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Evidence for sustained mechanical pain sensitization in women with chronic temporomandibular disorder versus healthy female participants

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Keywords: temporomandibular disorder; pain; chronic pain; sensitization; pain threshold; mechanical pain

Abstract: Generalized dysfunction of the nociceptive system has been hypothesized as an important pathophysiological process underlying TMD pain. To date, studies have not identified sensitization among TMD participants with chronic pain to painful stimuli administered prospectively across consecutive days. We attempted to isolate an empirically derived laboratory-based marker of sustained mechanical pain sensitization. We examined whether this index accounted for variance in prospective assessments of clinical TMD pain. Participants were women with a clinical diagnosis of chronic TMD (n = 30) and healthy female controls (n = 30). Pain thresholds were assessed using digital algometry four times in 12-hour intervals over 48 consecutive hours, and clinical TMD pain via follow-up telephone assessments. Sustained mechanical pain sensitization, defined by statistically significant linear decrements in pressure pain thresholds across the consecutive testing sessions, discriminated chronic TMD and controls participants. An index of sustained sensitization at the masseter accounted for unique variance in clinical TMD pain over the subsequent 3-month assessment period, even controlling for mean pain threshold and baseline pain severity. These preliminary findings highlight discriminant and predictive validity characteristics of a novel marker of protracted pain sensitization among women with chronic TMD pain.

Perspective: A laboratory-based and empirically defined marker of sustained mechanical pain sensitization over the course of days with acceptable discriminant and predictive validity was identified. This marker may represent a clinically useful marker of chronic TMD pain in women.

Introduction

The etiology and pathophysiology of TMD is not fully understood, though generalized dysfunction of the nociceptive system has been offered as one explanation [24; 36-38]. Relative to pain-free controls, patients with TMD evidence greater sensitivity to painful mechanical stimuli applied to affected as well as distal, unaffected anatomical sites [1; 7; 16-18; 25; 26; 29; 36; 38; 42]. Additionally, temporal summation—a phenomenon reflecting endogenous facilitation of pain resulting from repeated application of stimuli of equal intensity—may be amplified in patients with TMD relative to healthy controls [26; 35; 36]. Evidence from a recent large-scale prospective case-control study revealed that sensitivity to mechanical pain is associated with greater risk of developing first-onset TMD, although within-session indexes of mechanical pain summation were not associated with greater risk [21]. Despite these findings, a number of studies have reported mixed or null findings concerning hyperalgesic responses to pain-evoking stimuli in TMD [30; 41; 42].

To our knowledge, studies have not yet investigated the sensitization of patients with TMD to noxious stimuli administered prospectively across consecutive days. Evidence of a progressive and more protracted sensitization to noxious mechanical stimuli over longer periods of time might be an important laboratory-based model by which investigators can probe more durable nociceptive mechanisms of myofascial pain, especially that of a chronic nature. We propose that nociceptive system sensitization sustained over several days or assessments might represent a prolonged state of nociceptive system sensitization that accounts for variability in chronic TMD pain.

In the present study, we attempted to isolate a laboratory-based and empirically derived index of sustained pain sensitization by examining changes in mechanical pressure pain

thresholds assessed across serial testing sessions conducted over two consecutive days. Empirical evidence for this hypothesized somatosensory phenomenon could provide insight into an untapped but potentially clinically relevant pathophysiological process of chronic TMD pain. We hypothesized that compared to healthy female controls, women with chronic TMD would evidence increased mechanical pain sensitivity (diminished pressure pain thresholds) at affected (masseter) and unaffected (forearm) anatomical sites across four consecutive pain testing sessions conducted over a contiguous 48-hour period. We also examined the predictive validity of sustained sensitization by examining the association of an empirically-derived index of the proposed phenomenon with self-reported clinical TMD pain outcomes over a subsequent three-month telephone-based assessment epoch.

Methods

Participants

We recruited women with TMD (n = 30) from a dental school-based, tertiary care, orofacial pain clinic and media advertisements for a larger prospective study concerning sleep disturbance and TMD pain and function. To be eligible, TMD participants had to receive a primary myofascial TMD diagnosis based on published Research Diagnostic Criteria [8]. All TMD diagnostics were conducted by an experienced dentist who has completed formal training in RDC procedures and undergoes periodic reliability calibration. Additional major eligibility criteria for TMD patients included: typical pain severity > 2 out of 10 and minimum symptom duration ≥ 6 months. We excluded patients reporting primary pain conditions or serious medical disorders other than TMD, current alcohol or drug abuse problems, and use of narcotics, antidepressants, anticonvulsants, or muscle relaxants within two weeks of study participation. Additionally, for the purposes of the present study, only TMD participants who did not meet

diagnostic criteria for primary insomnia were included in the analysis. This approach minimized the potential influence of sleep-related characteristics on hypothesized between-groups differences in sustained sensitization.

Female healthy controls (n = 30) were recruited from fliers posted at a major teaching hospital and medical school, and from newspaper advertisements. Major eligibility criteria for healthy controls included an absence of: significant medical/psychiatric history within the prior 6 months, and lifetime history of Raynaud's disease, bipolar or psychotic disorder, recurrent major depression, substance abuse disorder, use of antidepressant medications within the past 6 months, any history of chronic pain (i.e., lifetime history of persistent pain for ≥ 6 months), and the presence of insomnia or other sleep disorders.

Procedure

All procedures took place in a university hospital-based Clinical Research Unit (CRU). TMD participants were enrolled in a larger study aimed at characterizing associations between objective polysomnography (PSG) sleep architecture and continuity indexes and pain sensitivity, and healthy controls were enrolled in a study of the effects of sleep deprivation on pain sensitivity. Sleep data from the full sample of TMD participants from which the current sample was selected were presented in a prior publication [40]. Although insomnia was a rule out for TMD participants in the current study, we found that individual differences in self-reported sleep quality (assessed with the Pittsburgh Sleep Quality Index, [2]) were not associated with mean pain sensitivity or between-session changes in pain sensitivity at any testing site (p-values > .20). Questionnaires were completed as part of larger packet of questionnaires provided upon study entry. The analyses of the present investigation are based on mechanical pain testing procedures (see below). PM sessions were conducted between 1500 and 1700 hours and AM sessions were

conducted 40-minutes post-awakening (all participants were allotted an uninterrupted 8-hr period for sleep that was structured around participants' habitual sleep-wake times that were ascertained from a 2-week daily sleep diary). The control afforded by the inpatient environment ensured that all participants had not smoked, eaten, ingested caffeinated or calorie-rich beverages, or exercised vigorously prior to AM or within 2 hours of PM pain testing sessions, effectively ruling out these potential confounding factors.

All participants underwent an identical standardized 45-minute pain testing battery consisting of thermal (heat) and mechanical (pressure) pain threshold testing, temporal summation of heat pain, always followed by cold pain testing [11; 14; 40]. For the purposes of the present study, we were interested in mechanical pain sensitization given the myofascial nature of TMD, and because PPTh appears to be a particularly robust concurrent and prospective correlate of TMD [39]. All participants completed four consecutive pain testing batteries over a 48-hour period: an initial PM session was followed by an AM and PM session next-day, and a final AM session on a subsequent day. Approximately 12 hours separated each testing session. Following the laboratory visit, clinical pain was assessed bi-weekly for 3 months by brief telephone interview. All procedures were approved by the Institutional Review Board. Written informed consent was obtained for all study participants prior to initiation of any study procedures.

Apparatus and Measures

Quantitative Sensory Testing

To assess mechanical pain sensitivity, a Somedic algometer (Sollentuna, Sweden) was used to assess responses to mechanical pressure using a 0.502-cm^2 probe covered with 1-mm polypropylene material. Pressure was increased in a graded fashion at a rate of 30 kPa/sec until

the participant reported pain threshold, defined as first felt pain [11]. Once threshold was determined, application of pressure was terminated. PPTh was assessed bilaterally at masseter and forearm muscle sites, over three trials, separated by 1 minute. Because we observed no laterality effects for PPTh at masseter or forearm muscle sites, recorded values at left and right sites were averaged to create overall masseter and forearm PPTh indexes.

Questionnaires

Brief Symptom Inventory (BSI) [6]. The BSI is a 53-item self-report questionnaire that taps the participant's degree of psychological distress *over the past two weeks* across a number of symptoms domains. Responses are given on a 0 (not at all) to 3 (very much) scale. Possible scores range from 0 to 3 with higher scores indicating greater levels of distress. Here, we utilized the General Severity Index (GSI) of the BSI, which is a composite index of a participant's overall level of distress collapsed across each symptom dimension.

The Brief Pain Inventory (BPI) [43]. The BPI is a widely-used pain-rating instrument that provides information on the intensity of pain as well as the degree to which pain interferes with function. Respondents rate their worst, lowest, average, and current pain severity (on numerical 0–10 scale), and functional interference caused by pain in the areas of daily activity, mood, relationships with others, etc. For the present study, we used the Pain Severity subscale to quantify baseline levels of clinical pain severity. Possible responses range from 0 (no pain) to 10 (pain as bad as could be).

Clinical Pain. After participants were discharged from their inpatient stay, clinical pain was assessed every two weeks for 3 months by brief telephone interview. Subjects rated their usual level of TMD pain experienced during the past two weeks (0 = "no pain"; 100 = "worst pain imaginable"). At each phone assessment, participants also estimated the total number of

days that TMD reached at least a moderate level of intensity (50 or greater on the 0 to 100 scale.) for *at least half of the days*. Subjects were instructed to rate their "TMD-related pain", defined as including jaw pain, but also pain in the face, neck, shoulders, and headaches, if pain in these regions were considered to be related to their TMD.

Data Analysis

Data was analyzed using SPSS Version 21. To examine between-groups differences in mean levels of masseter and forearm PPTh values, we conducted between-groups analysis of variance (ANOVA) with Group (TMD, control) as the between-subjects and mean masseter and forearm PPTh values (averaged across pain testing sessions) as the dependent variable.

To examine between-groups differences in sustained mechanical pain sensitization (i.e., decreases in pain threshold across sessions), we conducted two-factor repeated measures ANOVAs with Group (TMD, control) as a between-subjects factor and Session (1,2,3,4) as a within-subjects factor. Separate ANOVAs were conducted with masseter and forearm PPTh values as dependent variables. A greenhouse-geisser correction was used to adjust significance levels for violation of assumptions of sphericity (note that we report *df* values based on uncorrected models). Following significant omnibus Group x Session effects, we conducted two focused follow-up analyses. First, we conducted a linear trend contrast to examine between-groups differences in the linear rate of change across sessions. To do so, we created an orthogonal contrast coding scheme whereby sessions 1, 2, 3, and 4 were recoded as -3, -1, 1, and 3, respectively [34]. In no analysis did a quadratic trend emerge (all $Fs < 1$). Second, we conducted planned single-*df* within-groups repeated measures ANOVAs with Session as a within-subjects factor and respective PPTh values as the dependent variable.

We were particularly interested in the degree to which sensitization (i.e., decreases in PPTh) between sessions was prospectively associated with self-reported TMD pain over a 3-month follow-up period. Average usual TMD pain ratings were computed as one index of clinical TMD pain (average clinical pain). We also computed the average number of days per each 2-week assessment epoch in which TMD pain levels were at least moderate severity or greater (i.e., > 50 out of 100) for at least half of the day (frequency of moderate to severe pain days).

To quantify the magnitude of sustained sensitization, we first conducted analyses to determine at which point statistically significant changes from baseline PPTh values occurred, and then computed standardized residuals by regressing subsequent Session PPTh values on Session 1 (baseline) PPTh values. This yielded relevant sustained sensitization markers for masseter and forearm sites represented in standardized (SD) units by quantifying the degree of change in PPTh values from the baseline mechanical pain assessment session. Residualized change scores are uncorrelated with initial values and therefore represent a marker of change that has statistical advantages over simple (arithmetic) change scores, which are dependent on (correlated with) initial (baseline) values [5].

We examined zero-order correlations between mean PPTh values, masseter and forearm residuals, and the aforementioned clinical TMD pain indexes. Lastly, we examined whether PPTh residuals for the masseter and forearm testing sites accounted for incremental variance in clinical TMD pain outcomes above and beyond mean PPTh values and possible confounders. This was achieved by conducting hierarchical multiple regressions in which age, baseline BPI pain severity, TMD duration, and mean PPTh were entered at Step 1, and relevant PPTh residuals at Step 2.

Results

Sample Demographic and Clinical Characteristics

All TMD participants met Research Diagnostic Criteria (RDC) criteria for myofascial TMD; 30% had significant joint involvement and 27.6% had significant disc involvement. The average reported duration of TMD pain was 124 (SD = 98.11) months. Mean BPI pain severity scores of TMD patients was 3.18 (SD = 1.64) and mean GSI score was 0.3 (SD = 0.23), suggesting relatively low levels of pain and psychiatric distress, respectively, in our TMD sample [6]. TMD patients reported a mean age of 27.6 (SD = 5.95); 87% were Caucasian; 6.7% African-American; and 6.7% Asian; 47% graduated college; and 36.7% attended at least some graduate studies. Healthy controls reported a mean age of 26.3 (SD = 6.09); 60% were Caucasian; 23.3% African American; and 16.7% Asian; 29% graduated college; and 35.5% attended at least some graduate studies. Mean GSI among healthy participants was 0.06 (SD=0.10).

TMD and healthy control groups did not differ with respect to age or educational attainment (*p*s > .20). TMD participants had higher GSI scores than healthy participants ($p < .01$). Moreover, there was a greater percentage of Caucasians in the TMD (86%) versus the healthy control group (60%; $p < .05$). Statistical control for age (modeled for within-group regression analyses), GSI scores, and ethnicity did not affect any of the findings reported below.

Sustained Mechanical Pain Sensitization in Chronic TMD versus Healthy Participants: Tests of Discriminant Validity

Mean (SD) masseter and forearm PPTh assessments are provided in Table 1. Between-groups differences did not emerge for mean masseter or forearm PPTh, *F*'s(1,58) < 1, with the exception of 4th trial masseter PPTh being significantly lower for TMD participants versus

healthy controls ($p < .05$). Hence, in general, mean levels of mechanical pain sensitivity were comparable between TMD and healthy control participants. A repeated measures ANOVA revealed a significant omnibus Group x Session effect for PPTh at the affected masseter site, $F(3,174) = 3.70$, $p < .05$, $\eta^2 = .06$ (see Figure 1). The linear trend contrast was significant by Group, $F(1,58) = 6.73$, $p < .05$, $\eta^2 = .10$. Specifically, the linear slope of diminishment in masseter PPTh was steeper in TMD patients versus healthy controls. Planned within-groups comparisons revealed a significant decrease in masseter PPTh across sessions for TMD patients, $F(3,87) = 5.31$, $p < .01$, $\eta^2 = .16$. In contrast, there was no change in masseter PPTh for matched healthy controls, $F(3,87) = 1.01$, $p = .40$, $\eta^2 = .03$. We also conducted simple interactions to determine where between-groups differences in changes in masseter from baseline PPTh values became evident. There was evidence for a differential rate of PPTh change between TMD and control participants from baseline to the 2nd session [$F_{\text{Group x Session1 v Session2}}(1,58) = 4.50$, $p < .05$, $\eta^2 = .07$] and from baseline to the 4th session [$F_{\text{Group x Session1 v Session2}}(1,58) = 9.33$, $p < .01$, $\eta^2 = .14$]. There was no evidence for change in PPTh values from baseline to the 3rd session, $F_{\text{Group x Session1 v Session3}}(1,58) < 1$, $p = .33$, $\eta^2 = .02$.

For forearm PPTh, We observed a significant Group x Session effect, $F(3,174) = 2.57$, $p < .05$, $\eta^2 = .04$ (see Figure 2). Again, the linear contrast was significant by Group, $F(1,58) = 7.05$, $p < .01$, $\eta^2 = .11$, suggesting that TMD patients showed a different linear rate of change in forearm PPTh across sessions compared to matched healthy controls. Planned within-groups comparisons supported this contrast and revealed a significant decrease in forearm PPTh across sessions for TMD patients, $F(3,87) = 5.44$, $p < .01$, $\eta^2 = .15$, but not among pain-free controls, $F(3,87) < 1$. Similar to the masseter PPTh findings reported above, we conducted a series of additional simple interactions to determine where between-groups differences in changes in

forearm from baseline PPTh values became evident. Greater reductions in forearm PPTh values were evident for TMD participants versus healthy controls only at the 4th pain testing session, $F_{Group\ x\ Session1\ v\ Session4}(1,58) = 8.19$, $p < .01$, $\eta^2 = .13$. There was no evidence for group differences in rate of forearm PPTh change between Session 1 and Session 2 [$F_{Group\ x\ Session1\ v\ Session2}(1,58) = 1.88$, $p = .18$, $\eta^2 = .03$] or Session 1 and Session 3 [$F_{Group\ x\ Session1\ v\ Session3}(1,58) = 2.10$, $p = .15$, $\eta^2 = .04$].

Predictive Validity of Sustained Mechanical Pain Sensitization: Associations with Clinical TMD Pain

We first examined whether mean pain sensitivity averaged across all four PPTh assessment sessions was correlated with self-reported TMD pain measured prospectively at bi-weekly phone interviews. We were also interested in determining whether the degree of between-session mechanical pain sensitization at masseter and forearm sites was associated clinical pain. We thus examined zero-order correlations between standardized residuals representing sustained mechanical pain sensitization (i.e., subsequent session values regressed on baseline session values) and mean PPTh values (for forearm and masseter assessments) with average pain and frequency of moderate to severe pain days. As presented in Table 2, significant and negative zero-correlations were observed between Session 4 masseter PPTh residuals and average clinical pain and frequency of moderate to severe pain days, such that greater decreases in masseter PPTh from Session 1 (baseline) to Session 4 were associated with both a greater average clinical TMD pain intensity and the mean number of days per each 2-week follow-up assessment with TMD pain severity ratings of at least 50/100 (see Figures 3 and 4). Residuals for Session 2 masseter PPTh values, Session 4 forearm PPTh residuals , and mean PPTh values were not significantly correlated with either clinical TMD pain index.

Incremental Validity of Sustained Mechanical Pain Sensitization: Unique Associations with Clinical TMD Pain

The zero order correlations of sustained pain sensitization and average clinical pain and frequency of moderate to severe pain days are presented in Figures 3 and 4, respectively. However, we were specifically interested in the incremental validity of sustained mechanical pain sensitization with markers of clinical TMD pain. Hence, we examined the unique percentage of variance (i.e., incremental validity) accounted for in average clinical pain and frequency of moderate to severe pain days by Session 4 masseter PPTh residuals (i.e., across session sensitization). We conducted a hierarchical multiple regression analyses whereby we partialled variance attributable to baseline BPI pain severity, TMD duration, and mean masseter PPTh values from Session 4 masseter PPTh residuals. Results of this regression analysis are provided in Table 3. Session 4 residuals accounted for 12% and 11% of the variance in average clinical pain and frequency of moderate to severe pain days, respectively. Concerning average clinical pain, each 1 SD decrease in masseter PPTh from values Session 1 to Session 4 was associated with a 6.5 point increase in mean self-reported pain across the 3-month follow-up. For frequency of moderate to severe pain days, each 1 SD decrease in masseter PPTh values from Session 1 to Session 4 was associated with 1.14 greater average days per each 2-week assessment across the 3-month follow up with pain at least 50/100.

Discussion

We found that women with chronic TMD evidenced linear decrements in mechanical pain thresholds at affected and unaffected sites across four serial pain testing sessions conducted over a 48-hour period; no such evidence was observed among the healthy, pain-free controls. However, this effect was only found consistently 48 hours following the baseline assessments

across both anatomical sites studied. We also observed that the magnitude of sustained sensitization measured at the masseter accounted for up to 15% of the variance clinical TMD pain over a 3-month follow-up, even after controlling for baseline clinical pain severity, TMD duration, and mean mechanical pain sensitivity. This represents a moderate effect size [4], one that is in fact substantially larger than within-session assessments of mechanical temporal summation between case-controls and TMD patients in the largest cohort study conducted to date [22]. To our knowledge, these data provide the first empirical evidence suggesting that TMD patients manifest sustained mechanical pain sensitization compared to healthy female controls. These findings suggest that psychophysical methods can be used to uncover a protracted sensitization of the nociceptive system over consecutive days. Our finding that sustained mechanical pain sensitization discriminated controls and patients at affected and non-affected sites suggests a role for generalized nociceptive system pathophysiology in the maintenance and aggravation of TMD pain [1; 7; 16-18; 25; 26; 29; 36; 38; 42]. However, only the empirically-derived index of masseter mechanical pain sensitization was predictive of variability in clinical TMD pain. These findings are consistent with data suggesting that mechanical pain sensitivity at affected sites are more reliable predictors of first-onset TMD than unaffected sites, though a marker of within-session temporal summation was not associated with increased risk of disease onset [21]. Within-session site-specific temporal summation of repeated noxious cutaneous stimulation at the knee was prospectively associated with clinical OA pain, though it only accounted for approximately 4% of the variability in OA pain reports for the full sample [20].

Sustained sensitization of mechanical pain in the present study predicted clinical TMD pain over a subsequent 3-month reporting period. In fact, this novel marker pain accounted 11-

12% of variance in clinical TMD pain measures above and beyond TMD duration and baseline clinical TMD pain severity. This represents a moderate effect size (r = .35; [4]). Mean mechanical pain thresholds were virtually unrelated to clinical TMD pain. Moreover, mean levels of mechanical pain threshold generally did not discriminate TMD from healthy participants. Prior studies designed to predict clinical pain from quantitative sensory testing have yielded mixed results [9; 12-14; 27; 44], and several studies have failed to demonstrate significant mean differences in within-session mean pain threshold measures between TMD participants and case-controls [3; 15; 23; 30; 33; 42]. It is important to note that we excluded TMD participants in the current study for the presence of insomnia, which are common in chronic TMD [40], and our sample had rather low levels of psychological distress. While we believe it was critical to optimize the internal validity for this preliminary examination, doing so will likely restrict the generalizability of these findings to the TMD population at-large. Nonetheless, our findings raise the possibility that a longer-term serial assessment of nociceptive system sensitization might enhance our ability to distinguish TMD patients from healthy controls, as well as represent a more ecologically valid tool for the prediction of subsequent clinical pain in this chronic pain population. In fact, it seems plausible that repetitive mechanical stimulation of the affected area may trigger a clinical pain flare and maintain chronicity through sustained and gradual sensitization of nociceptive pathways.

This was an exploratory study that utilized extant data not specifically designed to address the hypotheses under consideration. Replication and extension is needed to further validate and determine the reliability of the proposed construct. Moreover, whether the sustained sensitization observed in the present study extends beyond 48 hours is not known, nor is it known whether this phenomenon might be observed with greater frequency of within-day

assessments, which would aid in the usefulness of this marker should it be replicated in future studies. It will be important to further investigate the boundaries of a marker of sustained sensitization in future studies. Taken together, these findings provide support for discriminant and predictive validity for a laboratory based and empirically derived marker of sustained pain sensitization. Chronic TMD is especially characterized by episodic but tonic pain, which might be due to heightened sensitivity to an initially mild painful event. In this vein, our laboratory procedure appears to promote pain facilitation by sensitizing the nociceptive system through repeated mildly noxious stimulation over a 48-hour period. Our sensitization index proved to be associated with both usual TMD pain and the number of days in which *at least* moderate pain was experienced for at least half of the day. Future investigations should determine if additional markers of sustained sensitization confer increased risk for the development and maintenance of TMD pain, and possibly other pain disorders. Although speculative, it is possible sustained sensitization of the nociceptive system is a harbinger for later development of chronic TMD pain.

This study has some additional limitations that warrant mention. First, we studied only women because there is a greater proportion of females with TMD, as well as to eliminate variability in pain responses across sexes [19]. Whether this phenomenon is evident in men with TMD cannot be determined and will require additional research. Given sex differences in clinical pain and pain processing and modulation [19], as well as activity of biomarkers mediating pain processing and modulation [e.g., pro-inflammatory cytokine activation; [28]], it will be important to characterize similarities and differences in sustained sensitization across men and women. Second, the present study had a small sample size and was not specifically designed to examine these hypotheses. As alluded to earlier, the spacing and timing of between-session

assessments were not determined *a priori* and the results of the present study should be considered in the context of the study's exploratory nature. Another problem with the limited sample size was the inability to reliably examine the influence of potential moderator variables, such as pain catastrophizing [31] and ethnicity [20]. Indeed, the ability of site-specific mechanical pain summation may be related to clinical pain most robustly in non-Hispanic Caucasians [20]. Third, the present data are based on a sample of TMD patients that reported relatively low levels of psychiatric distress. Hence, these data might not generalize to more severe cases of TMD, or other idiopathic pain conditions, in which clinical depression and high levels of state and trait anxiety are more common (e.g., Fibromyalgia). Relatedly, we excluded TMD participants who met criteria for primary insomnia and other sleep disorders that are prevalent in chronic TMD [10; 32; 40]. This decision was made to enhance statistical power and internal validity, and to maximize the comparability between the healthy control sample (who were required to be "good sleepers") and the sample of chronic TMD participants. Finally, the current study cannot speak to potential processes that underlie a sustained sensitization phenomenon.

To conclude, the results of this study suggest that sustained mechanical pain sensitization discriminates females with TMD from healthy female controls. Moreover, the empirically-derived marker of sustained sensitization at an affected anatomical site appears to possess predictive validity evidenced by significant associations with self-reported clinical TMD pain over a 3-month assessment window. Sustained pain sensitization appears to represent a novel psychophysical marker that may reflect a more durable form of nociceptive sensitization with potential clinical relevance for chronic TMD pain.

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Figure Captions

Figure 1.

Mean (SE) Masseter PPTh values (kPa) and Linear Trend by Group and Pain Testing Session.

Figure 2.

Mean (SE) Masseter PPTh values (kPa) and Linear Trend by Group and Pain Testing Session.

Figure 3.

Scatterplot of the zero-order correlation between Session 4 Masseter standardized residuals and mean 3-month follow-up self-reported TMD pain severity

Figure 4.

Scatterplot of the zero-order correlation between Session 4 Masseter standardized residuals and mean 3-month follow-up self-days with moderate to severe TMD pain.

Table 1. Mean (SD) Masseter and Forearm PPTh (kPA) values by Group and Session.

	Masseter	
	TMD	Healthy Controls
Session 1	146.15 (62.84)	143.26 (37.90)
Session 2	137.68 (59.91)	155.76 (58.65)
Session 3	141.02 (63.10)	146.71 (54.74)
Session 4 [a]	126.61 (56.12)	152.87 (54.36)
	Forearm	
	TMD	Healthy Controls
Session 1	277.53 (136.84)	245.19 (82.93)
Session 2	249.13 (135.20)	245.79 (92.94)
Session 3	252.82 (126.17)	249.22 (109.13)
Session 4	220.28 (98.16)	243.89 (90.23)

Note. PPTh = Pressure Pain Threshold. Subscript indicates a statistically significant group difference at $p < .05$.

Table 2. Zero-order Correlations of Mechanical Pain Sensitivity Indices with Clinical TMD Pain

	AVGPAIN	DAYSMODPAIN
Mean Masseter PPTh	-.17	-.25
Mean Forearm PPTh	-.13	-.17
Masseter Session 2 PPTh Residuals[a]	-.05	-.13
Masseter Session 4 PPTh Residuals[b]	-.36*	-.39*
Forearm Session 4 PPTh Residuals[c]	-.11	-.14

Note. PPTh = Pressure Pain Threshold; [a] standardized residualized Session 2 masseter PPTh values regressed on Session 1 masseter PPTh values; [b] standardized residualized Session 4 masseter PPTh values regressed on Session 1 PPTh values; [c] standardized residualized Session 4 forearm PPTh values regressed on Session 1 forearm PPTh values. For residuals, lower values indicate greater decreases in PPTh from Session 1 to Session 4 (i.e., greater sensitization). Residual values were correlated r = .28 to .56. AVGPAIN = Mean usual pain ratings over the 3-month follow-up; DAYSMODPAIN = Mean number of days per two weeks with pain ≥ 50/100 over the 3-month follow-up.

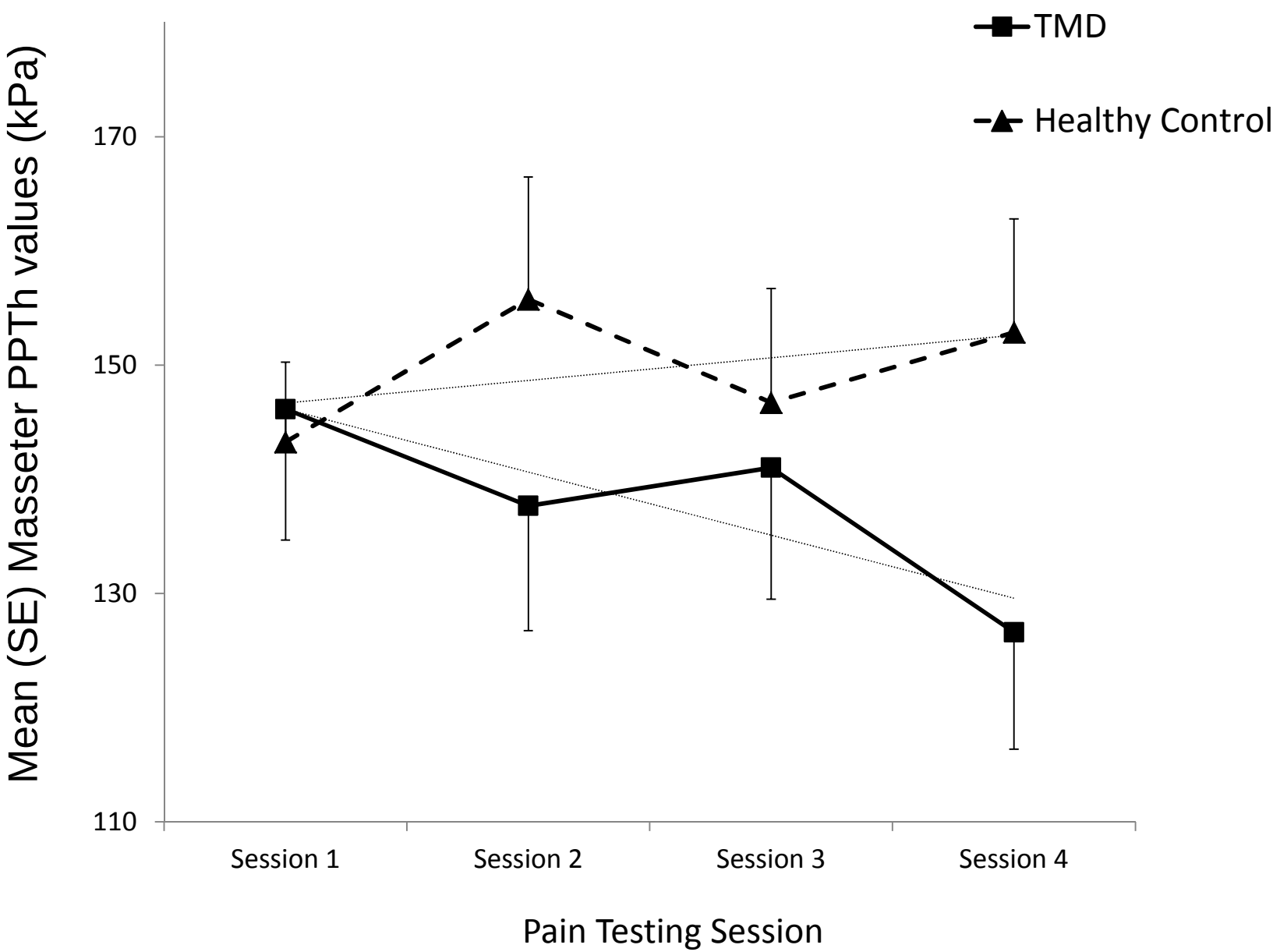
* $p < .05$

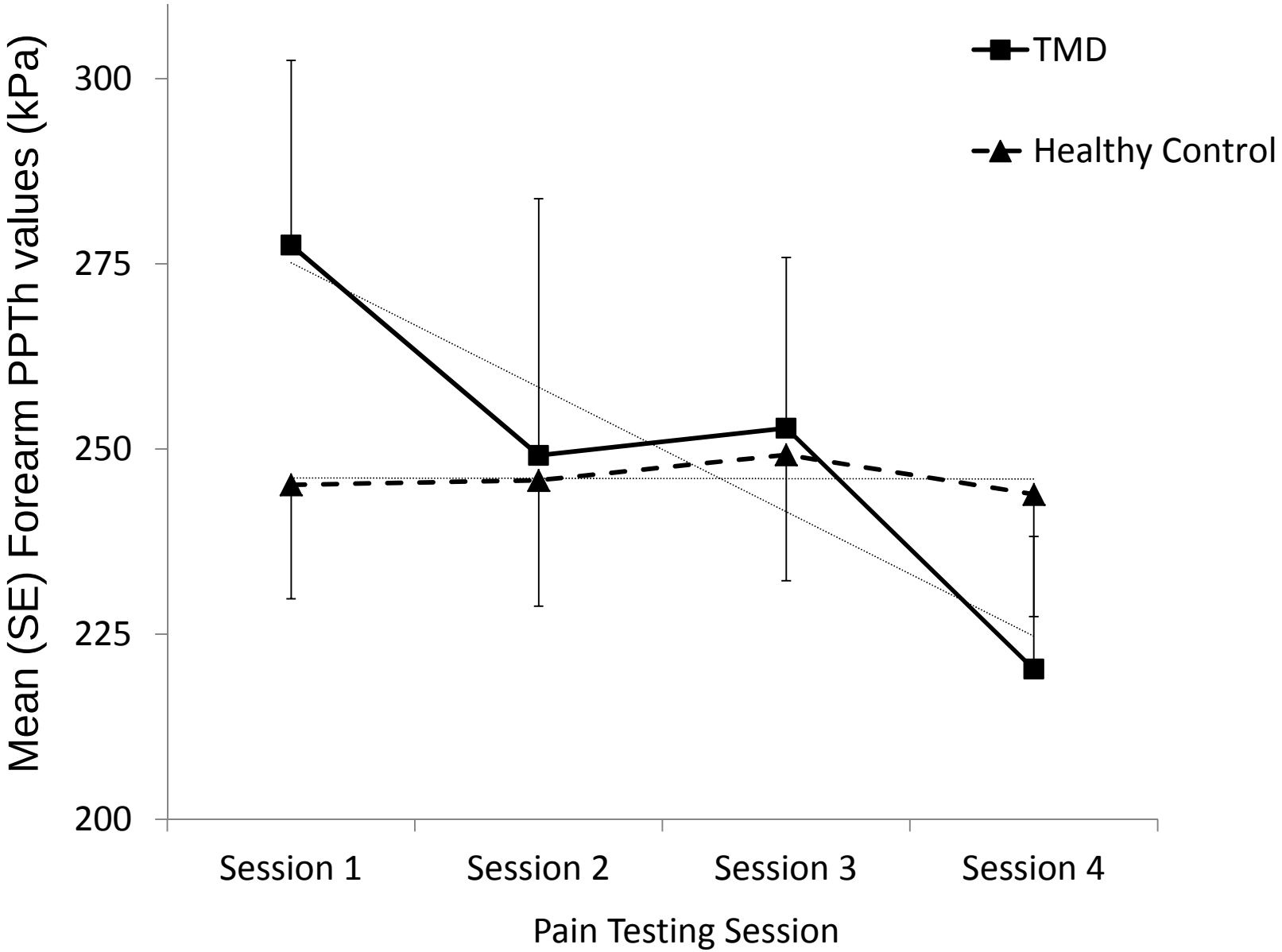
Table 3. Results of Hierarchical Multiple Regression Analyses for Clinical TMD Pain

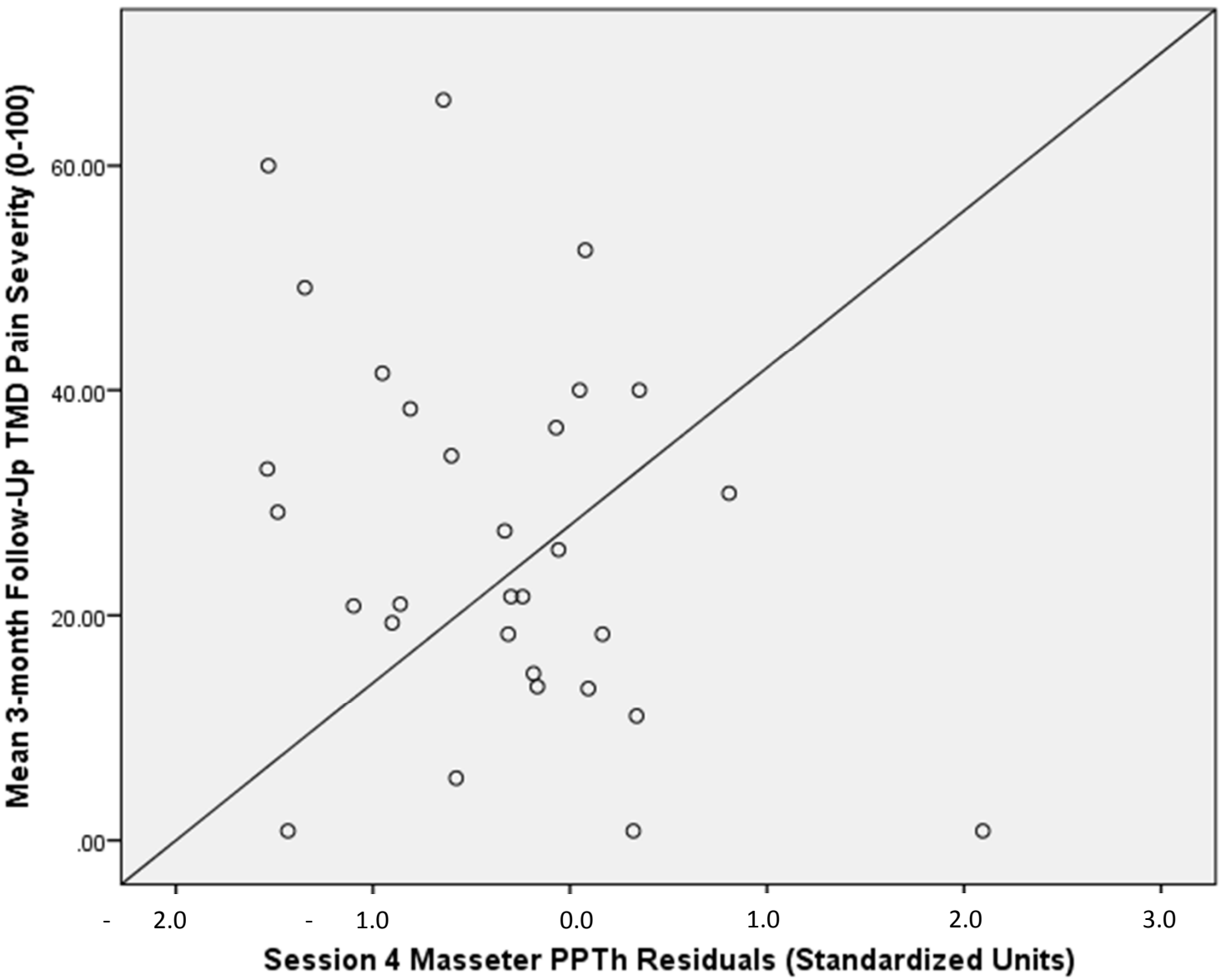
	$R^2\Delta$(Step)	b (SE)	95% C.I.
DV = AVGPAIN			
Step 1	.23		
TMD Duration		-.05 (.03)	(-.11, .01)
BPI Pain Severity		4.29 (1.87)	(.45, 8.13)*
Mean Masseter PPTh		-.03 (.05)	(-.14,.08)
Step 2	.12		
Session 4 Masseter PPTh Residuals[a]		-6.50 (3.09)	(-12.86, -.14)*
DV = DAYSMODPAIN			
Step 1	.27		
TMD Duration		-.01 (.01)	(-.02, .003)
BPI Pain Severity		.83 (.32)	(.17,1.50)*
Mean Masseter PPTh		-.004 (.01)	(-.03, .01)
Step 2	.11		
Session 4 Masseter PPTh Residuals[a]		-1.14 (.53)	(-2.23, -.04)*

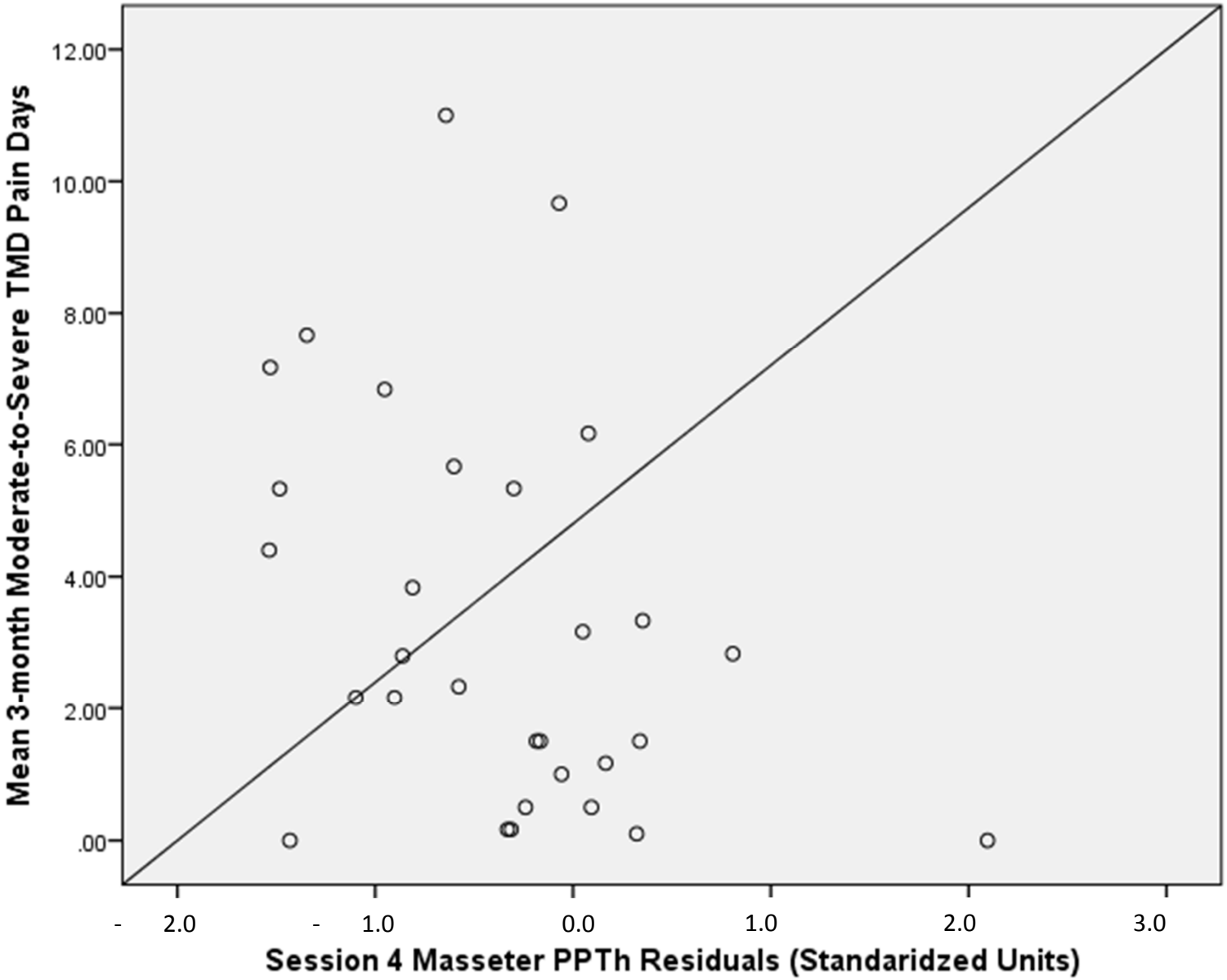
Note. PPTh = Pressure Pain Threshold; DV = Dependent Variable; [a] "Sensitization Index" defined as standardized residualized Session 4 PPTh values regressed on Session 1 PPTh values. Lower values indicate greater decreases in PPTh from Session 1 to Session 4 (i.e., greater between-session sensitization). AVGPAIN = Mean usual pain ratings over the 3-month follow-up; DAYSMODPAIN = Mean number of days per 2 weeks with pain > 50/100 over the 3-month follow-up.

* $p < .05$






Mean 3-month Follow-Up TMD Pain Severity (0-100)
60.00
40.00
20.00
.00
- 2.0
- 1.0
0.0
1.0
2.0
3.0
Session 4 Masseter PPTh Residuals (Standardized Units)


Mean 3-month Moderate-to-Severe TMD Pain Days
12.00
10.00
8.00
6.00
4.00
2.00
.00
- 2.0
- 1.0
0.0
1.0
2.0
3.0
Session 4 Masseter PPTh Residuals (Standaridzed Units)

Highlights:

- Sustained mechanical pain sensitization discriminated TMD patients and controls
- Sustained pain sensitization evidenced predictive validity for clinical TMD pain
- Sustained pain sensitization might represent one marker of chronic TMD pain