



Research papers

Depression increases onset of tension-type headache following laboratory stress

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Abstract

The aim of this study is to examine the influence of depression on headache onset following laboratory stress and on psychophysiological variables associated with tension-type headaches (TTHs). Diagnostic interviews identified three groups: headache prone and depressed (HP/D, $N = 13$); headache prone not depressed (HP/ND, $N = 22$); and healthy controls (HC, $N = 13$). Ss completed a laboratory stress task. Blind evaluations of pericranial muscle tenderness (PMT) and pressure pain thresholds (PPT) were obtained immediately before, immediately after and 24 h post-task. Ss also recorded headaches (HA) before, during, immediately post-task and for 24 h post-task. HP/D Ss were more likely than HP/ND Ss or HC Ss to report a headache during and immediately following the stress task ($P < 0.05$). HP/D Ss exhibited higher PMT than HP/ND Ss or HC Ss before and following the stress task ($P < 0.05$). HP/D Ss exhibited lower finger PPT at all assessments and lower temporalis PPT at two of three assessments than HC Ss ($P < 0.05$) but did not significantly differ from HP/ND Ss at most assessments. Depression increased vulnerability to TTH following laboratory stress and was associated with elevated PMT. In individuals with frequent headaches, depression may aggravate existing central sensitization increasing vulnerability to TTHs.

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1. Introduction

Research establishing the relationship between recurrent headache disorders and depression has focused almost exclusively on migraine (Breslau et al., 1994a,b; Merikangas and Rasmussen, 2000). Epidemiological studies have revealed that migraine and depression are associated and that the relationship is bi-directional: individuals who are depressed are at increased risk for developing migraine and individuals with migraine are at increased risk for developing depression (Breslau et al., 1994a, 2000, 2003; Pine et al., 1996). This has led investigators to postulate that shared mechanisms may underlie both disorders (Breslau et al., 1994a).

Less information is available concerning the relationship between depression and tension-type headache (TTH). Depression is central to some clinical formulations of TTH but remains controversial as an etiological or risk factor in TTH (Diamond and Dalessio, 1992; Lance, 1993;

Penzien et al., 1993; Schoenen and Wang, 1997). Depression is highly prevalent in chronic TTH sufferers seen in clinical settings (Goncalves and Monteiro, 1993; Guidetti et al., 1998; Holroyd et al., 2000; Puca et al., 1999), but selection factors are likely operating to overestimate comorbidity (Ziegler and Paolo, 1995). Epidemiological findings suggest that the mere diagnosis of TTH is not associated with depression (Merikangas, 1994; Merikangas et al., 1993; Wang et al., 1999), possibly because occasional TTHs are both ubiquitous and clinically insignificant (International Headache Society, 2004). However, these findings do not generalize to chronic TTH, which by definition occurs 15 or more days per month (International Headache Society, 2004). The one epidemiological study to examine the relationship between chronic TTH and depression found an elevated prevalence of depression in chronic TTH (Wang et al., 1999). Additional support for the association between depression and TTH comes from studies of individuals with major depressive disorder who show elevated levels of pain complaints including TTH (Magni et al., 1994; Romano and Turner, 1985; Von Korff and Simon, 1996; Waxman et al., 1985).

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We asked whether the presence of depression and/or a significant history of TTHs influenced the risk of experiencing TTHs during and following a laboratory stress task. Stress is the most common precipitant of TTH identified by patients (Rasmussen, 1993) and prolonged laboratory stressors may elicit headaches in susceptible individuals (Hovanitz et al., 1999, 2002). We thus reasoned that if depression increases vulnerability to TTHs, depressed individuals would be more vulnerable than similar euthymic individuals to TTHs induced by laboratory stress. We also assessed pericranial muscle tenderness (PMT), cephalic pressure pain thresholds (PPT) and peripheral PPTs. We wished both to replicate previous findings of psychophysiological abnormalities in TTH (Bendtsen et al., 1996a; Hatch et al., 1992; Jensen, 1995; Jensen et al., 1993; Langemark and Olesen, 1987; Lipchik et al., 1996, 1997, 2000; Lous and Olesen, 1982; Schoenen et al., 1991) and to determine if similar abnormalities might be present in clinical depression.

2. Method

2.1. Participants

Forty-eight females were recruited in a two-stage screening of 1192 college students enrolled in undergraduate psychology courses. In an effort to eliminate confounding gender differences on physiological measures, only female subjects were recruited. Previous research has found females demonstrate significantly greater pain sensitivity compared to males in their perception of noxious experimental stimuli (Fillingim and Maixner, 1995; Riley et al., 1998) and in particular in their sensitivity to pressure pain (Chesterton et al., 2003). TTHs are also more prevalent in females than in males.

Headache prone (HP) participants were required to meet International Headache Society (2004) diagnostic criteria for frequent episodic TTH and to experience at least eight TTHs per month. Depressed participants were required to meet DSM-IV (American Psychiatric Association, 1994) diagnostic criteria for major or minor depression as assessed by the Primary Care Evaluation of Mental Disorders structured interview (PrimeMD; Spitzer et al., 1994) and to score above 12 on the Beck Depression Inventory II (BDI; Beck et al., 1996). Non-depressed individuals were required to score below 5 on the BDI and could not receive a mood disorder diagnosis on the PrimeMD. We attempted to recruit participants for the four groups formed by crossing the factors of headache prone–headache free and depressed–not depressed but failed to identify any female who met our criteria for depression and also reported experiencing fewer than 12 headaches per year (our criteria for headache ‘free’). Thus, we were unable to form a fourth group of headache-free but depressed participants.

Table 1
Participant characteristics for all three groups

	HP/D* (N = 13)	HP/ND (N = 22)	HC (N = 13)
Age	18.62	18.50	18.31
<i>Headache characteristics</i>			
Frequency (per month)	13.38 (4.57)	12.40 (6.02)	–
Mean intensity (1–10 scale)	5.58 (1.46)	5.36 (1.43)	–
Duration untreated (h)	7.69 (16.11)	5.53 (4.27)	–
Chronicity (years)	3.32 (2.70)	4.30 (2.77)	–
<i>Psychological tests</i>			
Beck Depression Inventory	21.08 (7.97)*	4.55 (2.54)	5.54 (2.57)
Trait Anxiety Scale	54.31 (11.83)*	36.55 (7.08)	34.15 (8.50)
<i>Prime MD diagnosis (number/total)</i>			
Major depression ^a	12/13*	0/22	0/13
Anxiety disorder ^b	11/13*	1/22	0/13

HP, headache prone; D, depressed; ND, non-depressed. *Significantly different from headache prone/non-depressed and healthy control.

^a One participant was diagnosed with minor depression.

^b Anxiety disorders assessed by the prime MD include panic disorder, generalized anxiety disorder and anxiety disorder NOS.

Age, headache and psychological symptom characteristics for the three remaining groups are presented in Table 1, with the headache-free/non-depressed group designated as health controls (HC).

2.2. Screening process

In the first screening stage, questionnaires were completed by 1192 undergraduate psychology students in order to assess symptoms of both headache and depression. A modified version of Lipchick et al.’s (1996) Headache Screening Questionnaire was used to identify students who reported symptoms of TTHs and experienced at least eight headaches per month (headache prone) and participants reporting fewer than 12 non-problem headaches per year (headache free). The Beck Depression Inventory II (BDI; Beck et al., 1996) was administered to screen for symptoms of depression. Females who scored above 12 or below 5 on the BDI and met the above criteria for headache prone or headache free were contacted to participate in the study.

In the second screening stage, approximately 150 individuals who met the above criteria at the first screening stage were scheduled for a diagnostic evaluation. Headaches were evaluated with a modified version of the Structured Diagnostic Interview for Headache, Brief Version as described in previous studies from our lab (Lipchik et al., 1996, 1997; Neufeld et al., 2000), and psychiatric disorders were evaluated with the PrimeMD diagnostic interview (Spitzer et al., 1994). Participants also completed psychological and psychophysiological assessments. Participants were excluded if they experienced more than one migraine per month, a headache disorder other than TTH (e.g. cluster headache, analgesic overuse headache), a concurrent pain

disorder (e.g. a temporal mandibular joint or occlusional disorder), reported any significant health problem, or used prescription pain, psychiatric or analgesic medication. Using the above inclusion/exclusion criteria, the following three groups were formed: headache prone/depressed ($N = 13$); headache prone/non-depressed ($N = 22$); and healthy control ($N = 13$).

2.3. Psychological measures

The Beck Depression Inventory II (Beck et al., 1996) was used to assess the symptoms and severity of depression and the State Trait Anxiety Inventory to assess symptoms of anxiety (STAI; Spielberger et al., 1970). A modified version of the Subjective Ratings Scales (SRS; Thackray et al., 1977), a self-report measure of acute emotion, was used to assess stress symptoms experienced prior to, during and immediately following the experimental stress task. The SRS has been used in other studies of stress and headaches (Hovanitz et al., 1999). The SRS is comprised of six items assessing attention, energy, strain, interest, irritation and stress that are rated on 9-point scales ranging from 1 (corresponding with the most negative rating of a particular item, i.e. extremely stressed) to 9 (corresponding to the most positive rating of a particular item, i.e. free of stress). The sum of three items (the participant's report of stress, strain and irritation) provided our measure of subjective stress.

2.4. Psychophysiological measures

Physiological assessments were conducted by one of two female experimenters who were blind to both the participant's headache and depression status. Both experimenters were trained to agreement by the same experienced neurologist. The same experimenter assessed a participant at each time point. Psychophysiological measurements were assessed when participants were in a headache-free state.

2.4.1. Pericranial muscle tenderness

Pericranial muscle tenderness was assessed by manual palpation following Langemark and Olesen (1987) and modified to include the use of a fingertip palpometer (Dolorimeter Systems Inc, Victoria, BC). This procedure is described in previous studies from our lab (e.g. Lipchik et al., 2000). Five pericranial muscles (temporalis, masseter, suboccipital, posterior cervical, middle trapezius) were palpated bilaterally with a fingertip pressure of 500 g/cm². Participants were asked to report tenderness for each palpation site and the assessors rated the participant's responses on a scale from 0 to 3 as follows: 0, no report of tenderness; 1, report of mild pain and no withdrawal response; 2, report of moderate pain and slight withdrawal response; and 3, report of severe pain and vigorous withdrawal response (Hatch et al., 1992; Langemark and Olesen, 1987). The sum of the ratings (total tenderness score: TTS) for the 10 sites was used as the PMT score for

each assessment giving the TTS a range of 0–30. Previous research has found this total tenderness score to be reliable (Bendtsen et al., 1995).

2.4.2. Pressure pain thresholds

Pressure pain thresholds were measured at two points—the left anterior temporalis and the left middle digit—using a hand-held pain threshold meter (Pain Diagnostics and Thermography, Great Neck, NY). This device consists of a spring-loaded dial that registers pressure applied to the 1 cm² rubber tip of the instrument as it is pressed into the tissue. Such a device is commonly used in muscle pain assessments (Fischer, 1993). The body of the anterior temporalis was located by palpation and pressure was applied and increased at a constant rate of about 0.5 kg/s. (Langemark and Olesen, 1987). Pressure was applied to the medial fat pad of the left middle digit in a similar manner. Participants were asked to indicate when the pressure first became painful. Pressure was immediately released when participants verbally indicated pain. The maximum force applied was then read from the dial. The average of three readings taken 10 s apart was used as the PPT score.

2.5. Headache ratings

Participants rated their headache activity at three separate points during the laboratory stress task. First, participants were asked to rate their headache activity on a 0 ('no pain') to 10 ('I can't do anything when I have such pain') scale before beginning the stress task to insure participants were headache-free. Participants also rated their headache activity using the same scale after 30 and 60 min of the experimental task.

Participants were also asked to record their headache activity following the stress task using a headache diary. The headache diary prompted participants to record the location and intensity of headache pain at 2-h intervals for a total of 24 h following the experimental task. Intensity of pain was rated on a 0–10 scale (0, 'no pain' to 10, 'I can't do anything when I have such pain'). Participants were also asked to record any analgesic medication taken.

2.6. Experimental procedure

2.6.1. Experimental sessions

The experiment was conducted in three sessions during approximately 1 week. During the first session (the second stage of screening), an overview of the study was provided and informed consent approved by the Ohio University Institutional Review Board was obtained. Participants also completed a structured diagnostic interview to collect information about headaches and health; the PrimeMD interview (as described above); the BDI; the STAI (as well as other self-reported measures unrelated to this study) and the psychophysiological assessment. The psychophysiological assessment was administered to all participants so

they could familiarize themselves with this assessment procedure prior to actual data collection. Finally, participants were provided a headache diary with instructions and asked to practice recording headaches experienced in the following 24 h. The 24-h training period allowed the experimenters to correct any recording errors or inconsistencies prior to use of the diary for data collection.

The second and third sessions, scheduled on consecutive days, consisted of the experimental stress task and a 24-h follow-up session. At the second session, baseline assessments of psychophysiological variables and the SRS were obtained. Next, the participant received instructions for the experimental stress task. The task was divided into two 30-min blocks with the SRS re-administered at the 30-min midpoint and upon completion of the stress task. Immediately following the stress task, participants also were re-administered the psychophysiological assessment. Finally, instructions for completing the headache diary were reviewed and the participant was asked to complete a diary for the following 24 h.

The third and final session took place 24 h (± 4 h) later. The experimenter collected and reviewed the participant's headache diary and administered the final psychophysiological assessment. Participants were then debriefed and, if they wished treatment for headache problems or depression, referred for treatment.

2.6.2. Experimental stress task

The experimental stress task consisted of a 60-min, automated arithmetic task administered by computer. Arithmetic problems involving addition, subtraction, multiplication and division were administered one item at a time. The task began with simple, 1-digit operations and became progressively more difficult as the participant responded to the questions correctly. The computer algorithm added a digit to one of the operands every time the participant gave five consecutive correct answers. A digit was dropped from an operand if the participant gave eight consecutive incorrect answers. Participants were allowed to use paper and pencil to calculate their answers.

Participants were told that the items on the task were drawn from a widely used intelligence test and that individuals with average intelligence should be able to easily answer all the questions. However, after every 20 questions, computer feedback was presented indicating they were performing, '...below the average for a college freshman. Remember this test is graded on speed AND accuracy.'

3. Results

3.1. Participant characteristics

Participant characteristics are presented in Table 1. It can be seen that the two headache prone groups did not differ in

headache characteristics. However, only headache prone/depressed participants received a diagnosis of depression and exhibited elevated Beck Depression Inventory II scores. As would be expected of individuals experiencing a current episode of depression, headache prone/depressed participants also exhibited higher Trait Anxiety Scores and were more likely to receive an anxiety disorder diagnosis than participants in the other two groups. Additionally, approximately one-quarter of the participants in the headache prone/depressed group reported seeking medical treatment for their headaches while nearly one-third of the participants in the headache prone/non-depressed group reported seeking headache treatment. No participants in the healthy control reported ever seeking treatment for headaches.

3.2. Subjective stress scores

Mean subjective stress scores are displayed in Fig. 1 where it can be seen that the headache prone/depressed group reported the highest levels of stress at all three assessments. Stress levels also increased during the math stressor in all three groups. A 3 group (HP/D, HP/ND, HC) \times 3 time (baseline, 30 min, 60 min) mixed model ANOVA was conducted on subjective stress scores. This analysis revealed significant group ($F[2, 45] = 34.74$, $P < 0.001$) and time ($F[1.7, 76.9] = 34.74$, $P < 0.001$) effects. Post-tests for the time effect revealed that subjective stress scores were significantly higher at the 30 and 60 min assessments than at the baseline assessment ($P < 0.05$), but subjective stress scores obtained at the 30 and 60 min assessments did not differ significantly. Post-tests for the group effect revealed that the headache prone/depressed group reported significantly higher levels of stress than the other two groups at all three assessments ($P < 0.05$). Additionally, the headache prone/non-depressed group reported higher levels of stress than healthy controls at the 30 and 60 min assessments ($P < 0.05$).

3.3. Headache activity

Fig. 2 displays the percentage of participants in each of the three groups reporting headache pain during the math

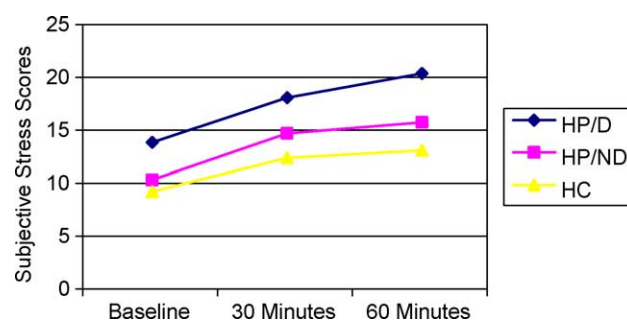


Fig. 1. Mean subjective stress scores by group taken at baseline, 30 and 60 min into the laboratory stressor. HP/D, headache prone/depressed; HP/ND, headache prone/non-depressed; HC, healthy control.

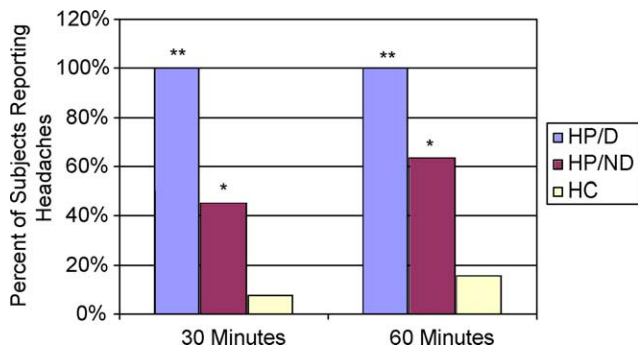


Fig. 2. Percentages of participants in each group reporting headache activity at 30 and 60 min into the stress task. No participant reported headache during baseline assessment (not shown). HP/D, headache prone/depressed; HP/ND, headache prone/non-depressed; HC, healthy control. **Significantly different from both HP/ND and HC groups, $P < 0.05$. *Significantly different from HC group, $P < 0.05$.

stressor. No participant reported experiencing a headache at the baseline assessment. However, during the math stressor 100% of headache prone/depressed participants and about 40–60% of headache prone/non-depressed participants reported a headache. χ^2 -Tests confirmed that headache prone/depressed participants were more likely to experience a headache than either headache prone/non-depressed participants or healthy controls at both assessments ($P < 0.05$). In addition, headache prone/non-depressed participants were more likely to experience a headache than healthy controls at both assessments ($P < 0.05$).

Analyses of headache recordings from the 24 h following the stress task also were conducted. Participants were considered to have a headache if they reported headache pain with an intensity of 1 or greater. The average maximum severity rating for participants reporting a headache was 4.5 for the headache prone/depressed group and 2.3 for the headache prone/non-depressed group. Additionally, approximately 15% of the participants reported taking

analgesic medication for their headache during the 24 h period following the stress task.

Fig. 3 displays the percentage of participants in each of the three groups who recorded a headache during each 4-h block of the 24-h period following the math stressor. It can be seen that the two headache prone groups, especially depressed participants, frequently recorded headaches throughout the 24-h assessment period. χ^2 -Tests confirmed that headache prone/depressed participants were significantly ($P < 0.05$) more likely to record a headache than healthy controls during each 4-h time period. Headache prone/non-depressed participants also were significantly ($P < 0.05$) more likely to record a headache than healthy controls in all but one time period. Finally, the headache prone/depressed group recorded more headache activity than those in the headache prone/non-depressed group with significant differences from 6 to 8 and from 22 to 24 h ($P < 0.05$).

3.4. Psychophysiological measures

3.4.1. Pericranial muscle tenderness

Fig. 4 displays median total tenderness scores (TTS) at all three assessments (baseline, post-task, 24-h post-task) for all three groups. At all three assessments the median value for healthy controls was zero indicating these participants were unlikely to exhibit signs of allodynia. In contrast, headache-prone participants exhibited PMT at all three assessments, especially if they were depressed. Correlations between TTS values and headache severity ratings obtained at the three assessments revealed that reports of head pain and PMT values were correlated at each assessment, with ρ ranging from 0.37 to 0.53 (mean $\rho = 0.45$; all $P \leq 0.005$).

A Kruskal–Wallis one-way analysis of variance ($\alpha = 0.05$) indicated there were significant differences in TTS between the three groups. Follow-up post-tests

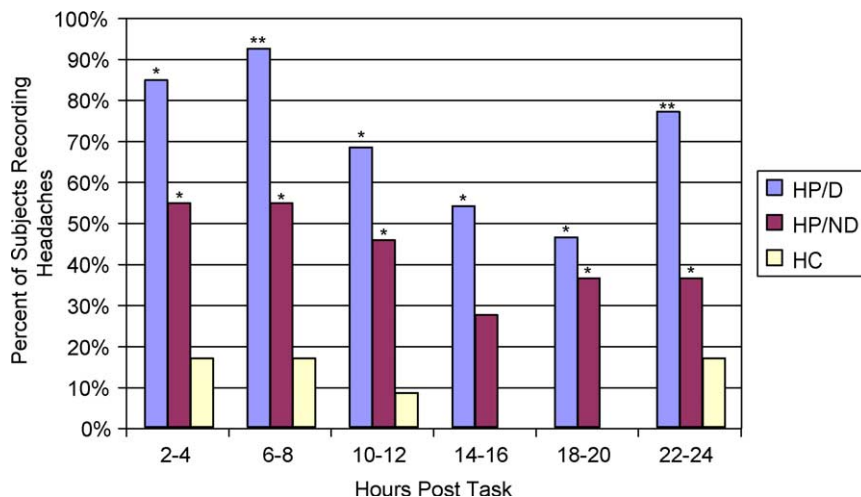


Fig. 3. Percentages of participants in each group recording headache activity during the 24 h following the stress task. HP/D, headache prone/depressed; HP/ND, headache prone/non-depressed; HC, healthy control. The absence of a bar indicates no participants recorded a headache. **Significantly different from HP/ND and HC groups, $P < 0.05$. *Significantly different from healthy control group, $P < 0.05$.

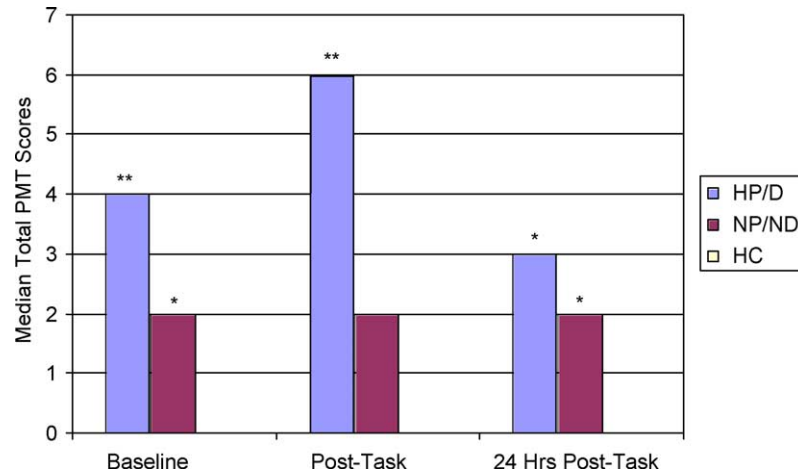


Fig. 4. Median total pericranial muscle tenderness (PMT) scores assessed immediately prior to the stress task (baseline), following the stress task (post-task) and 24 h post-task. HP/D, headache prone/depressed; HP/ND, headache prone/non-depressed; HC, healthy control. Absence of a bar indicates a median PMT score of zero. **Significantly different from HP/ND and HC groups, $P < 0.05$. *Significantly different from HC group, $P < 0.05$.

revealed that headache prone/depressed participants exhibited higher levels of PMT than health controls at all three assessments ($P < 0.05$) and higher levels of tenderness than headache prone/non-depressed participants at the baseline and post-task assessments. In addition, headache prone/non-depressed participants exhibited significantly higher levels of PMT than healthy controls at the baseline and 24-h post-task assessments. Correlations between TTS obtained at the three assessments revealed that participants generally maintained the rank order of their total PMT values across assessments, with ρ ranging from 0.85 to 0.91 (mean $\rho = 0.87$; all $P < 0.001$).

3.4.2. Pressure pain thresholds

Figs. 5 and 6 display median values for temporalis and finger PPT, respectively, for the three groups. It can be seen that the two headache prone groups generally exhibited lower PPT than healthy controls. A Kruskal–Wallis one-way analysis of variance indicated significant

group differences on both temporalis PPT ($\alpha = 0.05$) and finger PPT ($\alpha = 0.05$). Follow-up post-tests revealed that the two headache prone groups exhibited lower temporalis PPT than healthy controls at both the post-task and 24-h post-task assessments; differences at the baseline assessment were similar in magnitude but not statistically significant. Follow-up post-tests on finger PPT revealed that headache prone/depressed participants exhibited lower PPT than healthy controls at all three assessments, and lower PPT than headache prone/non-depressed participants at the post-task assessment. Finally, headache prone/non-depressed participants exhibited lower finger PPT than healthy controls at the 24-h post-task assessment. Correlations between PPT at the three assessments further revealed that participants generally retained the rank order of their PPT across assessments (ρ between 0.84 and 0.92 for the temporalis assessment and between 0.85 and 0.96 for the finger assessment; mean $\rho = 0.89$; all $P < 0.001$).

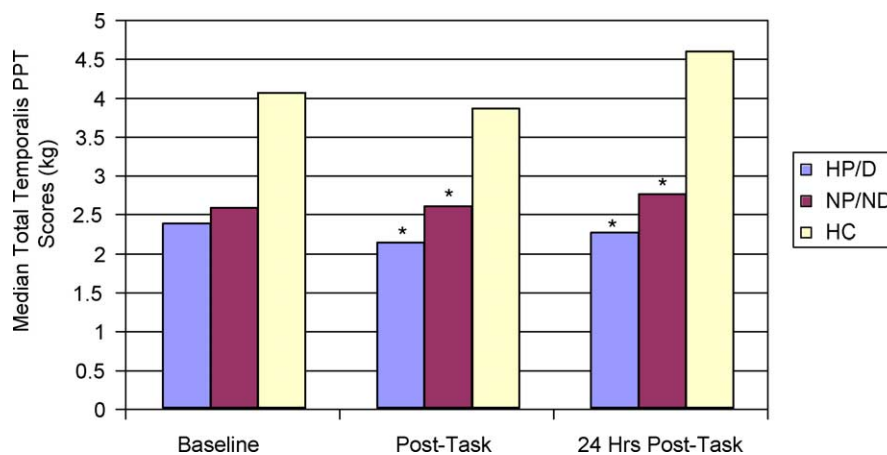


Fig. 5. Median total temporalis pressure pain threshold (PPT) scores assessed immediately prior to the stress task (baseline), following the stress task (post-task) and 24 h post-task. HP/D, headache prone/depressed; HP/ND, headache prone/non-depressed; HC, healthy control. *Significant difference from HC group, $P < 0.05$.

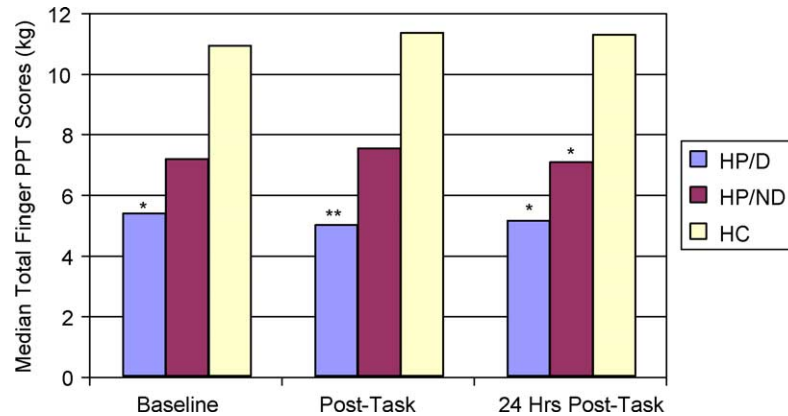


Fig. 6. Median total finger pressure pain threshold (PPT) scores assessed immediately prior to the stress task (baseline), following the stress task (post-task) and 24 h post-task. HP/D, headache prone/depressed; HP/ND, headache prone/non-depressed; HC, healthy control. **Significant difference from HP/ND and HC groups, $P < 0.05$. *Significant difference from HC group, $P < 0.05$.

4. Discussion

4.1. Headaches

Depression increased the risk of TTHs both during and following the laboratory stress task. At both the midpoint and end of the hour-long laboratory stress task, 100% of the individuals in the headache prone/depressed group reported experiencing a headache. This was about twice the rate at which headache prone/non-depressed participants experienced headaches, and about 10 times the rate at which healthy controls experienced headaches. Moreover, headaches persisted in the 24-h period following the laboratory stress task for many participants. Headache prone/depressed participants experienced the highest levels of TTH activity during this follow-up period, with over 80% of headache prone/depressed participants recording headaches in the 8 h following the laboratory stress task compared to about 50% of headache prone/non-depressed participants and fewer than 20% of healthy controls. Depression status, at least when combined with a history of headaches, thus proved to be a strong risk factor for stress induced headaches. This is the first demonstration that depression influences the onset of TTHs.

We were unable to determine if depression alone—depression in the absence of a history of TTHs—increased vulnerability to TTHs during or following a laboratory stressor. Every woman who met our criteria for clinical depression reported at least monthly headaches. Thus, no depressed participant was without a significant headache history. While this observation provides additional evidence of a link between headache proneness and depression, it prevented us from determining if depression increased vulnerability to stress-induced headaches in individuals with no significant history of TTHs.

4.2. Psychophysiological findings

Consistent with the findings of previous studies (Hatch et al., 1992; Jensen, 1995; Jensen et al., 1993; Langemark and

Olesen, 1987; Lipchik et al., 1996, 2000, 1997; Lous and Olesen, 1982) we found that participants prone to TTHs—even when assessed in the headache-free state—exhibited higher levels of PMT than individuals with no significant headache problems who showed few signs of tenderness. We also found that PMT was associated with depression status as well as headache history, as the headache prone/depressed group exhibited higher levels of tenderness than the headache prone/non-depressed group at two of three assessments.

Only headache prone/depressed participants exhibited lower peripheral (finger) PPTs than healthy controls at all three assessments. However, peripheral pain thresholds in the two headache prone groups differed at only one of three assessments providing only limited indication that depression influences peripheral pain thresholds. Reduced peripheral PPTs have been observed in TTH in other studies (Bendtsen et al., 1996a; Marlow, 1992; Schoenen et al., 1991). Reduced cephalic pain thresholds have been observed in some (Bendtsen et al., 1996a; Sandrini et al., 1994; Schoenen et al., 1991) but not other (Bovim, 1992; Gobel et al., 1992; Jensen et al., 1993) studies, but appear more likely in chronic TTH (Bendtsen et al., 1996a; Schoenen et al., 1991) than in episodic TTH or in mixed samples of episodic and chronic TTH (Bovim, 1992; Gobel et al., 1992; Jensen et al., 1993).

Studies that have examined pain thresholds or pain tolerance in depression have yielded mixed results. Cephalic PPTs were lower in depressed patients than in healthy controls in the only other study to obtain this measure in depressed participants (Merskey, 1965). Reports of ischemic arm pain also were higher and pain tolerance times lower in depressed patients than in healthy controls in a second study (Pine-rua-Shuhaibar et al., 1999). In addition, laboratory manipulations of depressed mood have been associated with reduced cold pressor pain tolerance in two studies (Willoughby et al., 2002; Zelman et al., 1991). However, depression has been associated with increased, rather than decreased pain thresholds in other studies. Thus, pain thresholds to brief heat, pressure, pinprick or electrical stimuli (Bezzi et al., 1981; Dworkin et al., 1995; Hall and Stride, 1954; Lautenbacher and

Krieg, 1994; Lautenbacher et al., 1999) were higher in depressed patients than healthy controls, though cold pressor and heat pain thresholds were unaltered in depressed patients in some studies (Lautenbacher et al., 1999; Otto et al., 1989). Differing results across studies may reflect differences in pain stimuli and in participant populations. Lautenbacher and Krieg (1994) have argued that *decreased* pain sensitivity in depression might be expected with brief pain stimuli that fail to elicit the activity of the central pain modulation systems likely impaired in depression. At the same time, *increased* pain sensitivity would be observed with pain stimuli that effectively challenged these pain modulation systems.

Because depression was associated with both vulnerability to stress-induced headaches and PMT in the present study, these results raise the possibility that depression increases vulnerability to TTHs by altering pain processing in ways that are indexed, at least partially, by PMT. Elevated PMT or allodynia observed in TTH likely reflects sensitization at the trigeminal nucleus/dorsal horn (Bendtsen et al., 1996b); sensitization of peripheral nociceptors or alterations in higher-level pain processing mechanisms appear less likely, but have not been completely ruled out (Ashina et al., 2003; Bendtsen, 2000; Bendtsen et al., 1996b). Thus, depression may aggravate the central sensitization already present in frequent TTH. Although depressed TTH sufferers did not report more frequent or severe headaches than their euthymic counterparts with TTHs, they were more likely to show signs of central sensitization and exhibited an increased vulnerability to laboratory induced TTHs, suggesting depression may influence the pathophysiology of TTHs. Long-term follow-up would be necessary to determine if depressed TTH sufferers were more likely than their euthymic counterparts to evolve to the chronic form of TTHs, and if abnormalities in psychophysiological variables were predictive of this transformation.

4.3. Limitations and conclusions

Several limitations of this study require mention. First, to eliminate the confounding effects of gender only females were studied. Results thus cannot be generalized to males. Second, in the absence of a control condition we cannot know what proportion of participants in each group would have experienced headaches if exposed to a non-stressful condition, and thus what proportion of headaches were in fact induced by the laboratory stressor. Use of a non-stressful control task would have allowed us to further examine the unique contribution of depression—apart from stress—on vulnerability to headaches and tenderness in these participants. However, our primary goal was to determine if the incidence of new headache episodes differed in depressed and non-depressed individuals in response to a laboratory stressor, not to document that stress can induce headaches. Future studies of this nature might include a non-stress control condition in order to better

isolate the contribution of depression to headaches. Finally, the small number of participants studied and the relatively large number of statistical tests conducted requires that these findings be replicated in a larger sample.

Despite the limitations, this study is the first to demonstrate that depression increases the onset of TTH. Elevations in PMT also were associated with depression as well as with headache history, suggesting that depression may aggravate sensitization that is already present in frequent TTH.

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