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The cortisol response to psychological stress in temporomandibular dysfunction

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Abstract

The salivary cortisol response to psychological stress and its relationship to psychological variables was examined in 36 female temporomandibular dysfunction (TMD) sufferers and 39 female control participants. Saliva samples were taken at baseline, after completion of a modified version of the Trier Social Stress Test, and after rest. Participants also completed a battery of measures, including Visual Analog Scales for measuring pain intensity and disability and a number of established psychological scales. The TMD group showed a significantly higher cortisol response to experimental stress than the control group. Closer examination of the data revealed that the TMD group was heterogeneous and composed of a group that hypersecreted cortisol in response to stress (Hi-SC TMD group) and another group whose cortisol response was not significantly different from the control group (Lo-SC TMD group). The Lo-SC TMD group showed significant negative relationships between cortisol response and self-reported symptoms of both anxiety and depression, plus significantly more use of the Praying or Hoping coping strategy on the Coping Strategies Questionnaire. A dual relationship between TMD symptoms and the stress response is proposed. First, a biological predisposition to TMD is suggested by the stress response in the Hi-SC TMD group. Second, both psychological and biological variables appear to be important factors in those TMD patients who respond to stress with low cortisol secretion. © 1997 International Association for the Study of Pain. Published by Elsevier Science B.V.

Keywords: Temporomandibular dysfunction; Salivary cortical response; Psychological stress

1. Introduction

Biopsychosocial models emphasizing the multifactorial nature of temporomandibular disorders (TMD) and considering the role of cognitive, social, and biological factors in the etiology of TMD have emerged in recent years (Marbach and Lipton, 1987; Rudy et al., 1989; Grzesiak, 1991). Such models recognize that the importance of each of these factors will vary for each individual affected by the disorder. When guided by a biopsychosocial model, the clinician's task is ultimately to identify how much of each factor is involved, and to design appropriate treatment for each individual depending upon this analysis.

Clark (1991) indicated that because the etiology of TMD is multifactorial in nature, and because different proportions of each factor will be operating in each individual, there can be no grand unifying etiologic theory of TMD. He reasoned that TMD likely consists of several diseases. The challenge is to separate and define the different temporomandibular disorders and to identify the specific etiological factors responsible for each one before we can properly treat and prevent TMD. Rudy et al. (1995) questioned the validity of relying primarily on physical variables for diagnosing and designing treatment for TMD. They felt that there are subgroups of TMD patients sharing common physical signs and symptoms who may exhibit differences in psychosocial and behavioral variables. More importantly, they documented differential treatment responses in TMD subgroups that were created using psychosocial and behavioral criteria.

According to biopsychosocial models, future research on TMD etiology should emphasize both physiological and psychological factors and the relationship between them. Clark (1991) drew on a theory by Schwartz (1984) to

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describe stress induced musculoskeletal pain (which includes TMD) as 'psychobiological dysregulation'. According to this theory, our regulatory systems are constantly cycling for the purpose of maintaining homeostasis, aided by various forms of feedback. Schwartz suggested that dysregulation of regulatory systems could occur because of faulty feedback stimuli which might be physiological, psychological, or social. He stressed that each of these stimulus classes can ultimately induce alterations in the central nervous system.

Physiological mechanisms that have been considered in TMD etiology include endocrine and immune system responses to stress and pain. Marbach et al. (1990) studied immune function in a TMD population and controls, finding no differences. In contrast, there is evidence that the endocrine stress response could play a role in TMD etiology, although few unequivocal conclusions can be drawn. Attempts to relate the physiological hypothalamic-pituitary-adrenal (HPA) axis stress response to psychological coping strategies in chronic pain populations have been rare, to date. However, recent research showing that estrogen binding at receptors on the corticotrophin releasing hormone (CRH) gene can increase CRH activity (Vamvakopoulos and Chrousos, 1993), provides a potential link between the HPA response to stress, female sex hormones, and the high proportion of women who seek treatment for TMD.

There have been three previous attempts to link stress and the HPA response in TMD patients. Evaskus and Laskin (1972) measured both catecholamine and 17-hydroxysteroid levels in the urine of myofacial pain patients, showing that they had significantly higher levels of both hormones than control subjects. They concluded that myofacial pain patients were under more emotional stress than the control group. Geissler (1985) measured normal overnight urinary cortisol/creatinine ratios as an operational measure of stress, finding 30% higher levels in TMD patients compared to a control group. However, that study requires replication due to small sample sizes and because the results did not demonstrate a causal relationship between stress and TMD etiology. Hampf et al. (1989) studied both cortisol and β-endorphin levels in chronic orofacial pain patients, but found no correlation between endocrine markers and either pain or mental disturbance. That study also had problems regarding sample size, a heterogeneous pain population, and operational definitions of 'mental disturbance'.

Thus, there appears to be a need to rigorously study the possibility that individual differences in the HPA response to stress could be a potential biological predisposing factor for the presence of TMD symptoms and pain. Although researchers have been interested in using plasma levels of unbound, active cortisol as an index of HPA activity, there are problems associated with blood assays, including complications with venipuncture, reactivity to giving blood samples, and ethical implications (Kirschbaum and Hellhammer, 1989). The ease with which saliva samples can be collected, together with recent developments in biochemical assays, have made salivary cortisol assays a convenient, valid, and reliable alternative for determining the unbound, active cortisol fraction in plasma (Kirschbaum and Hellhammer, 1994).

This study was designed to assess group differences between control participants and a clinical sample seeking treatment for symptoms of TMD. More specifically, we tested three major hypotheses. Firstly, that clinical populations seeking treatment for pain associated with TMD symptoms will show increased cortisol response to an experimental stress situation compared to people in a control population. Secondly, because the perceived inability to exert control over stressful situations is important in activation of the HPA response (Frankenhaeuser, 1986; Henry et al., 1992; Henry, 1993), we predicted that the TMD participants will more likely perceive their health status as being due to external factors than the control participants, whom we expected to view their health with more of an internal locus of control. Similarly, we expected the TMD group to endorse using more maladaptive coping strategies to cope with pain when compared to the control group. Finally, we anticipated that the hypothesized differences between the TMD and control groups in their HPA response to stress will be related to psychosocial factors, such as differences in appraisal of locus of control, strategies used to cope with pain, and measures of somatization and trait positive and negative affect.

2. Method

2.1. Subjects

A TMD group consisting of 36 participants (mean 31.86 years, SD 11.40) was recruited from people seeking treatment for TMD pain through the Faculty of Dentistry at the University of Western Ontario or through the Department of Dentistry at Victoria Hospital, both in London, Ontario, Canada. Since this study was concerned with pain experience rather than specific symptoms, the TMD participants were heterogeneous in regard to TMD symptoms. The criteria for inclusion in the TMD group were that all patients experienced pain upon palpation of their muscles of mastication and all had deviation of the mandible when opening. All TMD patients demonstrated abnormal joint sounds, although these were not a criterion for inclusion in the TMD group. None of the TMD patients presented any signs of osteoarthrosis or osteoarthritis.

A letter of information explaining the general purpose of the study was given to people seeking treatment at these centers, and individual appointments were made for people who were interested in participating. TMD participants were compensated $10.00 for their participation. The control group of 39 participants (mean 22.28 years, SD 6.37) was recruited from the Psychology Department undergrad-

uate subject pool at the University of Western Ontario, Ontario, Canada. Participants in the control group were screened to ensure that they had not received treatment for TMD pain or symptoms within the last 6 months. The control group was, therefore, a community sample which might contain some people with untreated TMD symptoms and pain and some who would report other pain problems.

In an effort to reduce the number of possible interactions between type of stressor, degree of stress, coping styles, and gender of participants, all subjects in this study were female. Controlling for gender also reduced the possibility of confounds due to differing effects of a single experimenter across genders, since the person doing the testing in this study was male. Attempts were made to match participants in the two groups according to age, by trying to recruit volunteers for the control group from mature students in an introductory psychology night class and from upper year dental classes. All participants completed a brief Health Questionnaire. Any person in the third trimester of pregnancy, on prednisone or prednisolone therapy, or having a known diagnosis of Cushing's disease, major depression, hypercortisolism, hypocortisolism, or cardiovascular disease were excluded from the study. All participants in the study refrained from eating or drinking anything besides water for 1 h before testing, and also refrained from smoking, heavy exercise, or brushing or flossing their teeth for the hour prior to testing.

2.2. Experimental stress protocol

A modified form of the Trier Social Stress Test (TSST) (Kirschbaum et al., 1993) was used to induce stress and activate the HPA axis. All participants were tested between 1300 and 1630 h to eliminate the effects of diurnal variation and large morning pulses in cortisol secretion. Upon arriving for their appointment, participants were introduced to the experimenter and asked to complete a brief Health Questionnaire to ensure that they met the requirements for inclusion in the study. They were asked to complete the Positive and Negative Affect Scale (PANAS) (Watson et al., 1988) as a measure of state anxiety then were asked to rate the amount of stress they had experienced that day on a 15 cm Visual Analog Scale (VAS). All participants provided informed consent for participation in the study. Participants were then given instructions for providing saliva samples and were asked to provide the baseline sample (time 0 min).

Immediately after giving the baseline sample, participants were given standardized instructions for the two tasks that they would be required to perform. They were told that they would have to stand in front of a video camera and play the role of a person being interviewed for a job. They were asked to choose a job that would be important for themselves personally, to introduce themselves to the person responsible for hiring, to tell why they would be the best person for the job, and to give as much information about themselves as possible in a 5 min speech. They were told that a panel of psychologists would be watching the video tape and scoring it for signs of anxiety, and were also told that a voice frequency analysis would be done on the audio soundtrack to detect signs of anxiety in their voices.

Participants were told that after their 5 min public speaking task was completed, they would spend the remaining 5 min doing a series of serial subtraction tasks (each lasting 20 s) as quickly and accurately as possible in front of the video camera. They were told that their performance on the subtraction task would be scored according to how far they could subtract without making any errors. Following these instructions, participants were allowed to ask questions to ensure that they were clear about their tasks, then were left alone for 10 min to prepare their 5 min speech. They were given a pencil and paper to help them prepare their speech, but were not allowed to use these notes for their speech. This modified version of the TSST differed from the protocol developed by Kirschbaum et al. (1993), in that participants in this study were required to perform the public speaking and mental arithmetic tasks in front of a video camera and microphone rather than a panel of three live 'experts' who were all strangers to the participants.

Upon completion of the preparation time (time 10 min), the experimenter returned, asked the participant to stand in front of the video camera so that he/she could be seen clearly on the monitor, and then asked him/her to begin. If the speaker finished before the 5 min was complete, a 10 s pause was followed by a standardized response from the experimenter, 'You still have some time left. Please continue'. If subsequent pauses of 10 s or more occurred, participants were given the standardized response, 'You still have some time left. Please think of some more to say about yourself'. After 5 min (time 15 min), the participant was asked to stop speaking and to start the series of serial subtraction tasks. If an error was made, the experimenter said 'stop', and the participant was required to begin that task again from the starting number. Upon completion of the serial subtraction task (time 20 min), each participant was told that the stressful tasks were completed, and that they could rest and complete the questionnaire at their own pace. Before beginning the questionnaire, participants were asked to rate (on separate 15 cm VASs) the amount of anxiety that the public speaking and mental arithmetic tasks caused them. Additional saliva samples were taken at time 30 min and time 50 min, while the PANAS measure of State Negative Affect was completed at time 20 min and time 50 min.

The experimenter displayed a standardized pattern of behavior for each participant. He was very friendly when greeting each participant to minimize apprehension regarding their participation in the experiment. However, between the time that participants were left alone to prepare for their speeches and the time that they completed the stress protocol, it was important for the experimenter to seem more aloof in order to (1) minimize feedback to participants, (2) create an atmosphere that the experimenter controlled the

testing session, and (3) ensure that the participants felt that failure on either of the tasks represented some threat to their ego. Kirschbaum (personal communication, October 1, 1994) felt that these three ingredients are essential to producing reliable HPA activation from an experimental stress protocol. Immediately upon completing the mental arithmetic task, the experimenter once again became as friendly as possible to facilitate the return to baseline levels of cortisol secretion.

After the last saliva sample was taken (time 50 min) and participants completed the questionnaire, they were debriefed about the goals of the study and informed that the video tape record of their tasks would not be scored for anxiety nor would a voice frequency analysis be done. Participants were assured that their taped performance would be erased and not shown to anyone. Both the experimental stress protocol and the questionnaire were approved by the Review Board for Health Sciences Research Involving Human Subjects, and by the Department of Psychology Ethics and Subject Pool Committee.

2.3. Psychometric measures

Participants were administered a battery of established questionnaires and a measure of TMD symptoms used by Schnurr (1988) and Schnurr et al. (1990), selected for their relevance to both TMD and the HPA response to stress.

2.3.1. Health Questionnaire

This questionnaire included items to assure that participants met previously mentioned criteria for inclusion in the study and to ensure that participants followed their instructions for avoiding eating, heavy exercise, smoking, as well as brushing and flossing for 1 h before their appointment. Two questions were also included regarding oral contraceptive use, since there has been conflicting evidence that this could possibly affect the cortisol response to stress (van Poll et al., 1992; Kirschbaum et al., 1995). This variable would be used as a covariate in the statistical analysis of the cortisol response if a significant relationship was shown to exist between oral contraceptive use and the cortisol response.

2.3.2. Ratings of pain intensity and pain-related disability

These variables were measured on 15 cm VASs using seven items from the Research Diagnostic Criteria for Temporomandibular Disorders (RDC) edited by Dworkin and Le Resche (1992). Separate scores ranging from 0 to 100 were calculated for pain intensity and pain-related disability.

2.3.3. The Positive and Negative Affect Scale (PANAS)

This inventory, constructed by Watson et al. (1988), measures the trait dimensions, Positive Affect and Negative Affect. Positive Affect refers to the extent that people feel enthusiastic, alert, and active, while Negative Affect reflects a variety of aversive mood states such as anger, fear, guilt, and nervousness. The questionnaire was also used to measure changes in current emotional state by asking participants to report Negative Affect at time 0, 20, and 50 min.

2.3.4. The Symptom Checklist 90 – Revised (SCL-90R)

The anxiety, depression, and somatization scales from the SCL-90R (De Rogatis, 1983) were included on the questionnaire to measure negative affective dimensions that are commonly associated with the pain experience. Based on the previously mentioned Research Diagnostic Criteria, five pain specific items were dropped from the original Somatization Scale to more precisely measure somatization that is not specifically related to a person's pain disorder.

2.3.5. The Temporomandibular Joint Pain and Dysfunction Index (TMJPDI)

This 11 item inventory developed by Schnurr and colleagues (Schnurr, 1988; Schnurr et al., 1990) was included as a brief self-report measure of TMD symptom severity and chronicity experienced over the last 6 months. Possible scores for pain severity range from 0 to 50.

2.3.6. The Multidimensional Health Locus of Control Scales (MHLC)

These scales were developed by Wallston et al. (1978) to measure the extent that people believe their health is determined by internal factors, powerful others, or by chance. Three scales correspond to the three factors mentioned above.

2.3.7. The Coping Strategies Questionnaire (CSQ)

Rosenstiel and Keefe (1983) designed this questionnaire to assess cognitive and behavioral strategies used to cope with chronic pain. TMD participants were asked to describe how they cope with their ongoing pain, while control participants were asked to relate the questions to typical pain experiences. Six subscales assess cognitive strategies including (1) Diverting Attention, (2) Reinterpreting Pain Sensations, (3) Catastrophizing, (4) Ignoring Sensations, (5) Praying or Hoping, and (6) Coping Self-Statements. Another subscale assesses frequency of behavioral coping strategies. In addition, respondents were asked to report their perceived extent of control over their pain and their ability to decrease their pain on two seven-point rating scales. Factor analysis has generally produced three distinct factors including (1) Cognitive Coping and Suppression, (2) Helplessness, and (3) Diverting Attention and Praying (Rosenstiel and Keefe, 1983; Lawson et al., 1990). In addition to computing scores for the seven cognitive and behavioral subscales, scores for these three factors were also computed for each participant in the study.

2.4. Saliva sampling and biochemical analysis

Three saliva samples were obtained from each participant at baseline (time 0 min), peak secretion (time 30 min), and after 20 min of rest (time 50 min). The peak secretion time had been previously determined by Kirschbaum et al. (1993) and confirmed in a pilot trial of the experimental stress protocol. For each sample, participants were given a fresh piece of peppermint flavored Extra Sugarfree Gum (Wrigley Canada, Toronto, Ontario, Canada) sweetened with Aspartame. This brand of gum had been previously tested by the laboratory doing the biochemical analysis and was not found to affect results of cortisol assays. Participants were asked to remove any lipstick with a tissue to prevent contamination of the saliva sample, then were asked to expectorate approximately 3–4 ml of saliva into a small test tube that was pre-treated with sodium azide to prevent bacterial growth. Samples were covered and allowed to stand at room temperature for 24 h to allow mucins in the saliva to settle. Samples were then stored at −20°C until analysis. After thawing, all samples were assayed in duplicate for cortisol by radioimmunoassay using a commercially available Coat-a-Count kit (Diagnostic Products Corporation, 1993, Los Angeles, CA, USA). Cortisol data presented in this study are the mean value of the duplicate cortisol assays. All samples were processed in a single assay. Sensitivity of the assay was 0.69 nmol, while the intra-assay coefficients of variation were ≤5%.

2.5. Statistical analysis

The statistical analyses proposed for this study were chosen specifically for each of the three major hypotheses mentioned previously. An α-level of 0.05 was used in all statistical tests. First, split-plot analysis of variance (ANOVA) was used to detect any differences between TMD and control groups in cortisol responses to experimental stress over the three repeated salivary cortisol measures. Degrees of freedom were adjusted where appropriate using the Huynh-Feldt approach to correct for violation of the sphericity assumption. A priori t-tests (one-tailed) were used to contrast salivary cortisol means, using a Bonferroni correction to control Type I error rates for individual contrasts.

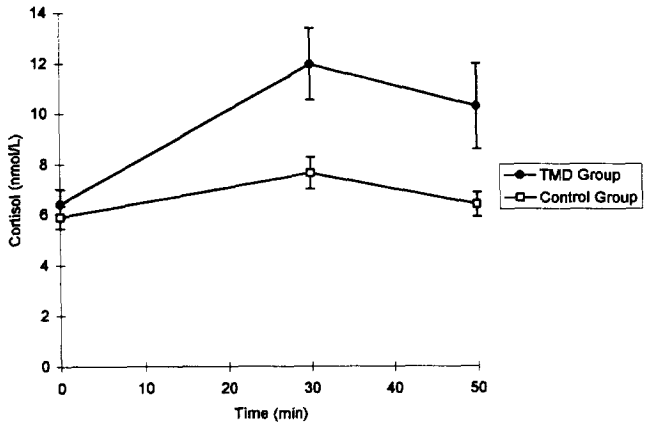

Fig. 1. Salivary cortisol repeated measures ± SE at 0 min (baseline), 30 min (peak), and 50 min (at rest) for TMD and the Control groups.

Table 1
Contrasts of cell means for salivary cortisol split-plot analysis of variance (two groups)

	0 min	30 min	50 min
TMD group (n = 36)	6.41[a,b]	11.96[a,c]	10.28[b,d]
Control group (n = 39)	5.89	7.63[c]	6.39[d]

Superscripts indicate paired contrasts which are significant.
[a,b]$P < 0.005$.
[c,d]$P < 0.05$.

To minimize Type I error while testing the second hypothesis, multivariate analysis of variance (MANOVA) was used to test whether the TMD and control groups differed on any of the psychological measures used in the study (Tabachnick and Fidell, 1989). One-way ANOVA was used to further analyze variables found to vary significantly between groups on the MANOVA, using a Bonferroni adjustment where indicated. For the third hypothesis, generalized multiple regression was used to assess the extent that the CSQ and MHLC scales were related to peak cortisol levels. All of the above statistical analyses were carried out using the SPSS/PC+ statistical package (Norusis and SPSS Inc., 1992).

3. Results

3.1. Cortisol response to stress

Baseline salivary cortisol levels were about 6 nmol/l for both the TMD and control groups before administering the experimental stress. The TMD group showed greatly increased salivary cortisol concentrations to almost 12 nmol/l in response to the stress protocol, with levels remaining high even after 50 min (see Fig. 1). In contrast, the control group showed a small but insignificant cortisol response to the stress protocol.

There was a statistically significant main effect between groups, $F_{(1,73)} = 8.67$, $P < 0.01$, and a significant main effect of salivary cortisol over time, $F_{(2,111)} = 11.22$, $P < 0.01$. More importantly, there was a significant group by time interaction, $F_{(2,111)} = 7.50$, $P < 0.05$. As shown in Table 1, there were no significant differences between the TMD and control cortisol levels at baseline, but values were significantly higher in the TMD group at both 30 and 50 min.

A pilot study of the experimental stress protocol had shown a tendency for some individuals to have elevated cortisol levels across the entire experiment, while other people appeared to have consistently low cortisol values. As a result of this observation, we examined the frequency dis-

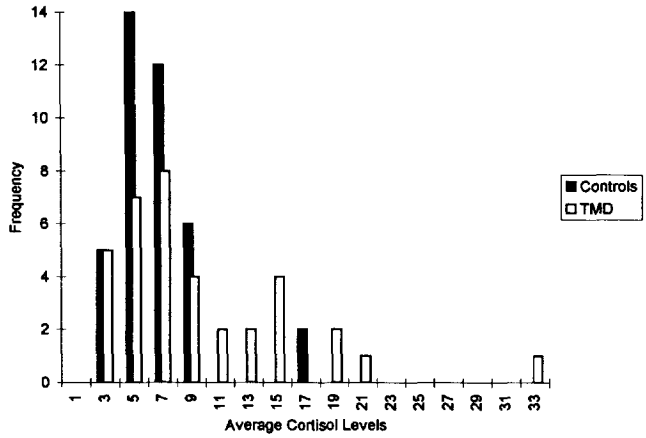

Fig. 2. Frequency distribution for average cortisol levels ((0 + 30 + 50 min)/3), showing a relatively normal distribution for the Control group (n = 39) and a relatively bimodal distribution for the TMD group (n = 36).

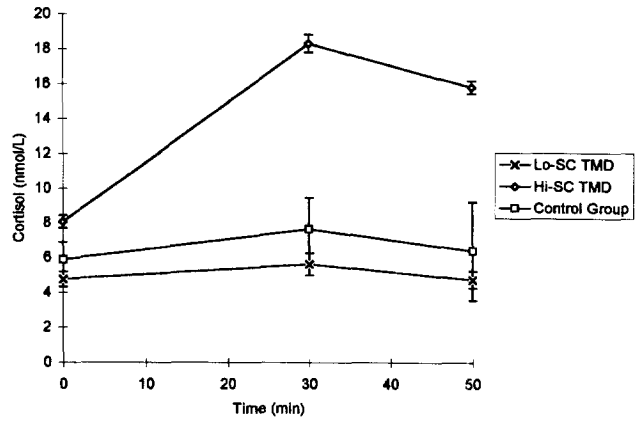

Fig. 3. Salivary cortisol repeated measures ± SE at 0 min (baseline), 30 min (peak), and 50 min (at rest) for Hi-SC TMD, Lo-SC TMD and the Control groups.

tribution of mean cortisol levels ((baseline + 30 + 50 min cortisol values)/3) in the final experiment. The distribution shows one subset of the TMD patients with a distribution of mean cortisol levels similar to that of the control group, and another subset of patients with much higher average cortisol values (see Fig. 2). As well, we noted that there were sizable SDs in cortisol values within the TMD group at both 30 min (SD 8.55) and 50 min (SD 10.18). Consequently, the TMD sample was divided into high and low average cortisol groups by a median split (median 7.68 nmol/l). The previous split-plot analysis was then repeated for the following three groups: (1) the control group, (2) the high salivary cortisol TMD group (Hi-SC TMD), and (3) the low salivary cortisol TMD group (Lo-SC TMD).

Examination of the results of this ANOVA showed that the main effect between the three groups, $F_{(2,72)} = 30.71$, $P < 0.01$, the main effect of cortisol levels over time, $F_{(2,112)} = 13.09$, $P < 0.01$, and the group by time interaction effect, $F_{(4,112)} = 6.51$, $P < 0.01$, were all significant. The baseline cortisol differences were not statistically significant, as shown in Table 2. Mean cortisol levels in the Hi-SC group rose significantly from the baseline level of 8.06 nmol/l in response to the stress protocol, peaking at 18.30 nmol/l after 30 min, then dropping to 15.82 nmol/l after 50 min (see Fig. 3). Both the peak response and the response at 50 min in the Hi-SC group were significantly greater than the corresponding values in the other groups.

Table 2

Contrasts of cell means for salivary cortisol split-plot analysis of variance (three groups)

	0 min	30 min	50 min
Lo-SC TMD group (n = 18)	4.76	5.62^{c}	4.74^{e}
Hi-SC TMD group (n = 18)	$8.06^{a,b}$	$18.30^{a,c,d,g}$	$15.82^{b,e,f,g}$
Control group (n = 39)	5.89	7.63^{d}	6.39^{f}

Superscripts indicate paired contrasts which are significant.
$^{a-f}P < 0.005$.
$^{g}P < 0.01$.

Like the control group, the Lo-SC TMD group showed a small but insignificant rise in peak cortisol in response to the stress protocol. Although it would appear from Fig. 3 that salivary cortisol levels in the Lo-SC TMD group were uniformly lower than those of the control group at 0, 30, and 50 min, Table 2 shows that these differences were not statistically significant. The results suggest that nearly all of the effect in the TMD sample in the first split-plot analysis could be attributable to the Hi-SC TMD group.

Examination of data from the Health Questionnaire revealed that there were eight oral contraceptive (OC) users in the TMD group and 15 OC users in the control group. In order to assess whether the insignificant cortisol response to the stress protocol in the control group could have been due to the larger number of OC users, a separate ANOVA procedure comparing cortisol levels over time between OC users (n = 15) and non-OC users (n = 24) in the control group was performed, showing a significant effect of OC use on mean cortisol levels, $F_{(1,37)} = 4.15$, $P = 0.049$. OC users in the control group had lower cortisol responses to stress at baseline (mean 4.92 vs. mean 6.50), 30 min (mean 5.95 vs. mean 8.69) and 50 min (mean 5.57 vs. mean 6.90) than non-OC users. Only the difference at 30 min was significant ($t = 1.70$, $P < 0.05$). Thus, there is some evidence that OC use may have decreased the overall peak cortisol response in the control group. There was no evidence of a similar effect in the TMD group, $F_{(1,34)} = 0.12$, $P = 0.731$, but the number of OC users was small. An analysis of covariance (ANCOVA), repeating the three-group split-plot cortisol analysis with OC use entered as a covariate, showed no significant effect of OC use on cortisol response for the experiment as a whole ($t = 0.425$, $P = 0.672$).

Despite attempts to match the TMD and control groups according to age, the mean age of the control TMD group (mean 31.86) was still almost 10 years older than the control group (mean 22.28), $F_{(1,73)} = 20.56$, $P < 0.0001$. Within the TMD sample, there was no significant difference (t = 1.603,

Table 3

Contrasts of cell means for State Negative Affect (SNA) by groups (2) split-plot analysis

	0 min	20 min	50 min
TMD group (n = 36)	42.500[a]	49.250[a,b]	41.472[b]
Control group (n = 39)	44.211[c,d]	48.737[c,e]	39.500[d,e]

Superscripts indicate paired contrasts which are significant.
[a–e]$P < 0.005$.

$P > 0.05$) between the mean age of the high cortisol secretors (mean 34.2) and that of the low secretors (mean 29.4). When a cortisol by three-group ANCOVA was done using age as the covariate, there was no significant effect of age on the cortisol response ($t = 0.286$, $P = 0.776$). Thus, the data do not provide evidence that age had any direct effect on group differences in cortisol response in this study.

3.2. Psychological variables

No significant differences on VAS reports were found between TMD and control groups for the amount of stress which participants had experienced before arriving for the experiment. There were also no group differences in the degree of stress reported while performing either the public speaking and mental arithmetic tasks. A similar result was obtained after the TMD group was divided into Lo-SC and Hi-SC TMD groups.

Changes in state Negative Affect on the PANAS scale across the experiment were also examined using split-plot ANOVA. The analysis showed a significant effect of Negative Affect over time, $F_{(2,137)} = 51.13$, $P < 0.01$, but no significant effect of Negative Affect between groups $F_{(1,72)} = 0.02$, $P > 0.05$ and no significant Negative Affect by group interaction $F_{(2,137)} = 2.53$, $P > 0.05$. A priori contrasts of specific cell means indicated that the experimental stress protocol resulted in significantly increased State Negative Affect in both groups after 20 min, returning to baseline or lower levels after 50 min (see Table 3). No significant differences in State Negative Affect between groups were found after the TMD group was divided into low and high cortisol secretors, $F_{(2,71)} = 0.18$, $P > 0.05$.

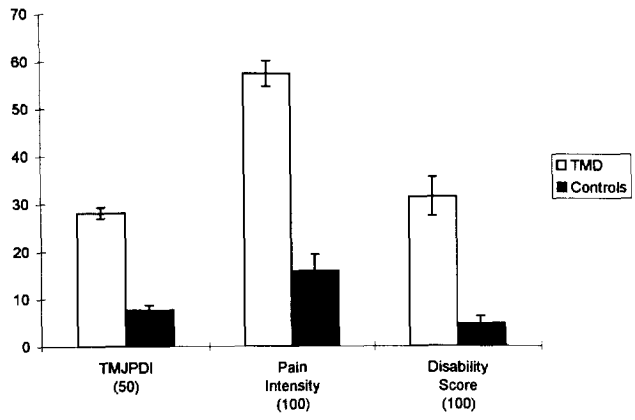

Fig. 4. Means ± SE for variables related to pain experience for both TMD and the Control groups. All differences significant at $P < 0.005$. Maximum values are indicated in parentheses.

Table 4

Mean scores and significant contrasts for psychological variables

Measure (maximum score)	Control TMD	Hi-SC TMD	Lo-SC TMD
Stress today (15)	5.69	4.28	4.46	4.10
Speaking stress (15)	10.40	9.33	8.44	10.22
Arithmetic stress (15)	10.80	11.24	11.21	11.26
CSQ scales				
Diverting attention (36)	10.41	13.64	14.28	13.00
Reinterpreting pain sensations (36)	6.34	6.89	8.94	4.83
Catastrophizing (36)	9.69	10.64	9.06	12.22
Ignoring pain sensations (36)	16.13	16.00	16.72	15.28
Praying or hoping (36)	10.11[a]	13.19	9.39[b]	17.00[a,b]
Coping self-statements (36)	19.60	22.39	21.72	23.06
Behavioral coping strategies (36)	13.48	16.54	16.83	16.24
Anxiety (SCL-90R) (40)	8.23	9.58	9.72	9.44
Depression (SCL-90R) (52)	15.46	16.94	15.83	18.06
Somatization (SCL-90R) (28)	3.95	5.97	4.22	7.72
MHLC scales				
ILC (36)	26.74[c,d]	23.50[c]	23.94	23.00[d]
PLC (36)	15.00	16.29	14.50	18.31
CLC (36)	16.10	16.56	16.33	16.81
Negative affect (PANAS) (50)	21.64	21.08	21.33	20.83
Positive affect (PANAS) (50)	29.95	30.39	31.28	29.50

Superscripts indicate paired contrasts which are significant after Bonferroni correction.
[a,b]$P < 0.01$.
[c,d]$P < 0.005$.

As expected, mean scores were significantly higher for the TMD group than the control participants on the TMJPDI and for measures of pain intensity and pain disability ($P < 0.005$) (see Fig. 4). The TMD patients also had, as anticipated, higher median Pain Chronicity scores (median 5.0) than the control participants (median 0.0), as measured on an ordinal scale ranging from zero to seven ($\chi^2 = 28.8005$, $P = 0.0000$). A score of five on this scale corresponded to pain duration of 1–2 years, while a score of zero corresponded to no current experience of pain. The only difference observed between the Lo-SC TMD and Hi-SC TMD groups on these variables (keeping in mind an α-level of 0.01 after the Bonferroni adjustment), was a near significant trend ($P \approx 0.04$) for the Lo-SC TMD group to report more pain disability (mean 37.09) than the Hi-SC TMD group (mean 25.94).

A significantly higher Internal Locus of Control (ILC) score was found in the control group (mean 26.74) compared to the TMD group (mean 23.50), $F_{(1,71)} = 9.38$, $P < 0.005$. After dividing the TMD patients into Hi-SC and Lo-SC groups, the control group ILC scores remained significantly higher than the Lo-SC TMD group (mean 23.00), $t_{(70)} = 2.78$, $P < 0.01$, but not the Hi-SC group (mean 23.94), $t_{(70)} = 2.17$, $P > 0.01$. There was no significant difference between the Hi-SC and Lo-SC group means on the ILC subscale.

In contrast, no significant group differences were found

when scores for the seven CSQ coping scales or the three CSQ coping factors were compared. However, when the TMD group was divided into Hi-SC and Lo-SC groups, the Lo-SC TMD group reported using the Praying or Hoping strategy significantly more (mean 17.00) than both the Hi-SC TMD (mean 9.39), $t_{(72)} = 2.91$, $P < 0.01$ or control group (mean 10.11), $t_{(72)} = 3.08$, $P < 0.01$.

No significant group differences between the TMD and control groups were found on scales measuring trait Negative Affect, Positive Affect, or SCL-90R Depression, Anxiety, and modified Somatization scales. A similar lack of significance was observed after dividing the TMD group into Hi-SC and Lo-SC groups. See Table 4 for a summary of group means and significant contrasts for the psychological variables.

3.3. Relationships between cortisol and psychological variables

Four different multiple regression analyses were performed for both the TMD and control groups to test whether peak cortisol levels measured at 30 min could be predicted from scores on the seven CSQ scales, the three CSQ factor scores, the three MHLC scales, the amount of stress reported today, or the public speaking or mental arithmetic tasks. No significant prediction of cortisol response to stress by either CSQ scales or factor scores was detected for either the TMD group or control group, even after the TMD group was split into Hi-SC and Lo-SC TMD groups. Similarly, no significant prediction of cortisol response in either group was detected from the MHLC scales. Contrary to what was expected, there was also no significant prediction of peak cortisol response in either group from the amount of stress reported for the day of testing or from self-reported anxiety arising from the public speaking and mental arithmetic tasks. This result was unexpected, since the physiological response to the stressful tasks was expected to be highly related to the anxiety that was subjectively reported from the tasks.

After viewing the descriptive statistics for cortisol response in this experiment, which suggested that the TMD group was not homogeneous, and after observing that the cortisol response in the Lo-SC TMD group was indistinguishable from that in the control group, an analysis was conducted to test differential hypotheses based on the work of Hubert and de Jong-Meyer (1992) and van Eck and Nicolson (1994). The latter study, which demonstrated a low, positive correlation between trait anxiety and cortisol levels in a community sample during a normal work week, led us to predict that peak cortisol levels in our control sample would show a similar relationship with the SCL-90R Anxiety and Depression scale scores. In contrast, Hubert and de Jong-Meyer noted lower than expected cortisol responses in more highly anxious subjects, suggesting that cortisol secretion may be attenuated in people whose anxiety states are more chronic. This led us to hypothesize that we would find a negative relationship between peak cortisol levels and Anxiety and Depression scale scores in our low cortisol secreting TMD patients.

As predicted, our control group showed a weak, but positive, one-tailed relationship ($r = 0.28$, $P = 0.04$) between peak cortisol and Anxiety, and also a positive but non-significant one-tailed correlation between peak cortisol and Depression ($r = 0.15$, $P = 0.176$). Our Lo-SC TMD group showed the expected negative relationship between peak cortisol and both Anxiety ($r = -0.41$, $P = 0.04$) and Depression ($r = -0.45$, $P = 0.03$). The Hi-SC TMD group showed virtually no relationship between peak cortisol and either Anxiety or Depression.

The differences between these correlations in the control and Lo-SC TMD groups were significant for both Anxiety ($z = 2.35$, $P = 0.018$) and Depression ($z = 2.07$, $P = 0.036$). Thus, although ANOVA analyses failed to show any significant differences between the three group means on Anxiety or Depression, and revealed no significant difference in cortisol response between the control and Lo-SC TMD groups, our data support the predictions of van Eck and Nicolson and of Hubert and de Jong-Meyer. These results suggest that there may be important differences between the control and Lo-SC TMD groups in the relationship that exists between emotional state and the endogenous cortisol response to psychological stress.

4. Discussion

4.1. The cortisol response to stress

The data from this study suggest that there may be two subgroups among the TMD patients. The Hi-SC TMD group hypersecreted cortisol in response to stress, yet the results showed that these patients are psychologically indistinguishable from the normal controls. Hypercortisolism in the Hi-SC TMD group could possibly reflect a biological dysfunction which creates a predisposition for disorders such as TMD. Alternatively, physical and psychological factors associated with TMD could lead to increased cortisol response to stress in some patients.

Finding a subgroup of TMD patients demonstrating a low cortisol response was unexpected. The cortisol response in this group appears, at first glance, to be similar to that of the control participants. However, our discussion will suggest that the low cortisol response in the Lo-SC TMD group, and its close inverse relationship with self-reported anxiety and depression, could indicate that the links between biological and psychological factors are different for these patients.

As noted previously, the control group did not show a significant change in cortisol levels following the stress protocol. The modified version of the TSST used in this study may not have been stressful enough to induce a significant cortisol response in a normal population. In contrast, the Hi-SC TMD group may have been so susceptible

to stressful stimuli that even a moderate stressor was sufficient to induce significant cortisol secretion. The lack of a significant stress response in the control group leaves some uncertainty as to whether the Lo-SC TMD group hyposecreted cortisol or simply responded in a manner similar to the control participants. However, the literature indicates that hyposecretion of cortisol can occur in other pain disorders which are, in many aspects, similar to TMD.

Recent studies have shown that individuals suffering from fibromyalgia show much lower than expected levels of cortisol in response to physical and biochemical challenge (Griep et al., 1993; Crofford et al., 1994). Griep and coworkers, using physical exercise to increase cortisol secretion, showed an exaggerated pituitary ACTH response from fibromyalgia patients but no significant difference in cortisol response between them and a control group. Crofford and coworkers also noted a decreased cortisol response to CRH challenge in fibromyalgia patients, despite a normal ACTH response.

There may be similarities between the neuroendocrine factors responsible for low cortisol secretion in our Lo-SC TMD group and fibromyalgia patients. Griep et al. hypothesized a number of possible mechanisms for cortisol hyposecretion in fibromyalgia, including abnormalities involving serotonin, growth hormone, endogenous opiates, GC feedback action and adrenocortical function. If the Lo-SC TMD group was demonstrating upregulation Crofford and coworkers suggested that their results indicate adrenal hyporesponsiveness in fibromyalgia patients. Other factors with demonstrated links to glucocorticoid response include long-term treatment with tricyclic antidepressants (Przegalinski and Budziszewska, 1993; Reul et al., 1993) and the action of estrogens (Desjardins et al., 1990; Ferrini and De Nicola, 1991). The latter relationship is particularly interesting given a report showing that women receiving postmenopausal hormone replacement therapy in the form of estrogens, were 77% more likely to have sought treatment for TMD than women not receiving hormone replacements (Le Resche et al., 1994).

Consequently, it may not be paradoxical to find both increases and decreases in cortisol levels in pain patients. Failure to maintain a homeostatic balance of cortisol levels could result from a number of mechanisms. Hypercortisolism has been shown to result from downregulation of glucocorticoid (GC) receptors at regulatory sites (Sapolsky and Plotsky, 1990; Arai and Chrousos, 1994), while decreased cortisol secretion can be associated with upregulation of GC receptors (Reul et al., 1993). Homeostatic regulation is further complicated by the close relationship between cortisol and the endorphins, since a number of researchers have demonstrated that cortisol and β-endorphin are responsive to feedback regulation by the other (Bacigalupo et al., 1990; Martín-del-Campo et al., 1992; McCubbin et al., 1993). Consequently, it may be that failure of cortisol feedback regulation could result from downregulation or upregulation of either GC or opioid receptors. This is especially relevant to chronic pain disorders, since Gescuk et al. (1995) demonstrated that chronic exposure to pain can lead to opioid receptor downregulation and tolerance to opioids.

4.2. Psychological variables

As hypothesized, the total TMD group reported feeling less Internal Locus of Control over their health compared to the control group. No significant mean differences between the TMD and control groups were found in the use of cognitive coping strategies as measured by the CSQ, or on any other of the psychological variables measured in the study. Only after the TMD group was split into the Hi-SC and Lo-SC groups, was it found that the Lo-SC group reported a significantly higher mean score on the CSQ's Praying and Hoping scale.

The MANOVA analyses served not only to examine differences in coping strategies and locus of control between the control and TMD groups, but also served as a validity check to ensure that the two groups were sufficiently different where expected and sufficiently alike where appropriate. As was anticipated from a group suffering from chronic pain, the TMD group had markedly higher scores for TMD symptom reporting, pain intensity, pain chronicity, and disability related to their pain.

There was no difference in the amount of stress experienced by members of the TMD and control groups before arriving at the experiment. Interestingly, there were also no significant group differences in the amount of anxiety related to the public speaking and mental arithmetic tasks. As well, both groups showed similar increases in State Negative Affect on the PANAS scale in response to the stressors after 20 min. Thus, the self-reported psychological data seem to suggest few differences between the entire TMD group and the control participants, in contrast to the striking biochemical differences.

The data from this study lend support to previous findings showing that the relationship between psychological factors and cortisol response can vary in different populations, and that there are large interindividual variations in cortisol response within apparently homogeneous groups. Cacioppo et al. (1995) observed physiological responses to stressors in a group of 22 older women, finding no significant group cortisol response to math and speech stressors, much like our control and Lo-SC TMD groups. However, they demonstrated that individual variations in cortisol response within the group were significantly related to cardiac sympathetic activation in these women. Within our control group, we predicted the weak positive relationship between anxiety scale scores and cortisol levels from the van Eck and Nicolson (1994) observation that mild or intermittent stress will have a tendency to increase cortisol secretion slightly in a normal population.

Within our Lo-SC TMD group, however, the data showed a significant negative correlation between peak cortisol and anxiety. These findings are in agreement with the relation-

ship between cortisol levels and anxiety observed in people suffering from Post Traumatic Stress Disorder and disorders such as recurrent abdominal pain in children, which are often labeled pejoratively as 'stress induced diseases' (de la Torre, 1994). Hubert and de Jong-Meyer (1992) theorized that in populations where anxiety is severe and prolonged, chronic downregulation of GC receptors may eventually result in an inability of the adrenal gland to respond adaptively with an adequate cortisol response to acute stressors.

As mentioned previously, the Lo-SC TMD patients appear to be rather interesting from a psychological perspective. In addition to showing a negative relationship between peak cortisol levels and their anxiety and depression scores, the Lo-SC TMD group reported using the Praying and Hoping coping strategy more than the Hi-SC TMD or control groups, a coping strategy often considered to be maladaptive. They also showed a trend to report more disability from their pain than did the Hi-SC TMD group.

The response pattern of the Lo-SC TMD group suggests three possible interpretations. First, the stress created by their disorder could have led to biological changes which diminished their ability to mount an adaptive cortisol response to chronic psychological stressors. Alternatively, perhaps earlier psychological stressors in their lives led to biological changes which placed them at greater risk for developing TMD or certain other disorders including fibromyalgia, Irritable Bowel Syndrome, ulcerative colitis, or recurrent abdominal pain. If so, our Hi-SC TMD group's pattern of cortisol hypersecretion could eventually lead to adrenal insufficiency and a pattern of low cortisol secretion resembling that of the Lo-SC TMD group. Finally, low secreting TMD patients may now respond to psychological challenge in a manner similar to that shown by the control participants but, over time, may become cortisol hypersecretors like patients in the Hi-SC TMD group.

4.3. Overview

This study has shown, initially, that a group of people seeking treatment for relief of TMD pain responded to an experimental stress protocol with higher levels of cortisol than a control group. The TMD group was composed of at least two subgroups that may react to stress with strikingly different response patterns. We suggest that downregulation of the GC or endogenous opiate feedback systems could be the basis of a biological tendency to hypersecrete cortisol in the Hi-SC TMD group. No relationship was found between psychological factors and hypersecretion of cortisol in the Hi-SC TMD group.

The cortisol response in the Lo-SC TMD group is similar to that seen in individuals suffering from disorders that have been linked to stress. Lower cortisol responses in this group could reflect the action of chronic psychological distress, possibly affecting upregulation of GC or opiate receptors or affecting the ability of the adrenal cortex to sustain continued cortisol secretion. We are not able to conclude from our results whether chronic psychological distress is a predisposing factor for their pain disorder or whether this group may respond to having TMD with a lower cortisol response.

There were age differences between the TMD and control groups despite efforts to minimize that discrepancy. However, previous research suggests that this is not the cause of the higher peak cortisol response in the TMD patients. Bohnen et al. (1990), studying cortisol reactivity to mental tasks, found no significant age effect on salivary cortisol levels. Brändstadter et al. (1991) observed no increase with age in unstimulated morning salivary cortisol levels in more than 700 adults, aged 35–65 years. Pollard et al. (1992) found no significant correlation between age and cortisol levels during daily activities in a community sample. Analysis of data from the present study also showed no significant direct effect of age on the differences in cortisol response between the two groups. Thus, if age had any systematic effects on cortisol response in this experiment, they would be indirect effects due to other age-related intervening variables such as differences in parity, menstrual status, or OC use between the two groups.

ANOVA results suggest that OC use in the control group may have attenuated their cortisol response, thus agreeing with preliminary evidence from Kirschbaum et al. (1995). This may have contributed to our inability to distinguish whether the cortisol response in the Lo-SC TMD group differed from that of the control group, and may also have widened differences between the Hi-SC TMD and control groups.

Another variable that could have been age related, or may have varied systematically within the two groups, is a difference in medication usage. For instance, while our experiment screened potential participants to exclude persons being treated for major depression, we did not restrict use of tricyclic antidepressants or any other medications besides those used as exclusionary criteria for the study. TMD participants could have been receiving more medications than the control group. Since prolonged use of antidepressants could potentially decrease cortisol activity, lack of documentation of medication usage is a limitation of our study that should be addressed in future research.

A number of other directions for further research are also suggested. It would be informative to measure plasma levels of β-endorphin as well as cortisol, as done by Hampf et al. (1989). This would help to differentiate between dysregulation of the GC and opiate feedback systems as possible factors in this chronic pain population. It would also be helpful to measure ACTH production in response to stress (Griep et al., 1993), to aid in determining where dysregulation may be occurring in the HPA response. It would, as well, be useful to include other chronic pain populations in future research to examine their biological and psychological responses to stress. Finally, further research should be conducted to determine in what ways the low cortisol response to stress observed in a subset of TMD patients

differs from the cortisol response in normal control populations, and whether the response patterns seen in either patient group are stable or, alternatively, are significantly altered over time.

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