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Abstract

Dysregulations of the hypothalamus-pituitary-adrenal (HPA) axis, as a physiological substrate of stress, have been observed in patients with different stress-related and chronic pain disorders. In this study, we investigated possible dysregulations of the HPA axis in patients with masticatory muscles pain. In 20 patients with myogenous facial pain and 20 healthy controls, awakening cortisol responses, i.e. cortisol rise in the first hour after awakening, as well as a short circadian free cortisol profile, i.e. four cortisol samples over 12h during the day, were assessed before and after administration of 0.5mg dexamethasone. Results: In comparison to controls, chronic myogenous facial pain patients showed enhanced and prolonged suppression of cortisol after the administration of 0.5mg dexamethasone. Unstimulated cortisol response (before dexamethasone-intake) to awakening and cortisol levels during the day did not differ between the groups. Dysregulation in terms of enhanced negative feedback suppression exists in chronic myogenous facial pain. These results 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.
ENHANCED NEGATIVE FEEDBACK SENSITIVITY OF THE HYPOTHALAMUS-PITUITARY-ADRENAL-AXIS IN CHRONIC MYOGENEUS FACIAL PAIN

Abbreviated running title:
HPA AXIS DYSREGUALTIONS AND FACIAL PAIN

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KEYWORDS: CHRONIC MYOGENEUS FACIAL PAIN, HYPOTHALAMUS-PITUITARY-ADRENAL AXIS, SALIVARY CORTISOL, LOW DOSE DEXAMETHASONE SUPPRESSION TEST
**Introduction**

Chronic facial pain is most often caused by a myoarthropathy (MAP) of the masticatory system in particular by a myogenic 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 myogenic 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 myoarthropatic 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 the 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). Up 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 men, 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 men, 17 female, mean age 37.0) were selected from a pool of healthy, pain-free subjects recruited from an unselected general population and that had been used as controls also 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 never had 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 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 didn’t alter the cortisol response on experimentally induced stress (Kudielka et al., 2008).

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/cm² for extraoral muscles and 5 N/cm² 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 sample 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 response 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 I 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 $\eta^2 = 0.35$ with a power $\geq 0.90$ and $\alpha = 0.05$ (statistical software G-Power (Buchner et al., 1997). For all analyses, the significance level was $\alpha=5\%$. 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 men 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 1). 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 2).
Day 2. In both groups the cortisol levels did neither increase significantly after awakening nor change 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: $AUC_g$ in nmol/time: myogeneous pain patients: 5.41 (1.8), controls: 22.07 (6.4), $F_{1, 39}=10.26$, $p=0.003$, Figure 3).

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 $AUC_g$ 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. Psychosomatic Med, 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: $F_1$,
y=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).
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 W 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 disorders (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 experimental 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. Wingenfeld et al., 2007 and Gaab et al., 2005). 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 matter.

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 an 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 adrenocorticotropic hormone (ACTH).

Some methodological shortcomings must be acknowledged. First: Previous studies has shown that objective compliance with protocol is lower than self-reported compliance especially when sampling period is over several days producing incorrect data particularly in the last sampling days. (Broderick JE, PNEC, 2003). 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.
References


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

<table>
<thead>
<tr>
<th>Questionnaire</th>
<th>Scale</th>
<th>Patients(^1)</th>
<th>Controls(^1)</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>HADS</td>
<td>Depression</td>
<td>4.6 (0.7)</td>
<td>0.8 (0.2)</td>
<td>F=23.1, P&lt;0.000</td>
</tr>
<tr>
<td></td>
<td>Anxiety</td>
<td>9.5 (0.7)</td>
<td>2.1 (0.4)</td>
<td>F=63.7, P=0.000</td>
</tr>
<tr>
<td>FS</td>
<td>Physical Fatigue</td>
<td>4.8 (0.5)</td>
<td>0.8 (0.3)</td>
<td>F=209.0, P&lt;0.000</td>
</tr>
<tr>
<td></td>
<td>Mental Fatigue</td>
<td>1.9 (0.3)</td>
<td>0.2 (0.2)</td>
<td>F=268.0, P&lt;0.000</td>
</tr>
<tr>
<td>VAS day 1</td>
<td>Pain(^2)</td>
<td>37.0 (4.0)</td>
<td>5.9 (3.9)</td>
<td>F=63.8, P&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Sleep Quality(^3)</td>
<td>28.4 (1.9)</td>
<td>5.5 (1.6)</td>
<td>F=79.3, P&lt;0.001</td>
</tr>
<tr>
<td>VAS day 2</td>
<td>Pain(^2)</td>
<td>32.5 (3.9)</td>
<td>5.8 (4.2)</td>
<td>F=51.5, P&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Sleep Quality(^3)</td>
<td>31.2 (1.6)</td>
<td>3.9 (1.3)</td>
<td>F=74.2, P&lt;0.001</td>
</tr>
</tbody>
</table>

\(^1\) mean (SEM), \(^2\) 0-100 (no-worst pain imaginable), \(^3\) 0-100 (good-very bad sleep quality)
FIGURE 1. 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, N=20) and healthy controls (l, N=20).
FIGURE 2. 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, N=20) and healthy controls (l, N=20).
FIGURE 3. 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, N=20) and healthy controls (l, N=20).