent study, reporting higher cortisol stress responses in patients with myofacial pain in comparison to healthy controls (Yoshihara et al., 2005). Higher basal circadian cortisol levels compared to controls were found in patients with temporomandibular disorders (TMD) (Korszun et al., 2002). This was in contrast to findings in other studies on chronic pain patients showing normal circadian cortisol levels compared to control subjects (Klerman et al., 2001, Wingenfeld, 2007; Gaab, 2005). The authors hypothesized that the high levels of cortisol in TMD patients may represent a physiologic response to chronic stress and pain of the facial region probably represents a greater stimulus to HPA axis activation than pain elsewhere in the body (Korszun, 2002). However further studies are clearly needed to elucidate this issue.

4.2.4. Psychological determinants of the HPA axis stress response

In the late 60s Mason postulated in his “Mason Principle” that psychosocial stimuli are among the strongest natural stimuli for HPA axis activation, capable of influencing the level of pituitary-adrenal cortical activity. He noted that in response to different stressors HPA axis activity could increase, decrease or remain unchanged and that emotions like anxiety or fear constituted the basis for similar neuroendocrine responses to different stressors (Mason, 1968). By this he contradicted the assumption of Selye that the stress response is unspecific According to this principle novelty, predictability, anticipation of negative consequences and ego-involvement are the most important personal and situational characteristics leading to HPA axis activation.

Cognitive stress theories are profoundly influenced by the work of Lazarus and colleagues, who postulated in their model of coping process, that individuals are constantly evaluating and appraising their transactions with their environment (Lazarus et al., 1984). They postulated two stages, primary appraisal (evaluation of the situation as irrelevant, positive or potentially harmful / a challenge or threat) and secondary appraisal (evaluation of the resources and the consequences of this action). Coping strategies can be divided into two categories: problem-focused coping, which is used when a person is actively seeking to solve a problem and emotion-oriented coping, which means use of passive and / or avoidance coping strategies. The more stressful a stressor is assessed to be and the lower the individual's ability to cope with this specific stressor, the more severe the experienced stress will be for that person. With this model they explained why persons react differently to the same stressor (Lazarus et al., 1984). In the 90s two other scientists based in the field of research on the relationship between psychological and HPA axis responses, Levin and Ursin, identified coping and defense mechanisms as the most important cognitive filters responsible for the regularly observed intra- and interindividual differences in HPA axis responses. Analogously to Lazarus' concept of primary and secondary appraisal these two constructs were defined as efficacy and outcome expectancies (Ursin et al., 1998; Ursin and Eriksen, 2004). Furthermore it has been shown that interventions targeting to modify the cognitive appraisal processes of stressors can modulate the extent and habituation of the HPA axis response to experimentally induced (Gaab et al., 2003; Hammerfald et al., 2006; Storch, 2007) as well as naturalistic stressors (Gaab, 2006).

One of the most important determinants of stress response is the socio-evaluative element. In a meta-analysis of 208 laboratory studies of acute psychosocial stressors and tests, evidence was provided that the largest cortisol and ACTH changes and the longest recovery times occurred in experiments with performance tasks characterized by socio-evaluative threat and/or uncontrollability. (Dickerson &

Kemeny, 2004). The authors concluded that threatening the social self is one of the strongest stressors for humans. “Social self-preservation is a key priority across human cultures; threats to this goal may be one important set of eliciting conditions for activating a central physiological system with psychological and health implications” (cited from (Dickerson & Kemeny, 2004, p. 383). A well-known phenomenon in stress research is the strong effect of anticipation. Indeed also for HPA axis activation, evidence was found that the anticipation of an event can be as strong an activator of the HPA system as the event itself. For example phobic patients show the highest elevation of cortisol on the day prior to being exposed to the phobic stimuli (Heuser & Lammers, 2003).

4.3. Conclusion

Stress is considered as one of the most important etiological factors for the development and maintenance of chronic orofacial pain. A physiological substrate of stress comprises dysregulations of the hypothalamic-pituitary-adrenal axis and HPA axis alterations have been linked to the development and maintenance of various psychiatric and somatic illnesses including chronic pain syndromes.

5 Leventhal's self-regulation model (SRM)

5.1. Description and development

Patients' illness beliefs, that is to say, patients' individual understanding of their illness are an important factor influencing both health seeking behavior and treatment outcome. They are also considered to be of major importance for the progression of the illness on the one hand and treatment outcomes on the other hand. (Jensen et al., 2001; Jones et al., 2006; Turner, 2006; Turner, 2007). One of the most significant models on illness beliefs and perceptions, which has been studied in a wide range of medical conditions, is the common sense model or self-regulation model (SRM) of health and illness (Leventhal H., 1997; 2003).

The fundamental idea of the model developed by Leventhal is if persons are confronted by a health threat, e.g. unknown physical symptoms, they develop emotionally regulating and action guiding cognitive schemata that explain these symptoms and enable a physical and psychological adjustment to the danger (Cameron and Leventhal, 1995; Leventhal et al., 1992; Leventhal et al,. 1998; Weinman and Petrie, 1997). Cultural factors, information from the social environment as well as personal experience with illnesses represent the main sources supplying the illness model (Leventhal et al., 1980).

The model assumes a parallel problem and emotionally centered processes which contribute on the one hand to the regulation of the objective health problem and on the other hand to the regulation of accompanying emotional stress. The assumed components comprise 1. Subjective perception and cognitive representation of a health problem, 2. Choice of coping strategies and 3. Evaluation of coping actions used (Leventhal et al., 2001). This means that according to the SRM model, the symptoms of the illness are influenced not only by concrete coping actions but also by the regulation of emotions and cognitions relevant to the illness. The assessment of the effectiveness of the applied coping strategies both affects the content of the subjective illness model and modifies it. (Leventhal et al., 2001). (See figure 5)

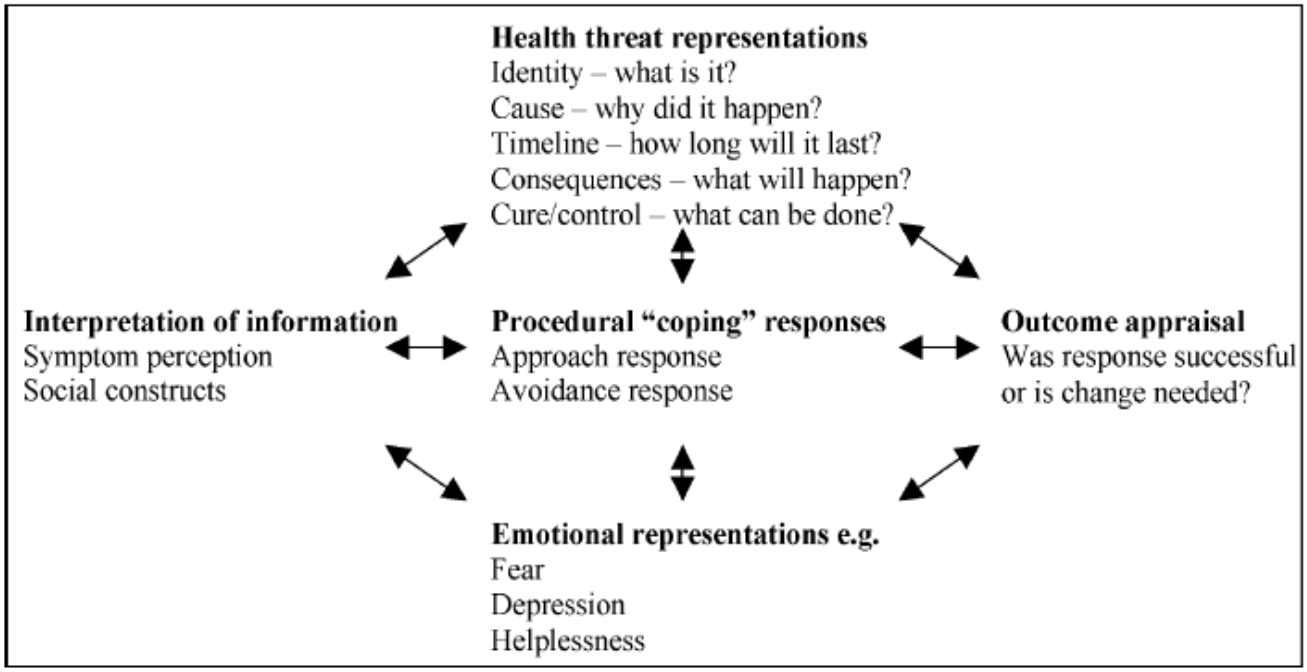


Figure 5: Components of the self-regulation model (taken from: Hobro, 2001)

5.2. Dimensions

The subjective illness model therefore corresponds to an organized pattern of cognitive representations, consisting of the dimensions: *identity, timeline, consequences, control* and *causes* (Leventhal et al., 1980). The model was later developed further and extended by the dimensions: *emotional representation* and *coherence* (understanding of illness) (Weinman et al., 1996; Moss-Morris et al., 2002).

The dimension *identity* forms the core of the subjective illness model and represents perceived or assumed symptoms caused by the illness. The illness identity of a patient can differ considerably from medical explanatory models (Leventhal et al, 1984).

The dimension *timeline* comprises subjective expectations about the duration of an illness and its cure as well as the length of time from the onset of the illness to death in the case of a terminal illness. The anticipated course of an illness as acute, chronic or cyclical can have a considerable affect on medication compliance. Hypertensive patients who expected a cyclical occurrence tended to take their medication only under acute stress, whereas patients who anticipated a chronic

course of illness tended to be more convinced of the necessity of constant long-term treatment (Baumann & Leventhal, 1985).

The dimension *consequences* refers to the perceived and expected short and long-term consequences of an illness with regard to physical, emotional, social and economic aspects. This evaluation is reflected in subjective perceived severity of an illness, which can considerably differ from objective clinical findings. (Croyle & Jemmott, 1991).

The dimension *control* comprises perceived and expected treatability of an illness and covers on the one hand individual coping strategies (personal control) und and on the other hand personal conviction regarding the effectiveness of therapeutic measures (treatment control). Subjective beliefs on personal and external control can considerably shape mental adjustment to an illness as well as the motivation to comply with necessary treatment measures (Lau & Hartman, 1983).

The dimension *cause* comprises subjective beliefs on activating conditions or causal facets and therefore considerably affects the choice of treatment. Causal attribution can apply to biological aspects (e.g. genetic predisposition and viruses), environmental influences (e.g. pollution) or psychological factors (e.g. stress, personality) (Moss-Morris et al., 1996; Moss-Morris et al., 2002).

5.3. Significance of the self-regulation model for adjustment to chronic pain

Although subjective illness beliefs are shaped by illness specific characteristics, as regards content the same logical relations can be found between dimensions in diverse clinical pictures. For example, there is a negative correlation between the amount of symptoms associated with the illness and personally perceived control and control of treatment, the expectation of a lengthy illness and serious consequences (Hagger & Orbell, 2003; Weinman et al., 1996). The dimensions *timeline*, *cyclical occurrence, consequences* and *emotional representations* are positively associated with each other and negatively related to the assumptions of *personal control* and *coherence,* which are in turn positively correlated (Hagger &

Orbell, 2003; Jopson & Moss-Morris, 2003; Moss-Morris et al., 2002). Patients with a strong locus of control and coherent understanding of their illness anticipate a shorter length of illness with less serious consequences and experience fewer illness-related negative emotions (Hagger & Orbell, 2003; Moss-Morris et al., 2002).

5.3.1. Pain intensity and symptom reduction

Emotional representations, consequences und *personal control* proved to be predictors of perceived pain intensity in patients with rheumatoid arthritis (Groarke et al., 2005; Hill et al., 2007). Symptom reduction in pain patients is related to perceived control over pain (Groarke et al., 2005; Hobro et al., 2004), perceived longer timeline (Hobro et al., 2004), anticipated consequences (Groarke et al., 2005; Hobro et al., 2004), number of symptoms associated with the illness (identity), lower negative emotions associated with symptoms (Botha-Scheepers et al., 2006) and assumed causes (Lacroix et al., 1990). Based on the SRM, Hobro et al. identified two groups of pain patients: adaptors und non-adaptors. The two groups of chronic pain patients reported different pain intensity, function levels and mood according to their subjective illness model.

5.3.2. Quality of life

A study on patients with fibromyalgia revealed that anticipated serious *consequences* and little *personal control* of the pain were predictors of a poorer illness-related physical quality of life, whereas high *emotional representations* proved to be the best predictor for the forecast of illness-related mental quality of life (Stuifbergen et al., 2006). In a study on osteoarthritis patients, negative beliefs with regard to *consequences* and *emotional representations* predicted a poor physical quality of life (Botha-Scheepers et al., 2006; Groarke et al., 2005).

5.3.3. Depression and anxiety

The predictive value of the subjective illness model was also found with regard to depression and anxiety. In patients with rheumatoid arthritis a predictive relation was found between low perceived *personal control* as well as anticipated serious *consequences* and the development of a depressive disorder (Groarke et al., 2005). In patients with musculoskeletal hand pain, a higher level of anxiety and depression was related to a higher level of emotional *representations* (Hill et al., 2007). Pain patients whose personal causal attribution corresponded to that of the physician experienced less pain and fewer negative emotions than patients who were unsure about the cause or did not agree with the clinical diagnosis (Geisser und Roth, 1998).

5.4. The "Illness Perception Questionnaire IPQ-R"

Since patients rarely spontaneously report on their subjective illness beliefs and extensive interviews are time-consuming and have low psychometric validity, the *Illness Perception Questionnaire (IPQ)* was developed (Weinman et al., 1996). This allows a valid and reliable quantitative recording of the dimensions *identity, timeline, consequences, control* and *causes.* The IPQ can be applied in modified forms to various clinical pictures, populations and cultural contexts, was used in numerous studies which examined adjustment to chronic illness (Petrie et al., 2007) and is recommended in a revised and psychometrically improved form, *Illness Perception Questionnaire (IPQ-R)* (Moss-Morris et al., 2002).

According to empirical evidence, which shows only low correlations between personal locus of control and treatment control, the original single scale *personal control/treatment control* was divided into two subscales. Furthermore, three new scales were added. The scale *cyclical occurrence* enables assessment in illnesses with fluctuating progression and therefore enhances the assumption of timeline. The dimension *emotional representations* enables the specific recording of negative emotions related to the illness, which according to the SRM occur in parallel to the cognitive representations. Finally, the scale *coherence* in the sense of a meta-

cognition reflects the purpose of the illness for the patient and also reflects his or her understanding of cause and symptom development (Moss-Morris et al., 2002). Recently a brief version has been published by Broadbendt (Broadbent et al., 2006).

5.5. Conclusion

The SRM characterizes the dynamic interaction of beliefs and behavior with the goal of optimal physical and psychological adjustment to illness. It implies that subjective illness beliefs not only affect the patient's illness behavior, but also the development of the illness. Patients' beliefs and emotional responses to their illness relate to a number of outcomes in chronic illness including psychological distress and quality of life. As yet, however, few interventions have been developed that are designed to change illness perceptions and improve illness outcomes. Emerging areas of research include the application of illness perceptions to mental illness and genetic and risk factor testing.

6 Perspective

The present findings have important implications for several reasons. Chronic orofacial pain is similar to other chronic pain conditions with regard to some etiologic features, risk factors, somatic and psychological comorbidity. Simple medical or dental interventions, based on a one-dimensional etiological view are out-dated. A multidisciplinary clinical approach that cuts across the traditional boundaries of medical and dental disciplines on the one hand and psychological and psychiatric disciplines on the other hand is highly recommended for diagnosis and treatment.

Dysfunctional illness beliefs are predictive for outcome in chronic orofacial pain patients and it would be interesting to look for causal effects of changes. Furthermore specific individualized treatments programs based on the SRM may be effective in modifying problematic illness perceptions.

7 Empirical studies

7.1. Enhanced negative feedback sensitivity of the hypothalamus-pituitary-adrenal-axis in chronic orofacial myogeneus facial pain

Introduction

Chronic facial pain is most often caused by a myoathropathy (MAP) of the masticatory system in particular by a myogeneous form. In a minority of 10-15% of the patients, the facial pain is associated to high pain-related disability and high rates of psychosocial distress so that these patients are to be considered as chronic pain patients (Von Korff et al., 1988; Dworkin and Massoth, 1994; Palla, 2006). Although the exact underlying pathophysiology of chronic myogeneous facial pain is poorly understood, there is growing evidence for a multifactorial etiology (Suvinen et al., 2005).

Many patients report stressful life events at the onset or during their painful state (Aghabeigi et al., 1992) and there is a substantial overlap between a chronic myoarthropathic pain and other stress related conditions like fibromyalgia and tension type headache (Aaron and Buchwald; 2001,Macfarlane et al., 2002; Glaros et al., 2007; Leblebici et al., 2007) as well as irritable bowel syndrome, chronic interstitial cystitis and premenstrual syndrome (Korszun et al., 1998). A physiological substrate of stress is constituted by dysregulations of the hypothalamus-pituitary-adrenal (HPA) axis, which have been observed in patients with chronic pain and fatigue disorders such as chronic fatigue syndrome and fibromyalgia (Parker et al., 2001), whiplash associated disorder (Gaab et al., 2005), chronic pelvic pain (Heim et al., 1998), low back pain (Griep et al., 1998), irritable bowel syndrome (Bohmelt et al., 2005) as well as in persons exposed to chronic or traumatic stress (Yehuda et al., 1993; Meinlschmidt and Heim, 2005). In patients with these chronic pain and fatigue symptoms as well as in traumatized persons reduced activity and / or enhanced negative feedback sensitivity of the HPA-axis was found. In other terms, for patients with these chronic somatic symptoms there is

accumulating evidence of a basal hypocortisolism and an altered cortisol response to stress challenge (Parker et al., 2001; Tanriverdi et al., 2006).

The low dose (0.5 mg) dexamethasone suppression test (DST) selectively assesses the negative feedback sensitivity of the HPA axis on the level of the pituitary gland (Yehuda et al., 1993). Dexamethasone mainly suppresses HPA axis functioning via hypophyseal pathways since it does not readily cross the blood-brain-barrier (De Kloet, 1997). The low dose DST has been shown to be of diagnostic value in depression, post traumatic stress disorders, chronic pain and fatigue syndromes (Hunt et al., 1991; Yehuda et al., 1993; Heim et al., 1998),(Gaab et al., 2002; Gaab et al., 2005). To date only a few studies investigated the role of HPA hormones in MAP patients under natural (Korszun et al., 2002) and experimental conditions (Jones et al., 1997; Yoshihara et al., 2005). The aim of this study was therefore to perform the DST in patients with chronic myogeneous facial pain, the hypothesis being that this group of patients has a dysregulation of the HPA axis compared to healthy controls. This could help to clarify the etiology of chronic myogeneous facial pain.

Methods

Subjects

20 patients (3 male, 17 female, mean age 35.2) with chronic myogeneous facial pain, recruited from a population of patients seeking treatment at the orofacial pain clinic were included in the patient group. 20 controls (3 male, 17 female, mean age 37.0) were selected from a pool of healthy, pain-free subjects recruited from an unselected general population and who had also been used as controls in a previous study (Gaab et al., 2002; Gaab et al., 2005). None of the controls had reported facial pain in the preceding 6 months and had never received treatment for a MAP. These controls were matched by age, gender and body mass index (BMI). All subjects filled out a written informed consent form. The study was approved by the Ethical Committee of the Medical Council of the Canton of Zurich.

The recruitment of the myogeneous pain patients consisted of two consecutive steps: First, patients with a diagnosis of myoarthropathic pain were informed about the study goal. Interested subjects in the age range 18-60 years, fluent in the German language and with facial pain were scheduled for a clinical examination by three reliable, calibrated dentists in order to select patients with myogeneous facial pain according to the the RDC/TMD (Dworkin and LeResche, 1992), i.e. (1) a report of pain in the jaw, temples, face, preauricular area, or inside the ear at rest or during function and (2) tenderness to palpation of three or more of the 14 examined muscle sites (see below), with at least one tender point on the painful side. At least two of the three diagnoses had to coincide. The presence of TMJ arthralgia and of a painless disc displacement with reduction did not lead to exclusion.

Exclusion criteria for all study participants including the controls were: A diagnosis of functional somatic disorders, pregnancy, lactation, drug addiction, acute injuries as well as inhalative or systemic treatment with glucocorticoids that were addressed by means of an interview and a check-list. Further exclusion criteria were a current

psychiatric diagnosis of a major psychiatric disorder (psychotic disorder, bipolar disorder, major depressive disorders, anxiety disorders, post-traumatic stress disorder, eating disorder, suicidality), use of antidepressants, anxiolytic, antibiotic, antihypertensive or steroid medication. These exclusion criteria were chosen in order to control for possible main effects of psychiatric disorders and medication on dependent variables. Occasional medication of NSAIDs was accepted (and reported by 3 patients), as NSAIDs did't or did not alter the cortisol response on experimentally induced stress (Kudielka et al., 2007).

Clinical examination

The clinical examination, which was performed only on patients, followed the protocol described in the RDC/TMD (Dworkin and LeResche, 1992). The clinical examination included measurement of active and passive maximum opening, of active protrusion and laterotrusion, palpation and auscultation of the TMJ area and palpation of masticatory muscles. In contrast to the RDC criteria, only seven muscle sites per side were examined, i.e. the anterior, medial and posterior portion of the temporal muscle, the insertions of the temporal and medial pterygoid muscles, the superficial and deep masseter. The lateral pterygoid muscle was not palpated, as it is inaccessible to palpation (Stratmann et al., 2000; Turp and Minagi, 2001). Pressure palpation was standardized at 10 N/cm^2 for extraoral muscles and 5 N/cm^2 for the joints and the intraoral sites. A muscle was considered tender to palpation if the subject reported pain on palpation or the palpation elicited a blinking of the eyelids or a withdrawal reflex.

Psychological evaluation

All patients and controls were screened for psychiatric disorders using a short screening questionnaire (Wittchen and Pfister, 1997) and interviewed by clinical psychologists (JG or UG) to ensure the absence of exclusion criteria (vide supra) for participating in the study. All subjects completed a battery of questionnaires, including the German version of the Hospital Anxiety and Depression Scale-

German Version (HADS-D, (Zigmond and Snaith, 1983), the Fatigue Scale (FS, (Chalder et al., 1993), and visual analogue scales (VAS; 0 = no pain, 100 = worst pain imaginable) to assess pain, sleep duration and sleep quality before, during, and after sampling days.

Cortisol assessment and biochemical analysis

In order to assess the salivary free cortisol level saliva was collected at home by means of Salivettes (Sarstedt, Rommelsdorf, Germany). Subjects had to chew on a cotton salivette during a 1-min period according to the manufacturer's instructions. They had to collect samples on two consecutive days, allowing the assessment of the variation of the cortisol levels after awakening (cortisol awakening response) and over the day (short circadian cortisol profile).

For the assessment of the cortisol awakening response samples were obtained immediately after awakening and 15, 30, 45 and 60 min thereafter. The subjects had to remain lying in bed for the first 15 min. and not to have breakfast or brush the teeth during the first hour after awakening in order to avoid false high cortisol values due to plasma exudates from minor bleeding in the oral cavity. For the measurement of the short circadian cortisol profile four additional saliva samples were collected at 8.00, 11.00, 16.00 and 20.00 o'clock. However, as subjects were free to wake up according to their normal schedule, the collection time for the first sample could vary individually. Subjects were asked not to eat or drink for 30 min before taking these four samples. In conclusion, each subject collected 18 samples, 9 per day. In order to assess a possible dysregulation of the HPA axis subjects and patients took an oral dose of 0,5 mg dexamethasone (Merck, Germany) at 11.00 p.m. on the first day.

The saliva samples were stored in the refrigerator until completion of sampling and then brought to our laboratory where they were stored at -20°C until biochemical analysis took place. The salivary free cortisol was analyzed by using commercial chemiluminescence immunoassay (IBL, Hamburg, Germany). Inter- and intraassay coefficients of variation were below 10%. To reduce error variance caused by

imprecision of the intraassay, all samples of one subject were analyzed in the same run. Collection and return of saliva samples as well as compliance with the protocol were supervised by study personnel. In order to calculate the sleep duration subjects had to record bed and awakening times.

Statistical analysis

Kolmogorov-Smirnov tests showed that salivary free cortisol data were not normally distributed. Calculating the log of cortisol values produced nearly normally distributed values so that Log-transformed cortisol values were used in order to perform parametric statistical tests. However, the results present means and standard deviations of the untransformed values. Data were also tested for homogeneity of variance using Levene´s test before statistical procedures were applied.

ANOVAs for repeated measures were computed to analyze cortisol data, with clinical diagnosis as a grouping variable and time as the repeated measures factor. All reported results were corrected by the Greenhouse-Geisser procedure when assumptions of sphericity were violated. Correlations were computed by Pearson product-moment correlation. Possible differences in the psychological scores between the two groups were analyzed by Student's t-test, ANOVA or MANOVA.

For salivary cortisol levels after awakening, the areas under the curve with respect to ground (AUCg) was calculated as an indicator for the integrated cortisol responses (Pruessner et al., 1997).

As several studies provided evidence that the cortisol awakening response (CAR) is a genuine repsonse to awakening and distinct from the circadian rise in HPA-activity in the early morning hours, we decided not to show the cortisol data as a function of clock time (Wilhelm et al,. 2007).

AUCg for the short circadian cortisol profile were not computed due to the large time intervals between the cortisol measures. Based on the results of previous studies using a similar approach (Gaab et al., 2002; Gaab et al., 2005) it was

calculated that a sample size of N = 40 was necessary in order to detect an expected multivariate effect size of f^2=0.35 with a power ≥ 0.90 and α = 0.05 (statistical software G-Power (•Buchner et al., 1997). For all analyses, the significance level was α=5%. Unless indicated, all results shown are the mean ± standard error of means (SEM).

Results

All patients fulfilled the criteria for a diagnosis of myogeneous facial pain according to the RDC/TMD (Dworkin and LeResche, 1992). Three of them had a diagnosis of myofacial pain (RDC/TMD category Ia) and seventeen had a diagnosis of myofacial pain with limited opening (RDC/TMD category Ib). Out of these, two had an additional diagnosis of arthralgia (RDC/TMD category IIIa) and five had a painfree disc displacement with reduction (RDC/TMD category IIa). The VAS mean pain intensity was 37.0, with a range of 8-75.

Myogeneous pain patients did not differ from control subjects in age (myogeneous pain patients: mean=35.2, range=19-60; controls: mean=37.0, range=21-59, $F_{1,38}$=0.24, p=0.62), gender (3 males and 17 females in both groups), and body mass index (myogeneous pain patients: mean=22.54, range=16.80-29.30; controls: mean=23.253, range=18.15-32.66, $F_{1,38=}$1.74, p=0.20). The mean pain duration was 71 months and the median was 48 months, with a range of 6 to 420 months. With the exclusion of the only patient with a pain duration of 420 months the group mean pain duration was 52 months, with a range of 6-120 months. Symptoms duration was not associated with any psychometric scores or cortisol levels (pain duration- HADS anxiety: r=0.12; -HADS depression: r=-0.28; -physical fatigue: r=-0.18: -mental fatigue: r=-0.23, -AUCg day 1: r=-0.41; -AUCg day 2: r=-0.01; -mean cortisol levels day 1: r=0.002 -mean cortisol levels day 2: r=-0.04; all n.s.).

Cortisol levels

Day 1. The salivary free cortisol levels increased significantly in both groups after awakening (time effect: $F_{2.4,\ 87.7}$=10.5, p<0.001), the differences between the two groups being statistically not significant (group by time effect: $F_{2.4,\ 87.7}$=0.6, p=0.59, Figure 6).

The cortisol levels significantly changed over the course of day 1 (time effect: $F_{.2.5, 93.9}$=34.4, p<0.000), but cortisol levels over the short circadian profile did not differ between myogeneous pain patients and controls (group by time effect: $F_{2.5, 93.9}$=1.6, p=0.21, Figure 7).

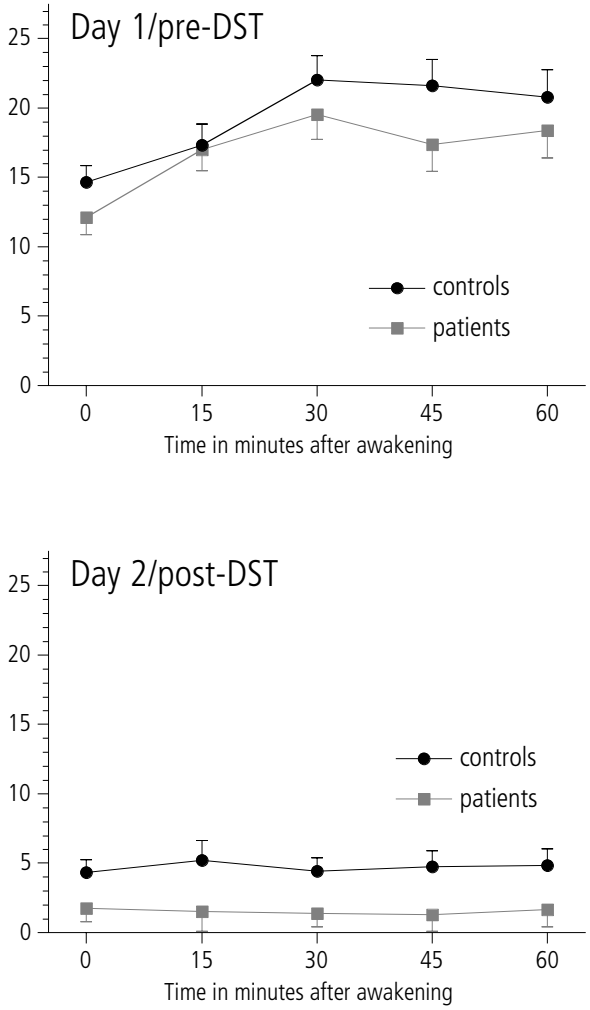


FIGURE 6. Awakening salivary cortisol levels before (top panel) and after (bottom panel) the administration of 0.5mg dexamethasone at 11 pm on Day 1 of patients with chronic myogeneous facial pain (, N=20) and healthy controls (, N=20).

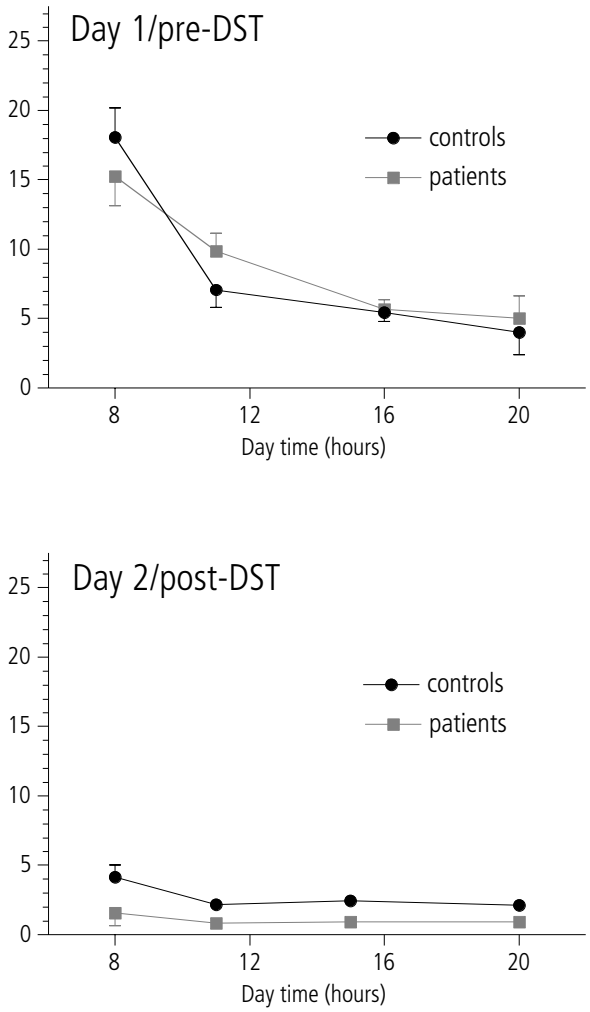


FIGURE 7. Circadian salivary free cortisol levels before (top panel) and after (bottom panel) the administration of 0.5mg dexamethasone at 11 pm on Day 1 of patients with chronic myogeneous facial pain (, N=20) and healthy controls (, N=20).

Day 2. In both groups the cortisol levels neither increased significantly after awakening nor changed during the day (time effects: $F_{1.7,\ 62.4}$=0.4, p=0.71 and $F_{1.6,\ 58.3}$=1.2, p=0.30, respectively). Due to the lack of significant changes over time, group effects rather than group by time effects were calculated. In both groups the intake of 0.5 mg of dexamethasone led to a significant decrease in the cortisol levels both during the awakening response as well as the short circadian profile (Fig. 1 and 2).

However, the decrease in the myogeneous pain patients group was statistically significantly larger than in the control group (group effects: awakening cortisol levels $F_{1, 37}$=4.3, p=0.04, Fig. 1 and short circadian profile $F_{1, 37}$=8.8, p=0.005, Fig. 2). These results were confirmed by group comparisons of the overall cortisol secretion (group effect: AUCg in nmol/time: myogeneous pain patients: 5.41 (1.8), controls: 22.07 (6.4), $F_{1, 39}$=10.26, p=0.003, Figure 8).

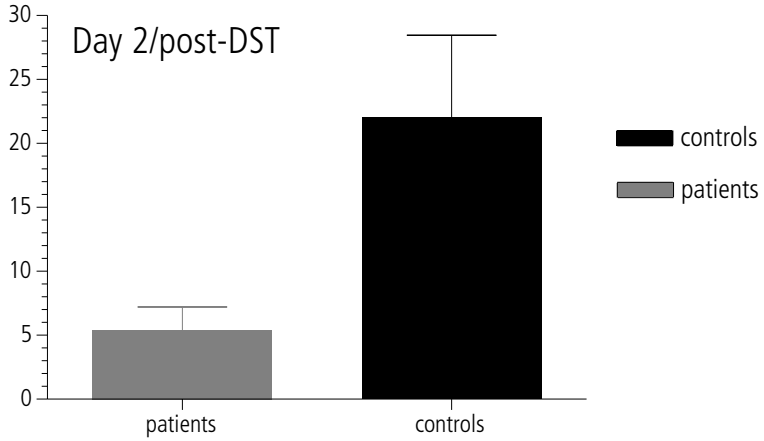


FIGURE 8. Area under the awakening cortisol response curve with respect to ground after the administration of 0.5mg dexamethasone at 11 pm on Day 1 of patients with chronic myogeneous facial pain (, N=20) and healthy controls (, N=20).

Compliance to protocol

All 20 myogeneous pain patients confirmed having taken dexamethasone. This is confirmed by the results as, in all subjects, an at least 50% reduction of the individual awakening AUCg and mean circadian cortisol levels on day 2 in comparison to day 1 was observed. The compliance was further confirmed by a second order interaction between cortisol measures x group x assessment day, with a significant interaction effect for awakening salivary cortisol ($F_{2.5, 91.7}$=9.6, p<0.000) and for the short circadian cortisol profile ($F_{2.5, 91.7}$=21.2, p<0.000).

As described above, all participants were informed in detail about the importance of adherence to the protocol. However we did not used any specific method or instrument for directly controlling sample time, i.e. electronic monitor caps or palm-pilots (Kudielka et al., 2003).

Psychometric and sleep variables

Myogeneous pain patients exhibited significantly higher scores on depression, anxiety, physical fatigue and mental fatigue. However, depression scores remained below the cut-off score for clinical relevance, whereas anxiety levels were above. (Table 1). Also, myogeneous pain patients exhibited a lower quality of sleep than controls on both assessment days (Table 1). Sleep duration did not differ significantly between groups (Day 1: $F_{1, 37}$=1.0, p=0.32, myogeneous pain patients mean 6h45min (95% CI 6 h 6 min- 7 h 30 min), controls mean 7 h 20 min (95% CI 6 h 40 min-8 h 10 min), Day 2: $F_{1, 37}$=3.2, p=0.08, myogeneous pain patients mean 6 h 6 min (95% CI 5 h 30 min-6 h 45 min), controls mean 6 h 55 min (95% CI 6 h 15 min-7 h 35 min).

TABLE 1. Psychometric characteristics of patients with myogeneous facial pain and healthy controls

Questionnaire	Scale	Patients[a]	Controls[a]	Statistics
HADS	Depression	4.6 (0.7)	0.8 (0.2)	F=23.1, P<0.000
	Anxiety	9.5 (0.7)	2.1 (0.4)	F=63.7, P=0.000
FS	Physical	4.8 (0.5)	0.8 (0.3)	F=209.0, P<0.000
	Mental Fatigue	1.9 (0.3)	0.2 (0.2)	F=268.0, P<0.000
VAS day 1	Pain[b]	37.0 (4.0)	5.9 (3.9)	F=63.8, P<0.001
	Sleep Quality[c]	28.4 (1.9)	5.5 (1.6)	F=79.3, P<0.001
VAS day 2	Pain[b]	32.5 (3.9)	5.8 (4.2)	F=51.5, P<0.001
	Sleep Quality[c]	31.2 (1.6)	3.9 (1.3)	F=74.2, P<0.001

[a] mean (SEM), [b] 0-100 (no-worst pain imaginable), [c] 0-100 (good-very bad sleep quality)

Discussion

This study investigated the possibility of a dysregulation of the HPA axis in terms of activity, reactivity and negative feedback sensitivity in patients with chronic myogeneous facial pain. Main findings are: 1) Before intervention, cortisol levels on awakening and across the circadian rhythm did not differ between myogeneous facial pain patients and healthy matched controls. 2) After administration of 0.5mg dexamethasone, myogeneous facial pain patients showed significantly lower cortisol levels at all measurement points. 3) Myogeneous facial pain patients scored significantly higher in measures of psychological distress as evidenced in clinically elevated levels for anxiety, but not for depressive symptoms. This is in line with results of other studies on TMD patients finding very similar results with higher scores on anxiety then on depression (Jerjes et al., 2007).

Before intervention, all cortisol levels were inconspicuous in our sample. This finding contrasts to the report by Korszun and colleagues (Korszun et al., 2002), who found significant higher basal circadian cortisol levels in temporomandibular disorder (TMD) patients compared to controls. However, methodological differences between the studies need to be noted. The TMD patients examined by Korszun et al. (2002) had low pain intensity, and high depression scores. Our myogeneous facial pain patients group on the other hand was characterized by a moderate to high mean pain intensity level, but low mean depression score. The reported cortisol differences between their study and our study may be due to these differences, since the awakening cortisol responses are sensitive to the individual symptomatic profile (Ehlert et al., 2005). Two studies investigated the HPA axis reactivity of TMD patients to experimentally induced psychosocial stress. One reported an elevated cortisol response to a standardized stress paradigm in a subgroup of TMD patients compared to controls (Jones et al., 1997). These results were partly confirmed by a recent study, reporting higher cortisol stress responses in patients with myofacial pain in comparison to healthy controls (Yoshihara et al.,

2005). However, it needs to be noted that these two studies examined cortisol responses to experimentally induced stress in contrast to our approach that observed cortisol levels upon awakening and across the circadian rhythm. The different findings could thus be due to disparate underlying neuroendocrine processes (Herman and Cullinan, 1997).

Our finding that myogeneous facial pain patients showed significantly lower cortisol levels at all measurement points after administration of 0.5mg dexamethasone is indicative of an enhanced and persisting suppression of cortisol levels. Similar findings have been reported in other medically unexplained syndromes including chronic fatigue syndrome (Gaab et al., 2002), fibromyalgia (Griep et al., 1998; Wingenfeld et al., 2007), chronic pelvic pain (Heim et al., 1998), chronic whiplash associated disorder (Gaab et al., 2005) as well as psychiatric disorders with a predominance of somatic symptoms, such as atypical depression (Levitan et al., 2002). This stresses the need to consider etiologic similarities between these conditions (Barsky and Borus, 1999; Wessely et al., 1999).

However, it needs to be noted that the observed enhanced negative feedback sensitivity to dexamethasone did not lead to a reduced output of salivary cortisol after awakening or over the circadian rhythm. A similar pattern has been observed in some (e.g. Gaab et al., 2002) but not all medically unexplained syndromes (e.g. Gaab et al. 2005; Wingenfeld et al. 2007). It remains unclear whether normal cortisol levels in the face of enhanced negative feedback sensitivity is either the result of a weak association between impaired glucocorticoid receptor-related negative feedback on the level of the pituitary and assessed salivary cortisol levels or a result of adaptive processes at the level of the adrenal. Further studies are clearly needed to elucidate this issue.

In case of a confirmation of the observed HPA axis dysregulations in patients with chronic myogeneous facial pain in further studies, with more sophisticated

neuroendocrine procedures, assessment of the HPA axis dysregulations could serve as a important constituent of a multidimensional understanding of chronic myogeneous facial pain, shifting the perspective away from a local towards a more central etiology with dysregulations in the stress and pain modulating system (Lariviere and Melzack, 2000).

There is evidence for generalized hyperalgesia in MAP patients and hormonal as well as neural mechanisms leading to hyperexcitability and amplification of the nociceptive inputs have been discussed (Sarlani and Greenspan, 2003). One possible mechanism leading to enhanced pain sensitivity may be a reduced release of corticotropin-releasing-hormone (CRH), since CRH seems to be involved in central as well as peripheral pain processing (Lariviere and Melzack, 2000). Interestingly the first human study on the CRH analgesic properties was done in dentistry: intravenous CRH administration lead to significantly less postoperative dental pain than with placebo (Hargreaves et al., 1987). However, this study did not assess CRH or other directly associated hormones, such as adrenocorticotropin hormone (ACTH).

Some methodological shortcomings must be acknowledged. First: Previous studies have shown that objective compliance with protocol is lower than self-reported compliance especially when the sampling period is over several days, producing incorrect data particularly in the last sampling days (Broderick et al., 2004). As we did not use electronic monitor caps or palm-pilots, compliance to protocol by the participants may be lower than expected. Although our study time was only two days and correct data collection more probable we strongly recommend these techniques in further studies.

Second: Dexamethasone bioavailability is considered to be important in interpreting cortisol suppression of dexamethasone. A study on depressed patients found a correlation between bioavailability of dexamethasone and cortisol suppression after dexamethasone intake, probably because of accelerated dexamethasone clearing.

(Cassidy et al., 2000). However, in several studies using the low-dose-dexamethasone-test, no different dexamethasone levels have been found in plasma or saliva nor was there a correlation between cortisol and dexamethasone levels (e.g. (Goenjian et al., 1996). Dexamethasone bioavailability may be influenced by age and body-mass-index but as we matched our groups with respect to these factors, we consider that possible differences in dexamethasone bioavailability could explain our results.

In summary, the results showed that patients with chronic myogeneous facial pain have enhanced negative feedback sensitivity after the intake of a low dose of dexamethasone, whereas the cortisol awakening response as well as the secretion of cortisol over the course of the day appear normal. These results are in line with a multifactorial etiology of chronic facial pain.
This supports multidisciplinary treatment approaches for patients with chronic myogeneous facial pain similar to those used in other chronic pain disorders, including interventions for pain- and stress-management.

7.2. Do illness perceptions predict treatment outcomes in chronic orofacial pain patients? A 6-month follow-up study

Introduction

Orofacial pain is one of the most common chronic pain conditions apart from headaches and musculoskeletal pain, accounting for 40% of all chronic pain syndromes (LeResche, 2001). It represents a heterogeneous group of painful conditions of the jaws, face, masticatory muscles, temporomandibular joint and neighboring areas. Close to 50% of persons experiencing orofacial pain had sought medical advice from a physician or dentist (Macfarlane et al., 2002) and, although orofacial pain has a good prognosis, in a minority of patients (10-15%) persistent facial pain is associated to high pain-related disability and high rates of psychosocial distress so that these patients are to be considered as chronic pain patients (Von Korff et al., 1988; Dworkin and Massoth, 1994; Palla, 2006). As risk factors for chronicity and pain-related disability, stress, depression and anxiety have been identified by longitudinal studies (Macfarlane et al., 2004; Sipila et al., 2001), pointing out the importance of psychosocial factors for the maintenance of chronic pain.

The role of patients' illness beliefs, i.e. patients' individual understanding of their illness, has been identified as an important factor influencing both health seeking behavior and treatment outcome (Petrie et al., 2007). For example in chronic pain patients with rheumatoid arthritis (Scharloo et al., 1998; Sharpe et al.,2001) and low back pain (Foster et al., 2008). Illness perceptions significantly predicted patients' lower satisfaction with medical consultations and were strong predictors for high health care use two years later (Frostholm et al., 2005; Frostholm et al., 2007) or the decision to seek medical care (Leslie et al., 2000; Sensky, 1996).

One of the most significant models on illness beliefs and perceptions, which have been studied in a wide range of medical conditions, is the common-sense model or self-regulation model (SRM) of health and illness (Leventhal et al., 1998; Sensky,

1996; Leventhal, 2003). In the SRM biological, psychological and social factors are converging in a parallel process forming patients' perceptions of their illness and directly influencing their behavioral and emotional response to the illness. (Weinman and Petrie, 1997). The original model consists of five dimensions: identity, cause and consequences of the health problem, the timeline or duration of it and beliefs about cure / control. There is one study examining the predictive value of illness perceptions on outcome in dentistry (recovery after oral surgery), finding that patients' expectations were more predictive of symptom severity than medical factors and underlining the importance of preoperative assessing of patients expectations (McCarthy, 2003). Longitudinal studies with chronic pain patients provided evidence for strong associations between baseline illness perceptions and outcome in low back pain six months later (Foster et al., 2008) as well as physical and psychological adjustment to illness in rheumatoid arthritis in a two year follow up (Groarke et al., 2005). After a multidisciplinary pain management program changes in pain related beliefs were strongly related to physical and mental improvement 6 months later (Moss-Morris et al., 2007). The goal of the current study was therefore to test the predictive value of the SRM on clinical outcomes of patients with orofacial pain over three and six months in the context of other clinical predictors in order to determine the relative contribution of each one. Primary outcome variable was pain related disability, secondary outcome was psychological well-being and functioning. To our knowledge this is the first study to assess the influence of illness beliefs in the treatment of patients with orofacial pain.

Methods

Participants and procedures

The study sample was recruited from newly referred patients to the interdisciplinary orofacial pain consultant service at the Center for Dental and Oral Medicine and Cranio-Maxillofacial Surgery, University of Zurich from June 2006 to October 2007. Based on the referral letter details, consecutive patients fulfilling inclusion criteria were contacted by telephone or by post (if not reached by telephone after three attempts). When accepted to participate they received routine pain questionnaires (see 2.4.) which is part of the usual practice of the clinic for new referrals. In addition they received the study questionnaires with the request to return them before the first consultation (T1). Three and six months after the first consultation (T2 and T3) patients' clinical records were checked for changes in diagnosis or etiology which could have led to exclusion from the study (e.g.. detection of a tumor in patients with trigeminal neuralgia). All participants remaining in the study received the follow-up questionnaires with a prepaid envelope. All non-responders were contacted by telephone to improve response rate.

Treatment consisted of a tailored multidisciplinary treatment including dental/ medical and psychological components. Dental /medical treatment focused on: information, instruction of self-administered physical exercises, splint therapy and medication. Psychotherapy was based on cognitive-behavioral concepts including psychoeducation, stress management and relaxation. (all components if individually indicated) (Turner et al., 2006).

All subjects completed a written informed consent form. The study was approved by the Ethical Committee of the Medical Council of the Canton of Zurich.

Clinical and psychological examination

Clinicians of the interdisciplinary orofacial pain service recorded the history, performed the clinical examination and evaluated for inclusion. All diagnoses were

controlled by the two responsible clinicians of the orofacial pain service. Examination included 1) evaluation of the oral cavity for dental and mucosal pathologies, 2) examination of the fifth cranial nerve for touch, cold, and pinprick sensation 3) cursory examination of the cervical spine and 4) assessment of the functional status of the masticatory system according to RDC/TMD. A muscle was considered tender to palpation if the subject reported pain on palpation or the palpation elicited a blinking of the eyelids or a withdrawal reflex. Patients scoring high on psychological screening questionnaires or indicating psychosocial difficulties in the history were interviewed in-depth by trained clinical psychologists to evaluate for exclusion.

Inclusion and exclusion criteria

Inclusion criteria were age range 18-75 years, fluency in the German language, facial pain for at least 3 months and one of the following diagnoses: temporomandibular joint disorders (arthralgia, osteoarthrosis, disc displacement), persistent idiopathic orofacial pain, masticatory muscle pain, burning mouth syndrome, classical trigeminal neuralgia, orofacial migraine, orofacial cluster headache, and orofacial tension type headache. Diagnoses were based on the research diagnostic criteria for temporomandibular disorders RDC/TMD (Dworkin and LeResche, 1992) and the diagnostic criteria of the International Headache Society (2004).

Exclusion criteria were pain of dental origin and actual diagnosis of the following psychiatric disorders: Psychotic disorders, bipolar disorders, personality disorders, drug dependencies, eating disorders. These exclusion criteria were chosen in order to control for possible main effects of psychiatric disorders and medication on dependent variables.

Measures

At baseline participants were asked to provide basic demographic information about gender, age, marital status and employment status. All referred patients (participants and non-participants) completed a standard battery of questionnaires before treatment. Participants completed in addition the same questionnaires three and six months after the first consultation. The following questionnaires were used:

Pain questionnaire: A modified version of the German pain questionnaire (German: Deutscher Schmerzfragebogen DSF) was used, which was developed and validated by the task force on "Standardization and Economy in Pain Management" of the German Chapter of the International Association for the Study of Pain. The DSF is a reliable and valid instrument for assessing the multidimensional experience of pain. Comparison with external criteria proved good content validity and excellent reliability of patients' statements in the questionnaire (Nagel et al., 2002). Based on a biopsychosocial pain model and constructed in a modular form the assessment consists of basic sociodemographic data and pain variables (e.g. pain sites, duration, intensity), causal attributions, previous pain treatment procedures and medication. The following questionnaires are part of the DSF:

Graded Chronic Pain Scale (GCPS). This was used as standard self-assessment instrument to assess the severity of chronic pain in terms of pain intensity and pain-related disability in four hierarchical classes: Grade I: low disability – low intensity, Grade II: low disability – high intensity, Grade III: high disability – moderately limiting, Grade IV: high disability – severely limiting (Vonkorff et al. 1992). The scale consists of questions on pain intensity (NRS) and questions about pain interference with daily activities, social/family/recreational activities and ability to work (including housework). The GCPS is part of the RDC/TMD and has been proven to be a valid screening approach to quickly identify orofacial pain patients with significant behavioral and psychological pain dysfunction and at risk for poor outcome (Dworkin et al., 2002).

Hospital Anxiety and Depression Scale (HADS). This was used to measure anxiety and depression (Zigmond and Snaith, 1983). Its psychometric properties have been extensively investigated and shown to be robust (Barczak et al., 1988; Dworkin et al., 2002; Moorey et al., 1991). Individual scores for depression and anxiety can be calculated with cut-off scores for "possible" (> 7) and "probable" (> 10) caseness for depression and anxiety.

SF12 short form health survey. The short version of the SF36 health survey was applied to measure health related quality of life. It is the most commonly used generic measure of health related quality of life and recommended for use in pain research (Bullinger, 1995; Dworkin et al., 2005). Physical and mental component summary measures (PCS-12 and MCS-12) were calculated according to the validated and standardized German version of the SF12 (Dworkin et al., 2005; Gandek et al., 1998).

In addition participants completed before treatment as well as three and six months later the Illness Perception Questionnaire, revised version (Moss-Morris et al., 2002) which was developed to rate illness perceptions on the theoretical background of Levental's self-regulation model (Weinman et al., 1996), German version Gaab, 2004). The original IPQ-R consists of three sections. The first section (identity) assesses patients' beliefs about the symptoms associated with their condition. The second section consists of seven subscales assessing pain-related beliefs. Rating is requested on a five-point Likert scale. The last section (cause) consists of possible causes of pain. However the authors encourage researchers to adapt the questionnaire to their particular illness and research setting (Moss-Morris et al., 2002). In our study we used the German version of the brief IPQ-R, which was recently validated by our group with a mixed sample of pain patients, among them orofacial pain patients. Principle components factor analysis showed a dimensional structure similar to the original IPQ-R with the following dimensions: consequences, emotional representation, illness coherence (extent to which patients

have a coherent understanding of their pain), chronic timeline, cyclical timeline and personal control (Gaab, 2004).

To operationalize the causal illness beliefs we used the pain questionnaire (DSF) items about causal attributions and beliefs about pain, creating a new item which was dichotomized into those who experienced any emotional or physical stress (e.g. psychological strain, physical strain) and those who did not. The identity section of the IPQ-R was omitted for the following reason: When validating the IPQ-R German version with orofacial pain patients, the number of symptoms associated with their condition, apart from pain, was low and consisted predominantly of symptoms inherent to the diagnosis of orofacial pain. We therefore hypothesized that orofacial pain patients have a well defined illness identity and the identity scale may probably be less meaningful in these patients. However this hypothesis needs to be confirmed in further studies with a larger sample size.

Design and data analysis

A prospective design, investigating illness perceptions, pain, mood and functioning at three and six months follow-up was used. Before testing the study hypothesis MANOVA and Pearson $?^2$ analyses were performed to determine whether participants and non-participants as well as participants and dropouts differed in their sociodemographic characteristics and predictive variables. All data analyses were performed using SPSS software version 15.0 for Windows. Power analysis was calculated a priori with the statistical software G-Power (Faul et al., 2007). For all analyses, the significance level was .05. Stepwise linear regression analyses were performed to determine the extent to which illness perceptions at baseline predict treatment outcome at three and six months, when controlled for symptom severity and mood. Independent variables were: pain intensity (VAS) and pain related disability (GCPS), causal attribution, illness perceptions (IPQ), health related quality of life (MCS-12, PCS-12), anxiety and depression (HADS). Primary outcome was pain related disability (GCPS), secondary outcome was psychological

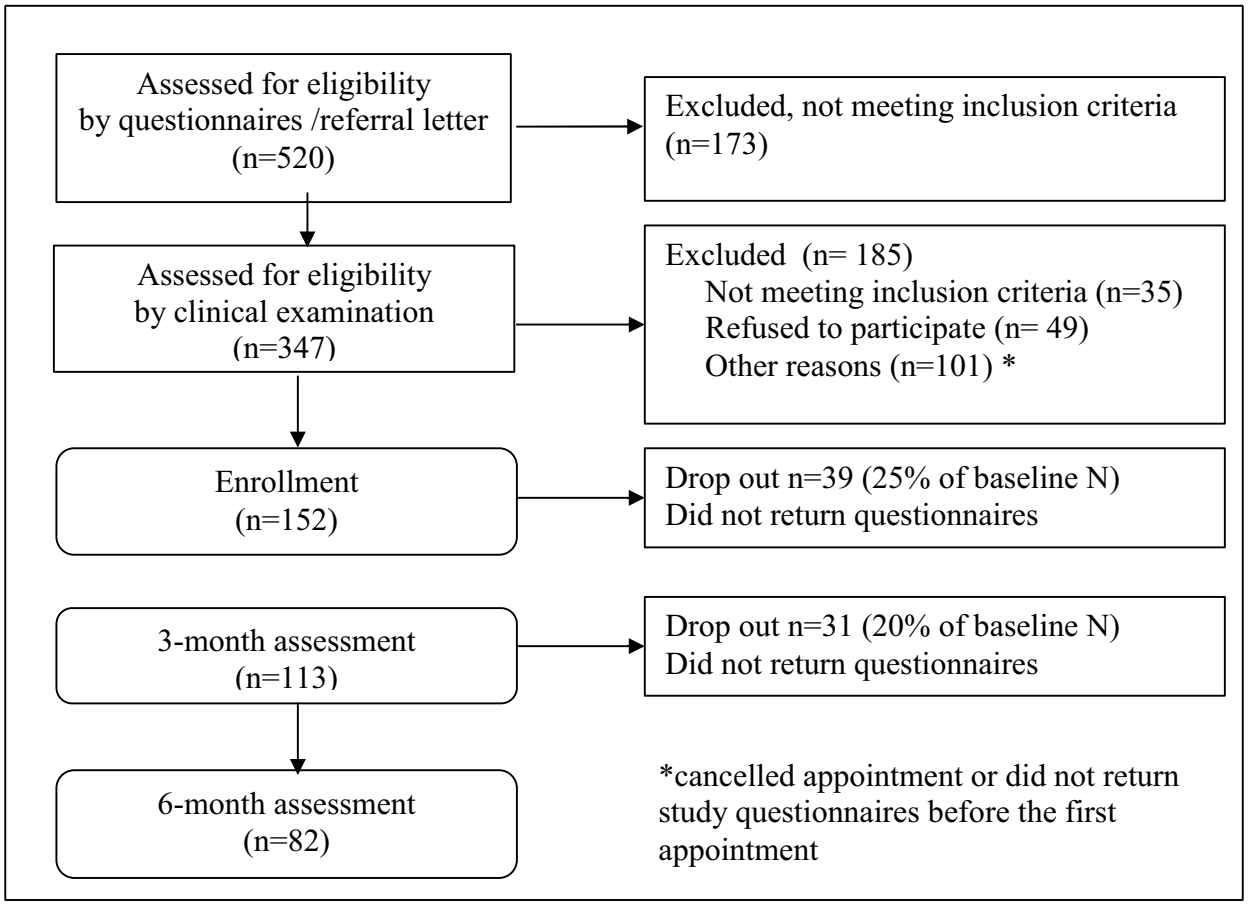
well-being and functioning (HADS anxiety and depression, SF12 mental component summary scale, MCS-12).

Results

Descriptives and psychometric variables at baseline

Of the 520 patients referred to the orofacial pain consultant service 347 patients met the basic inclusion criteria (age, language skills, pain duration) and were contacted. 195 of them did not take part in the study for the following reasons: 47 refused to participate, 84 did not return the questionnaires before the first consultation, 27 cancelled the appointment, 29 patients had to be excluded because of insufficient language ability and 6 patients had to be excluded because of other medical problems, resulting in a final sample of 152 patients (43.8% of the referred patients), (see Figure 9).

Figure 9 Flow chart of participants through the study



and mental health related quality of life. However, groups differed in levels of anxiety with lower mean scores in the non-participant group. (Table 2)

To assess possible differences between the groups, baseline variables of participants and drop-outs were compared. Participants with available data at all three assessments (completers) and all drop-outs (3 and/or 6 month assessment) did not differ for any demographic or psychometric variable (data not shown). Participants and drop-outs did not differ for any of the IPQ scores nor in their causal attributions. However groups differed in pain intensity (F = 9.104, P = 0.003) with mean values 1 point higher in the group with only baseline measures compared to the group of completers.

Table 2: Mean (SD) scores or percentage for participants and non-participants

Demographics	Participants (N=152)	Non-participants (N= 195)	Statistics
Age	45.7 (16.0)	45.8 (13.8)	F=0.03, P=.959
Female	75.0%	81.5%	$?^2$=2.104, P=.147 [a]
Pain descriptives			
GCPS Pain intensity[b]	5.5 (1.9)	5.4 (2.2)	F=0.105, P=.746
Pain > 5 years	30.6 %	21.5 %	$?^2$=2.516 [a], P=.113
GCPS Pain related disability[c]	26.2%	36.0%	$?^2$=3.537 [a], P=.060
Other pain sites	67.5%	64.7%	$?^2$=0.306 [a], P=.580
Psychometrics			
HADS Anxiety[d]	7.76 (4.38)	6.43 (4.15)	F=7.581, **P=.006**
HADS Depression[d]	5.72 (4.33)	5.02 (4.64)	F=1.878, P=.172
MCS-12	45.35 (7.62)	43.40 (10.86)	F=3.342, P=.068
PCS-12	53.18 (7.19)	52.96 (6.89)	F=0.89, P=.745

[a] Pearson chi-squared test of independence; [b] NRS 0-10 (no-worst pain imaginable);
[c] GCPS grade III or IV

Comparisons between participants and non-participants

Mean age of participants was 45.7 years (SD 16.0, range 18-75). The majority of participants was female, married and held jobs (Table 1). Mean pain intensity was 5.5 (SD 1.9), 30.6% had pain for more than 5 years and 26.2% had severe disabling pain (GCPS grade III or IV). 67.5% had another pain site additional to the orofacial pain. The most prevalent diagnoses were masticatory muscle pain (MMP 30.4%) and masticatory muscle pain + temporomandibular joint disorders (TMJ 31,1%). 6.7% had TMJ only, 13.3% had neuropathic pain (NP) and/or orofacial headache and 18.5% had multiple mixed diagnoses, that is a muscular or joint disorder with additional neuropathic aspects or orofacial headache. 61% received at least 1 session of psychotherapy in addition to dental/ medical treatment. The majority of patients believed in an organic cause (53.3%), 26.3% associated their pain to emotional or physical stress and 20.4% to both organic cause and stress. No significant correlation was found between any of the sociodemographic variables or pain duration and any of the outcome variables, respectively.

HADS anxiety and depression levels at baseline were 7.76 (SD 4.38) and 5.72 (4.33), respectively. 28.2% and 13.4% were above the cut off score (>11) for clinically relevant anxiety and depression, respectively. Mean values for mental (MCS-12) and physical quality of life (PCS-12) were 45.35 (SD 7.62) and 53.18 (7.19) respectively. 17.9% and 0.7% were out of normal range for mental and physical quality of life compared to the normal population (Gandek et al., 1998). Psychological distress (HADS anxiety and depression, MCS-12) as well as GCPS pain intensity did not differ across diagnostic groups (data not shown). However there was a significant difference between groups in physical quality of life (F=0.415; P=0.002) and GCPS pain related disability (? ^{2}=22.703, P=0.30) with the multiple mixed diagnoses group showing the highest percentage of patients with severe pain related disability (Grade III and IV) and lower physical quality of life. In this group 38.2% had severe pain related disability compared to 24.2%, 20.6%, 13.3% and 27.6% in the MMP, MMP+TMJ, TMJ and NP/orofacial headache

groups respectively. Mean values of physical quality of life were 50.57(SD 8.57) for the group with multiple mixed diagnoses and 54.20(SD7.39), 53.76(SD6.93), 56.28(SD4.54) and 53.63(SD6.34) for the other groups.

Changes over time in primary and secondary outcome variables

Table 3 indicates the means of the psychological and pain outcome measures across the three assessments. Patients improved significantly in pain intensity, pain-related disability, depression and anxiety over time. At 3 month assessment greatest changes in outcome scores were found, whereas little further improvement occurred from 3 to 6 month assessment. IPQ consequences and emotional representations changed significantly whereas scores of IPQ cyclical timeline, chronic timeline, personal control and illness coherence remained invariated. There was no significant change in physical and mental quality of life. We controlled for positive effects of individual interventions, e.g. medical treatment versus combined medical and psychological treatment. No effect of type of intervention was found for any of the outcome variables (data not shown).

Table 3: Mean (SD) scores or percentage for outcome variables T1 – T3 (three and six months after first consultation) and MANOVA

	T1 (N=152)	T2 (N=113)	T3 (N=82)	Statistics
GCPS Pain intensity [a]	5.5 (1.9)	3.9 (2.1)	3.4 (2.2)	F=31.551, **P<.000**
GCPS Pain related disability[b]	26.2%	15.0%	17.6%	Z=-3.136, **P<.000** [f]
HADS anxiety	7.76 (4.38)	5.87 (3.93)	5.52 (3.84)	F=12.563, **P<.000**
HADS depression	5.72 (4.33)	4.34 (3.80)	4.35 (4.05)	F=7.801, **P=.002**
MCS-12	45.35 (7.62)	44.90 (6.01)	44.29 (5.60)	F=1.189, P=.307
PCS-12	53.18 (7.19)	52.51 (7.08)	52.46 (7.53)	F=.342, P=.710
IPQ consequences[e]	2.62	2.48	2.27	F=7.777, **P=.001**
IPQ emot. representation[e]	3.08	2.82	2.66	F=11.349, **P=.000**
IPQ illness coherence[e]	2.86	3.11	3.20	F=2.133, P=.126
IPQ cyclical timeline [e]	3.42	3.14	3.16	F=1.825, P=.165
IPQ personal control[e]	3.30	3.42	3.20	F=1.661, P=.196
IPQ chronic /acute timeline[e]	3.28	3.15	3.18	F=.065, P=.937

[a] NRS 0-10 (no-worst pain imaginable) [b]GCPS grade; [e]IPQ-R scales (range 1-5); [f]Wilcoxon-Test

Cross-sectional analysis between IPQ scores and outcome measures

With the exception of IPQ personal control all IPQ subscales at baseline were significantly correlated with pain, depression and anxiety as well as with quality of life measures at baseline (see table 4). All correlations were in the expected direction.

Table 4: Correlations between IPQ subscales and outcome measures

	GCPS Pain intensity	GCPS Pain related disability	HADS Anxiety	HADS Depression	MCS-12	PCS-12
IPQ consequences	.455**	.413**	.282**	.453**	n.s.	-.424**
IPQ emotional representation	.284**	.279**	.254**	.348**	n.s.	-.216*
IPQ illness coherence	-.2.66**	n.s.	n.s.	n.s.	n.s.	n.s.
IPQ cyclical timeline	.301**	.185*	n.s.	.207*	n.s.	n.s.
IPQ personal control	n.s.	n.s.	n.s.	n.s.	n.s	n.s.
IPQ chronic/acute timeline	n.s.	n.s.	.183*	.276**	n.s.	n.s.

** significance level $p<0.01$; * significance level $p<0.05$

Baseline predictors of primary and secondary outcome variables

A series of stepwise linear regression analysis was conducted to calculate the relative contributions of baseline values of all IPQ-R, HADS and SF12 subscales on pain related disability, depression and anxiety symptoms and mental quality of life. For each outcome variable separate regression analysis for 3 and 6 month assessment was performed.

Predictors of pain related disability (GCPS): Results of the regression analysis indicated that a model_consisting of the baseline values of the IPQ scale consequences, HADS depression and GCPS pain related disability were the only significant predictors in the model of GCSP pain related disability at 3 month assessment, explaining a total of 34% of its variance ($F(3/86)=15.9$, $R=0.60$, $R^2_{adjusted}=0.34$; see Table 5). Values of the IPQ scale consequence explained 25%, with a further increase in explained variance of 7% and 2% for the HADS subscale depression and GCPS pain intensity at baseline, respectively. A similar regression analysis with 6 month assessment values of GCPS pain related disability as criterion

showed that GCPS pain intensity at baseline was the only significant predictor ($F(1/58)=14.9$, $R=0.45$ $R^2_{adjusted}=0.19$) and explained 19% of variance of pain related disability (see Table 6).

Predictors of Depression (HADS): A model consisting of baseline values of the HADS subscale depression, GCPS pain related disability and IPQ scale timeline predicted depression (HADS) at 3 months assessment, explaining a total of 43% of its variance ($F(3/89)=24.2$, $R=0.67$, $R^2_{adjusted}=0.43$. Baseline values of HADS depression explained 33% with a further increase in explained variance of 6% and 4% for the GCPS pain related disability and IPQ scale timeline at baseline, respectively. At 6 month assessment values of HADS depression were predicted by a model consisting of IPQ scale consequences, IPQ scale personal control and GCPS pain related disability at baseline explaining a total of 43% of its variance ($F(3/55)=15.74$, $R=0.68$, $R^2_{adjusted}=0.43$. Baseline values of IPQ scale consequences explained 29% with a further increase in explained variance of 7% and 7% for baseline IPQ scale personal control and GCPS pain related disability, respectively.

Predictors of Anxiety (HADS): A model consisting of baseline values of the IPQ scale consequences and baseline values of HADS anxiety predicted anxiety (HADS) at 3 months assessment, explaining a total of 25% of its variance ($F(2/90)=16.04$, $R=0.51$, $R^2_{adjusted}=0.25$. Baseline values of IPQ scale consequences explained 17% with a further increase in explained variance of 8% for baseline HADS anxiety values. At 6 month assessment values of HADS anxiety were predicted by a model consisting of IPQ scale consequences and baseline values of HADS anxiety explaining a total of 24% of its variance ($F(2/56)=10.36$, $R=0.52$, $R^2_{adjusted}=0.24$). Baseline values of IPQ scale consequences explained 18% with a further increase in explained variance of 6% for baseline values of HADS anxiety.

Predictors of mental quality of life (MCS-12): HADS depression value at baseline was the only significant predictor ($F(1/91)=7.0$, $R=0.27$ $R^2_{adjusted}=0.06$) explaining

7% of variance of mental quality of life at 3 month assessment. At 6 month assessment mental quality of life was predicted by a model consisting of baseline values of HADS anxiety and causal attributions explaining a total of 13% of its variance ($F(2/57)=5.407$, $R=0.40$, $R^2_{adjusted}=0.13$). HADS anxiety explained 7% with a further increase in explained variance of 6% for baseline causal attributions related to stress.

Table 5 Stepwise multiple regression for predicting pain intensity, pain related disability, mood and mental quality of life at 3-month assessment

Criterion at 3 month assessment	Predictors (all baseline assessment)	Partial correlations	β	T	P	R^2 change
GCPS pain related disability	**Pain intensity**	**.213**	**.204**	2.019	**.047**	**.030**
	Pain related disability	.074	.083	.681	.497	
	IPQ Consequences	**.300**	**.300**	2.921	**.004**	**.250**
	IPQ Emotional representation	-.095	-.098	-.880	.381	
	IPQ Personal control	-.039	-.032	-.362	.718	
	IPQ Chronic timeline	-.037	-.032	-.339	.736	
	IPQ Cyclical timeline	.049	.042	.449	.655	
	IPQ Coherence	-.004	-.003	-.035	.972	
	Causal attribution: Stress	-.055	-.045	-.512	.610	
	HADS Anxiety	-.113	-.130	-1.052	.296	
	HADS Depression	**.281**	**.260**	2.718	**.008**	**.077**
HADS Anxiety	Pain intensity	-.011	-.006	-.102	.919	
	Pain related disability	.142	.158	1.352	.180	
	IPQ Consequences	**.395**	**.372**	4.079	**.000**	**.169**
	IPQ Emot. representation	.146	.158	1.395	.166	
	IPQ Personal control	-.143	-.123	-1.360	.177	
	IPQ Chronic timeline	.038	.034	.355	.723	
	IPQ Cyclical timeline	-.100	-.089	-.950	.345	
	IPQ Coherence	.114	.105	1.080	.283	
	Causal attribution: Stress	.098	.085	.930	.355	
	HADS Anxiety	**.336**	**.309**	3.387	**.001**	**.094**
	HADS Depression	.036	.046	.336	.738	
HADS Depression	Pain intensity	.196	-.041	-.381	.704	
	Pain related disability	**.303**	**.256**	2.998	**.004**	**.071**
	IPQ Consequences	.318	.145	1.526	.131	
	IPQ Emot. representation	.191	.074	.794	.429	
	IPQ Personal control	-.227	-.139	-1.685	.095	
	IPQ Chronic timeline	**. .281**	**.223**	2.762	**.007**	**. 047**
	IPQ Cyclical timeline	-.032	-.074	-.905	.368	
	IPQ Coherence	.007	.049	.599	.551	
	Causal attribution: Stress	-.044	-.635	-.635	.527	
	HADS Anxiety	-.196	-.144	-1.308	.194	
	HADS Depression	**.480**	**.440**	5.166	**.000**	**.330**
Mental quality of health	Pain intensity	-.064	-.066	-.606	.546	
	Pain related disability	-.089	-.092	-.844	.401	
	IPQ Consequences	-.127	-.132	-1.211	.229	
	IPQ Emot. representation	.022	.024	.211	.022	
	IPQ Personal control	-.114	-.111	-1.092	.278	
	IPQ Chronic timeline	-.104	-.102	-.992	.324	
	IPQ Cyclical timeline	-.095	-.094	-.902	.370	
	IPQ Coherence	-.030	-.030	-.289	.773	
	Causal attribution: Stress	-.163	-.157	-1.564	.121	
	HADS Anxiety	.001	.002	.014	.989	
	HADS Depression	**-.267**	**-.267**	-2.643	**.010**	**.071**

Table 6 Stepwise multiple regression for predicting pain intensity, pain related disability, mood and mental quality of life at 6-month assessment

Criterion at 6 month assessment	Predictors (all baseline assessment)	Partial correlations	β	T	P	R^2 change
GCPS Pain related disability	**Pain intensity**	**.452**	**.452**	3.861	**.000**	**.204**
	Pain related disability	-.033	-.041	-.033	.805	
	IPQ Consequences	.160	.168	1.223	.226	
	IPQ Emotional representation	-.112	-.111	-.850	.399	
	IPQ Personal control	-.149	-.134	-1.137	.260	
	IPQ Chronic timeline	-.071	-.067	-.539	-071	
	IPQ Cyclical timeline	.122	.117	.929	.122	
	IPQ Coherence	.043	.039	.328	.744	
	Causal attribution: Stress	.099	.008	.069	.945	
	HADS Anxiety	-.016	-.015	-.124	.902	
	HADS Depression	.000	.000	-.004	.997	
HADS Anxiety	Pain intensity	-.082	-.086	-.613	.543	
	Pain related disability	.076	.074	.564	.575	
	IPQ Consequences	**.428**	**.407**	3.546	**.001**	**.190**
	IPQ Emot. representation	.024	.027	.176	.861	
	IPQ Personal control	-.144	-.125	-1.081	.284	
	IPQ Chronic timeline	-.030	-.030	-.225	.823	
	IPQ Cyclical timeline	-.041	-.038	-.308	.759	
	IPQ Coherence	-.073	-.067	-.542	.590	
	Causal attribution: Stress	.143	.122	1.069	.290	
	HADS Anxiety	**.315** .	**.285**	2.480	**.016**	**.080**
	HADS Depression	-.177	-.253	-1.336	.187	
HADS Depression	Pain intensity	.012	.013	.088	.930	
	Pain related disability	**.385**	**.348**	**3.095**	**.003**	**.089**
	IPQ Consequences	**.361**	**.326**	**2.867**	**.006**	**.292**
	IPQ Emot. representation	.177	.165	1.320	.192	
	IPQ Personal control	**-.365**	**-.289**	**-2.873**	**.006**	**. 081**
	IPQ Chronic timeline	.128	.109	.948	.347	
	IPQ Cyclical timeline	.160	.124	1.188	.240	
	IPQ Coherence	.002	.001	.012	.990	
	Causal attribution: Stress	-.131	-.101	-.971	.336	
	HADS Anxiety	.168	.126	1.254	.215	
	HADS Depression	.222	.185	1.675	.100	
Mental quality of health	Pain intensity	.051	.048	.381	.705	
(MCS-12)	Pain related disability	-.070	-.066	-.522	.604	
	IPQ Consequences	-.174	-.161	-1.323	.191	
	IPQ Emot. representation	-.106	-.101	-.797	.429	
	IPQ Personal control	-.226	-.215	-1.740	.087	
	IPQ Chronic timeline	-.116	-.108	-.873	.386	
	IPQ Cyclical timeline	-.209	-.195	-1.600	.115	
	IPQ Coherence	-.076	-.073	-.572	.570	
	Causal attribution: Stress	**-.283**	**-.270**	-2.224	**.030**	**.073**
	HADS Anxiety	**-.303**	**-.292**	-2.403	**.020**	**.087**
	HADS Depression	.012	.016	.088	.930	

Discussion

The aim of this study was to test the predictive value of subjective illness perceptions as measured by the self-regulation-model on clinical outcomes in a population of patients with chronic orofacial pain over three and six months in the context of other clinical predictors in order to determine the relative contribution of each. Primary outcome variable was pain related disability, secondary outcome was psychological well-being and functioning.

Overall, components of the SRM, as assessed by the IPQ-R, were found to be important predictors of our outcome variables with different subscales having a different impact on different outcome variables. High scores on the IPQ scale consequences predicted higher pain related disability and higher anxiety scores at three month assessment and higher depression and anxiety scores at six months assessment. The belief in a long timeline was predictive for higher depression scores at three month assessment, whereas at six month assessment depression scores were predicted by lower belief in personal control. Stress related causal attributions were predictive for lower mental quality of life at six months assessment. In summary, our results indicate that believing pain could have serious consequences on one's life is one of the most important predictors for treatment outcome. The belief in low personal control and in a chronic timeline as well as causal attributions related to stress were other significant predictors, which however explained a lower amount of variance.

The importance of perceived consequences for treatment outcome has been demonstrated in several other studies on chronic pain patients. For example in patients with rheumatoid arthritis perceived negative consequences of the illness and beliefs in strong illness identity as well as in a long illness timeline together with a passive coping style were associated with poorer outcome on functional abilities. (Scharloo et al., 1998; Sharpe et al., 2001). Foster shows in a very recent study that in patients with low back pain low experienced symptom control,

expectation of a poor outcome and perceived severe consequences on their life predicted disability six months later (Foster et al., 2008).

The IPQ concept of consequences shows similarities to the coping construct catastrophizing, which has been shown to be an important predictor for negative outcome in patients with chronic pain e.g. facial arthromyalgia (Madland et al., 2000), chronic TMD (Turner et al., 2000; Turner et al., 2002; Turner et al., 2005) or chronic low back pain and fibromyalgia (Thorn et al., 2002) rheumatoid arthritis (Beckham et al., 1994). Intervention studies provide strong evidence that improvements in pain related cognitions, particularly improvements in pain catastrophization are associated with outcomes for chronic musculoskeletal pain (Sullivan et al., 2005). Consequently, it has concluded that catastrophizing in particular should be addressed to reduce psychological distress and pain related disability (Turner et al., 2002). This is supported by our finding that both baseline pain related disability and baseline pain intensity were only minor predictors for pain and mood, providing further evidence that severity of chronic pain is determined mainly by psychological variables.

This raises the question about the stability of illness beliefs over time. Leventhal postulates that illness representations change continuously due to new information and personal experiences (Leventhal et al., 1998). Indeed recent studies provided evidence that indeed illness beliefs can be changed and interventions tailored to modify critical beliefs improved treatment outcome (Petrie et al., 2002).

However several studies found converse results and showed that values of the different dimensions of the SRM remained stable over time (Groarke et al., 2005; Sharpe et al., 2001). As our results show changes only in certain (consequences and emotional representation) but not in other (timeline, personal control, illness coherence and time cycle) SRM dimensions, it can be hypothesized that illness perceptions are differently influenceable and change requires support in terms of specific intervention.

Interestingly, personal control was only predictive for depression at six months follow-up but for no other outcome variable. This is in line with a very large study of musculoskeletal pain patients (Hill et al., 2007). The authors argued that it may be important to distinguish between personal control over symptoms or over disease. In addition we propose another possible explanation. Personal control is an important construct in "classic" cognitive-behavioral therapy concepts aiming to enhance patients symptom control and self-efficacy. However recent research on newer CBT concepts like acceptance based or commitment based CBT suggests that one of the most important factors for outcome is not control over pain but the capacity to accept pain, shifting the attention to other aspects of life beside pain (McCracken and Eccleston, 2003; McCracken and Eccleston, 2005). As for causal attributions our results suggest that perceiving physical or emotional stress as possible cause for pain before treatment beginning is not relevant for treatment outcome. These findings are supported by similar results on chronic fatigue patients, suggesting that physical illness attributions are less important in determining outcome than has been previously thought (Deale et al., 1998).

Significant improvement over time was found for all outcome measures, except mental quality of life. With respect to levels of anxiety and depression, our results are in line with results from other studies in patients with chronic orofacial pain (Mongini et al., 2007), supporting the finding that levels of anxiety are elevated in chronic pain patients. Our result that psychological distress did not differ across diagnostic groups contrasts with some studies revealing higher prevalences of both mood and anxiety symptoms in myofascial pain patients than in diagnostic groups with joint related orofacial pain (Auerbach et al., 2001; Dworkin et al.. 2002; Manfredini et al., 2004; Mccreary et al., 1991b). However it is in line with several recent studies providing evidence that chronic pain patients, regardless of the somatic pain cause and localization share similarities in psychological distress and functioning (Nifosi et al., 2007; Reissmann et al., 2008).

The results of this study should be evaluated in the light of the strengths and limitations of the study. A main strength of this study is that data collection was conducted before the first consultation, to ensure the assessment of "naive" personal illness beliefs. Furthermore it was a naturalistic design, providing relevant data for clinical practice. However at the same time this is a weakness because of the impossibility to control for confounding effects such as parallel treatments. As the drop-out rate in our study was 46% the self-selection among participants may have biased our sample. However groups differed only with regard to pain intensity. Although mean pain intensity was only 1 point higher on the VAS in the group with only baseline measurement a possible selection bias towards patients with less intense pain cannot be excluded.

In conclusion, our results suggest that even when controlled for pain and mood, beliefs about pain are important predictors for treatment outcome and need to be considered in the management of patients with chronic orofacial pain. Asking patients about their view of illness can provide essential information about these important predictors and changing dysfunctional pain related beliefs may constitute potential targets for therapy.

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