

Tactile processing at the painful and non-painful jaw in patients with unilateral Temporomandibular Joint Disorder (#20082)

1

First submission

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Important notes

Editor and deadline

Tjeerd Boonstra / 21 Sep 2017

Files

1 Figure file(s)

3 Table file(s)

1 Raw data file(s)

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Declarations

Involves the study of human participants/human tissue.

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- 1. BASIC REPORTING**
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BASIC REPORTING

-  Clear, unambiguous, professional English language used throughout.
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-  Methods described with sufficient detail & information to replicate.

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-  Impact and novelty not assessed. Negative/inconclusive results accepted. *Meaningful* replication encouraged where rationale & benefit to literature is clearly stated.
-  Data is robust, statistically sound, & controlled.
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7 Standout reviewing tips

3



The best reviewers use these techniques

Tip

Support criticisms with evidence from the text or from other sources

Example

Smith et al (J of Methodology, 2005, V3, pp 123) have shown that the analysis you use in Lines 241-250 is not the most appropriate for this situation. Please explain why you used this method.

Give specific suggestions on how to improve the manuscript

Your introduction needs more detail. I suggest that you improve the description at lines 57- 86 to provide more justification for your study (specifically, you should expand upon the knowledge gap being filled).

Comment on language and grammar issues

The English language should be improved to ensure that your international audience can clearly understand your text. I suggest that you have a native English speaking colleague review your manuscript. Some examples where the language could be improved include lines 23, 77, 121, 128 - the current phrasing makes comprehension difficult.

Organize by importance of the issues, and number your points

1. Your most important issue
2. The next most important item
3. ...
4. The least important points

Give specific suggestions on how to improve the manuscript

Line 56: Note that experimental data on sprawling animals needs to be updated. Line 66: Please consider exchanging "modern" with "cursorial".

Please provide constructive criticism, and avoid personal opinions

I thank you for providing the raw data, however your supplemental files need more descriptive metadata identifiers to be useful to future readers. Although your results are compelling, the data analysis should be improved in the following ways: AA, BB, CC

Comment on strengths (as well as weaknesses) of the manuscript

I commend the authors for their extensive data set, compiled over many years of detailed fieldwork. In addition, the manuscript is clearly written in professional, unambiguous language. If there is a weakness, it is in the statistical analysis (as I have noted above) which should be improved upon before Acceptance.

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Tactile processing at the painful and non-painful jaw in patients with unilateral Temporomandibular Joint Disorder

Stefaan Van Damme ^{Corresp., 1}, Charlotte Vanden Bulcke ¹, Linda Van den Berghe ², Louise Poppe ¹, Geert Crombez ¹

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Objective. Patients with persistent pain due to temporomandibular joint disorder (TMD) have been shown to display altered tactile perception at the jaw, such as increased intensity and reduced acuity, but the underlying mechanisms remain unclear. Furthermore, studies examining tactile processing at the jaw in patients with pain only in one side of the jaw, i.e., unilateral TMD, are lacking. The aim of this study was to investigate potential differences in tactile processing between the painful and non-painful side in patients with unilateral TMD. **Method.** Patients with unilateral TMD ($n = 20$) and matched healthy volunteers ($n = 20$) performed a temporal order judgment (TOJ) task indicated which one of two tactile stimuli, presented on each joint, they had perceived first. TOJ methodology allows examining spatial bias in tactile processing speed. Furthermore, after each block of trials, the participants rated the perceived intensity of tactile stimuli separately for both sides of the jaw. Finally, questionnaires assessing cognitive-affective variables such as pain catastrophizing, fear-avoidance beliefs, and pain vigilance, were completed. **Results.** TMD patients tended to perceive tactile stimuli at the painful side as occurring earlier in time than stimuli at the non-painful side ($p = .07$). In the control group, tactile stimuli were perceived as occurring simultaneously. Interestingly, the magnitude of this spatial bias in patients was positively correlated with the extent to which they reported fear-avoidance beliefs. Overall, intensity ratings of tactile stimuli were significantly higher in the TMD group than in the control group. Furthermore, no significant difference in perceived tactile intensity between the painful and non-painful side was found in the TMD patients. **Conclusion.** The results suggest that unilateral TMD patients, especially those characterized by fear-avoidance beliefs, show a tactile processing bias toward the painful side of the jaw. This finding is discussed within recent theories of pain-related attention.

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perhaps make this 'one presented over each temporomandibular joint'

Tactile processing at the painful and non-painful jaw in patients with unilateral Temporomandibular Joint Disorder

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25 **Abstract**

26 *Background.* Patients with persistent pain due to temporomandibular joint disorder (TMD) have
 27 been shown to display altered tactile perception at the jaw, such as increased intensity and
 28 reduced acuity, but the underlying mechanisms remain unclear. Furthermore, studies examining
 29 tactile processing at the jaw in patients with pain only in one side of the jaw, i.e., unilateral
 30 TMD, are lacking. The aim of this study was to investigate potential differences in tactile
 31 processing between the painful and non-painful side in patients with unilateral TMD.

32 *Methods.* Patients with unilateral TMD ($n = 20$) and matched healthy volunteers ($n = 20$)
 33 performed a temporal order judgment (TOJ) task indicated which one of two tactile stimuli,
 34 presented on each joint, they had perceived first. TOJ methodology allows examining spatial bias
 35 in tactile processing speed. Furthermore, after each block of trials, the participants rated the
 36 perceived intensity of tactile stimuli separately for both sides of the jaw. Finally, questionnaires
 37 assessing cognitive-affective variables such as pain catastrophizing, fear-avoidance beliefs, and
 38 pain vigilance, were completed.

39 *Results.* TMD patients tended to perceive tactile stimuli at the painful side as occurring earlier in
 40 time than stimuli at the non-painful side ($p = .07$). In the control group, tactile stimuli were
 41 perceived as occurring simultaneously. Interestingly, the magnitude of this spatial bias in patients
 42 was positively correlated with the extent to which they reported fear-avoidance beliefs. Overall,
 43 intensity ratings of tactile stimuli were significantly higher in the TMD group than in the control
 44 group. Furthermore, no significant difference in perceived tactile intensity between the painful
 45 and non-painful side was found in the TMD patients.

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Discussion. The results suggest that unilateral TMD patients, especially those characterized by fear-avoidance beliefs, show a tactile processing bias toward the painful side of the jaw. This finding is discussed within recent theories of pain-related attention.

Introduction

Temporomandibular disorder (TMD) is typically characterized by chronic pain in the temporomandibular joint (Suvinen et al., 2005). Also observed are abnormalities in tactile processing (Nebel et al., 2010). Specifically, it has been found that TMD patients perceive tactile stimuli at the jaw as more intense (Ayesh, Jensen & Svensson, 2007) and that they show enhanced cortical responses to such stimuli (Alonso et al., 2010), as compared to healthy controls. Furthermore, impaired tactile detection and acuity have been reported in these patients (Hollins & Sigurdsson, 1998; Hollins et al., 1996; Kothari et al., 2015).

In many cases temporomandibular joint pain is unilateral. Surprisingly, tactile processing in the painful and non-painful side of the jaw have rarely been compared. The few available studies suggest no differences in perceived tactile intensity or in detection threshold (Ayesh et al., 2015; Kothari et al., 2015). However, these studies did not exclusively include unilateral TMD patients, but also bilateral TMD patients who were "asked about the most painful side". Furthermore, perceived intensity and perceptual threshold are only two possible indicators of tactile abnormalities, and research on other indicators is required for a more profound understanding.

One aspect of tactile processing gaining research interest within the pain literature is spatial processing bias. It has been suggested that in unilateral chronic pain the brain may give less weight to tactile stimuli at the painful side, and that such "spatial neglect" may be part of a protective system serving to limit pain (Moseley, Gallace & Spence, 2009). In line with this idea are studies showing slower tactile processing at the painful relative to the non-painful side in

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perhaps make 'more profound' 'greater' - we don't know it will be more profound.

complex regional pain syndrome (Moseley et al., 2009, Moseley, Gallace & Iannetti, 2012a) and chronic low back pain (Moseley, Gallagher & Gallace, 2012b). However, this idea has not been investigated in TMD. Apparently contradictory to this idea are cognitive-affective pain models, stating that chronic pain is maintained by fear-avoidance beliefs which are associated with increased attention to pain-related information (Eccleston & Crombez, 1999; Van Damme et al., 2010; Vlaeyen & Linton, 2000). Recently, it has been proposed that such "hypervigilance" might emerge as enhanced somatosensory processing at pain-relevant body locations (Van Damme et al., 2016). Empirical evidence, however, remains limited to a series of studies using experimental pain induction on the hands in healthy samples (Durnez & Van Damme, 2015; Vanden Bulcke et al., 2013, 2014, 2015; Van Hulle et al., 2015).

The present study investigated spatial bias in tactile processing in unilateral TMD patients and matched controls, using a Temporal Order Judgment (TOJ) paradigm (Heed, & Azañón, 2014). Participants indicated which one of two tactile stimuli, presented at either joint, they had perceived first. We tested two rival hypotheses. According to the "spatial neglect hypothesis" (Murray et al., 2009), it should be expected that patients show slower processing of tactile stimuli at the painful relative to the non-painful side of the jaw. In line with the "hypervigilance hypothesis" (Van Damme et al., 2016), we expect faster tactile processing at the painful relative to the non-painful side of the jaw, especially in those patients displaying fear-avoidance beliefs related to their jaw (Turner et al., 2001; Visscher et al., 2010).

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also relevant here are the left right judgement tasks in people with complex regional pain syndrome (which suggest a bias away from the painful side - see moseley 2004 nuerology and reid 2017 cortex) and in healthy controls (which suggest a bias towards hte painful side - see moseley et al 2005 cog brain res)
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i don't think the hypotheses can be rivals. what about 'alternative'
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- Number: 4 Author: Reviewer Subject: Sticky Note Date: 21/9/17, 4:50:49 pm
moseley not mosley. i don't think you should suggest that there is a 'spatial neglect hypothesis' because such a hypothesis has not been proposed.
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this comparison of hypotheses is problematic because the work on somatospatial neglect (and you really should cite the paper that proposes that - Reid et al 2016 annals neurology) is specific for complex regional pain syndrome and has not been suggested, to my knowledge, for jaw pain. it would also be difficult to explain because the skin of the face is not used in normal function. moreover, if you are testing two hypotheses, you need to set up experiments to falsify them both and you have not done this here. finally, your wording here is much more consistent with the idea that you are testing the latter hypothesis not the former.
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just make sure this is clear. are you testing two hypotheses or three? i think you are testing at most two becuase i do not think you are testing the first one. you imply that you are testing first that processing will be faster for stim on the painful side than the non painful and second hypoth is that tthe PATIENTS who display fear avoidance beliefs (i think you should not use 'display' here but 'report') have a bigger difference between sides than the PATIENTS with low fear avoidance beliefs AND the controls. If you are not testing these hypotheses, i think you need to carefully reword this para.

Materials & Methods

Participants

TMD patients were recruited in the Department of Dentistry at the Ghent University Hospital. Inclusion criteria included having chronic (longer than 3 months) unilateral temporomandibular joint pain assessed by the dentist, having an age between 18 and 65 years, and being Dutch speaking. Exclusion criteria were the presence of a severe psychiatric/neurological condition, and the presence of non-TMD related chronic pain problem² based upon power calculations (see further), we recruited 20 patients and 20 controls. Potential participants were informed about the possibility of participating by means of a flyer and information given by the clinician. When they agreed to participate, they received a phone call from the researcher providing more detailed information about the study. Twenty-one patients agreed to participate in the experiment. One woman (40 years, right-handed) had to be excluded because she reported chronic widespread pain (fibromyalgia). The age of the remaining 20 TMD patients (17 females) was 36.8 years (SD = 11.6, range = 22-59 years). Mean duration of pain was about 14 months (SD = 11.3 months, range 4-36). The majority of the sample (70%) did not yet receive treatment at the moment of testing. An overview of the demographic characteristics is provided in Table 1.

The control group was recruited from an existing database, consisting of individuals from the general population who had expressed interest to participate in scientific studies of the Ghent Health Psychology Research Group, by registering at a website (<http://www.healthpsychology.ugent.be/vrijwilligers>). Potential participants were selected with the aim of obtaining a control group matched at group level with the TMD group for age, gender and educational level. Inclusion criteria for the control participants were being Dutch speaking and having an age between 18 and 65 years. Exclusion criteria were presence of chronic pain

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please state that this was a convenience sample

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please state how you identified presence of other chronic pain problems

complaints, presence of current orofacial pain, and presence of neurological/psychiatric conditions. Eligible participants were contacted and provided with information about the study. Twenty-one healthy volunteers were willing to participate. One man (23 years, right-handed) was excluded from further analysis due to not attaining the requested performance criteria during the task. The age of the remaining 20 participants was 36.9 years (range 20-63 years; SD = 13.9). An overview of the demographic characteristics is provided in Table 1. Statistical analyses showed no differences between groups in gender, $\chi^2(1) = 0.00$, *ns*, mean age, $t(38) = -0.03$, *ns*, and educational level, $\chi^2(3) = 0.69$, *ns*.

The study was approved by the Medical Ethical Committee of the Ghent University Hospital (B670201213538). At the end of the experiment, all participants received 25 Euro as reimbursement for their expenses. The experimental session lasted for approximately 1 hour and a half.

Insert Table 1 about here

Apparatus and materials

Our tactile stimulation procedure is highly similar as what has been described in previous studies (Vanden Bulcke et al., 2013, 2014, 2015). We presented tactile stimuli at both sides of the jaw with a duration of 10 ms duration and a frequency of 200Hz, using two resonant-type tactors (C-2 TACTOR, Engineering Acoustics, Inc., Florida, <http://www.eaiinfo.com/>) consisting of a housing of 3.05 cm diameter and 0.79 cm high, and a skin contactor of 0.76 cm diameter. Before the experiment, the perceived stimulus intensities at both sides of the jaw were individually matched using a double random staircase procedure (see Levitt, 1971; Weinstein, 1968). In a first phase, participants rated 24 stimuli presented on the left jaw relative to a

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how many females?

reference stimulus, which was defined as the maximum intensity (power = 0.21 Watt) on a 5-point Likert scale ranging from 1 ('no sensation') to 5 ('maximum intensity'). The intensity that elicited an averaged rating of 3 was used as the stimulus intensity for the left jaw, and was the reference stimulus for the second phase. In the second phase, participants rated 24 stimuli on the right jaw relative to the reference stimulus on the left jaw on a 5-point Likert scale (1 = 'much weaker', 2 = 'weaker', 3 = 'equally strong', 4 = 'stronger', 5 = 'much stronger'). The intensity that elicited an averaged rating of 3 was used as the intensity of the stimulus at the right jaw¹

The task was programmed and controlled by the INQUISIT Millisecond software package (Inquisit 3.0, Millisecond Software LLC, Seattle, WA, <http://www.millisecond.com/>) on a laptop (Dell Vostro 3550).

TOJ paradigm

The TOJ paradigm is considered a particularly suitable methodology to assess spatial biases in tactile processing (Heed & Azañón, 2014). Our description is based upon previous work reported with this paradigm² anden Bulcke et al., 2013, 2014, 2015). In the TOJ task (Piéron, 1952; Shore et al., 2005; Van Damme et al., 2009³), two tactile stimuli were administered, one on either side of the jaw (temporomandibular joint), separated by one of 10 randomly assigned stimulus onset asynchronies (SOAs) ranging from -200 to +200 ms (-200, -90, -55, -30, -10, +10, +30, +55, +60, +200 ms). Each trial was preceded by the presentation of a fixation cross (2000ms) in the middle of the screen. The participants were asked to verbally report at which side of the jaw they first had perceived the tactile stimulus. The experimenter registered their responses using a keyboard. Note that the SOAs in this study were modified (made larger) as compared with previous studies with undergraduate students (-120, -60, -30, -15, -5, +5, +15, +30, +60, +120; see Vanden Bulcke et al., 2013), because pilot testing with TMD patients and adults from the

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please state whether or not they could hear these stimuli - is that an issue?

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you really should cite the prior papers on this method, not simply three of your own group's.

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why add extra citations here - just pick the right ones - it feels a little like you are trying to cite as many of your own papers as you can, which i am sure you are not doing, but best not to give that impression.

general population indicated that with these values too many participants would not have been able to meet the required performance criterion.

Self-report measures

Pain severity and pain interference were assessed by means of the Dutch version of the Multidimensional Pain Inventory (MPI-DV; Kerns, Turk & Rudy, 1985). This questionnaire consists of 28 items rated on a 7-point scale measuring severity of the pain problem (e.g. ‘Rate the level of your pain at the present moment’), interference with daily-life activities (e.g. ‘In general, how much does your pain interfere with your day-to-day activities?’), perceived control (e.g. ‘During the past week how much control do you feel you have had over your life?’), affective anxiety (e.g. ‘During the past week how irritable have you been?’) and social support (e.g. ‘How supportive or helpful is your significant other to you in your relation to your pain?’). Cronbach’s alpha in this study for the pain severity and pain interference subscales was 0.70 and 0.96 in the TMD group, and 0.69 and 0.95 in the control group.

The Tampa Scale for Kinesiophobia for Temporomandibular Disorders (TSK-TMD; Visscher et al., 2010) consists of 12 items that need to be rated on a 4-point numerical rating scale [1 = “strongly disagree”, 4 = “strongly agree”]. The subscale ‘fear of movement’ (e.g. ‘I am afraid that I might injure myself if I move my jaw’) consists of 7 items, whereas the other subscale ‘Somatic focus’ (e.g. ‘My jaw is telling me that something is seriously wrong with it’) consists of 5 items. Cronbach’s α of the TSK-TDM in this study was 0.81 for the total score, and 0.78 and 0.63 for the activity avoidance and somatic focus subscales.

The Pain Catastrophizing Scale (PCS; Sullivan, Bisschop & Pivik, 1995) is a 13-item scale to assess catastrophic thoughts about pain in both non-clinical and clinical populations. Participants are asked to reflect on past painful experiences and to indicate the degree to which

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they experienced each of the 13 thoughts or feelings during pain (e.g., ‘I become afraid that the pain may get worse’) on a 5-point scale from 0 (not at all) to 4 (all the time). The Dutch version of the PCS has been shown to be valid and reliable in both healthy populations and chronic pain patients (Van Damme et al., 2002). Cronbach’s alpha of the PCS-DV in this study for the TMD sample was 0.96 for the total score, and 0.86, 0.85, and 0.93 for the respective subscales. For the control group, Cronbach’s alpha was 0.93 for the total score, and 0.90, 0.73, and 0.89 for the respective subscales.

The Pain Vigilance and Awareness Questionnaire (PVAQ; McCracken, 1997) contains 16 items rated on a 6-point scale measuring self-reported vigilance for pain sensations (e.g., I focus on sensations of pain [1= “never”, 5= “always”]). The Dutch version of the PVAQ has been shown to be valid and reliable in both healthy populations and chronic pain patients (Roelofs et al., 2002, 2003). In the TMD group Cronbach’s α was 0.94 for the total score, and 0.91 and 0.88 for the subscales. In the control group Cronbach’s α was 0.85 for the total score, and 0.77 and 0.94 for the subscales.

After each test phase, the participants were asked to rate the intensity of the tactile stimuli (‘How intense did you experience the stimuli on your left/right jaw?’) on an eleven-point numerical rating scale (anchored 0 = not at all and 10 = very strongly).

Procedure

Upon arrival at the laboratory, participants were informed about the experimental procedures and provided written informed consent. After this, they completed the MPI-DV, TSK-TMD (only TMD patients), PCS, and PVAQ (see self-report measures). Next, they were seated in front of the experimental apparatus. Their forearms were positioned symmetrically on the table. The tactors were placed in the middle of the superficial head of the masseter muscle of each side of

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did you stipulate the order in which these self report questionnaires were completed?

the jaw. The participants were informed that they had to decide on each trial which stimulus had been presented first. The accuracy of participants' responses was emphasized, rather than the speed. Participants wore noise-cancelling headphones (PXC 350 Sennheiser) to prevent any interference from environment noise. Following this, the session began with a practice block of twenty trials (2 trials per SOA). Next, four blocks of 70 trials (7 trials per SOA) were presented. The participants were not given any feedback about their performance. After each block, they were asked to rate perceived intensity of tactile stimuli at both jaw and they completed several other rating scales gauging concentration, effort, attention, and fatigue (not reported).

Data-analyses

TOJ data handling. We used the guidelines proposed by Spence, Shore & Klein (2001), and described in previous studies (Vanden Bulcke et al., 2013, 2014, 2015). Specifically, we excluded participants from statistical analysis when any of their PSS values was larger than the highest SOA (± 200 ms), and when less than 80% of the responses on trials with the largest SOA (± 200 ms) was incorrect. As a result, one participant of the control group (male, right-handed) was removed from data analysis. The analyses were based on the procedure that has been commonly described in the literature (Shore et al., 2005; Spence et al., 2001; Van Damme et al., 2009; Vanden Bulcke et al., 2014). The proportions of 'left-jaw-first' and 'right-jaw-first' responses for all trials at each SOA, were converted into the corresponding z-scores using a standardized cumulative normal distribution. The best-fitting straight line was computed for each participant and the derived slope and intercept values were used to compute the just noticeable difference (JND) and the point of subjective simultaneity (PSS).

JND is monotonically related to the slope of the psychometric function and indicates the interval needed to achieve 75% correct performance, and as such provides a standardized

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aha - disregard previous question

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i am intrigued that you saw this as important when you actually matched the stimuli for perceived intensity.

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please state all assessments they performed.

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measure of the sensitivity of participants' temporal perception. PSS refers to the (virtual) SOA at which participants report the two events (right jaw first and left jaw first) equally often (Vanden Bulcke et al., 2011). The PSS is computed as the opposite of the intercept divided by the slope from the best-fitting straight line. It is customary to code SOAs so that negative values indicate that the *test* stimulus was presented before the *reference* stimulus. In the TMD sample, we regard stimuli at the painful joint as test stimuli, while stimuli at the other joint are labeled as reference stimuli. In the remainder of the manuscript, positive SOAs refer to trials in which the stimulus at the non-painful joint preceded the stimulus at the painful joint. When interpreting effects on the PSS measurement, it is thus important to keep in mind that positive values indicate that stimuli stemming from the non-painful joint should be presented *before* stimuli originating from the painful joint for both to be perceived as simultaneously occurring. Correspondingly, positive PSS values indicate that tactile input at the painful joint is prioritized over tactile input at the other joint. In the control group, we made the (arbitrary) choice to consider stimuli at the right joint as test stimuli, while stimuli at the left joint were reference stimuli. Here, positive values indicate that stimuli stemming from the left joint should be presented *before* stimuli originating from the right joint for both to be perceived as simultaneously occurring. Correspondingly, positive PSS values indicate that tactile input at the right joint is prioritized over tactile input at the left joint.

TOJ hypothesis testing. We tested in each group whether the obtained mean PSS value was significantly different from the actual point of simultaneity (virtual SOA of 0 ms) using one-sample *t*-tests. Based upon the studies by Moseley et al. (2009, 2012a, 2012b), showing a large effect size for attenuated tactile processing at the painful side in unilateral chronic low back pain, and by Vanden Bulcke et al. (2013), reporting an effect size of 0.70 for enhanced tactile processing at a hand threatened by experimental pain (relative to the other hand) in healthy

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volunteers, the current study was powered to detect an effect size of 0.70 with 80% power at $\alpha < .05$ for a one-sample t -test (two-tailed because expectations about the direction of the effect are conflicting). As a result, at least 19 patients were needed. Note that we did not compare PSS values between groups, because the meaning of these values is different for these groups (see TOJ data handling). In the control group a positive PSS simply means that tactile input at the right joint is prioritized over tactile input at the left joint. In the TMD sample a positive PSS means that tactile input at the painful joint (irrespective of whether this is left or right) is prioritized over tactile input at the non-painful joint. As an additional exploratory analysis, we tested within the TMD group whether the PSS was different between those that had pain at the left joint ($N = 10$) and those that had pain at the right joint ($N = 10$), using an independent-samples t -test. We had no specific hypotheses regarding the JND.

Perceived intensity of tactile stimuli. We calculated average intensity ratings across the 4 blocks, separately for the left and right jaw. We compared average perceived tactile intensity between the TMD and the control groups, using an independent samples t -test. Next, we compared perceived intensity between the painful and the non-painful joint in the TMD group, and between the left and the right joint in the control group, using paired-samples t -tests.

Questionnaires. For the TSK-TMD we only provide descriptive statistics for the TMD group. For all other questionnaires (MPI, PCS, PVAQ) we compared scores between TMD patients and controls, using independent-samples t -tests. In the TMD group, we also calculated exploratory Pearson correlations to detect possible associations between questionnaire scores and the behavior measure of spatial bias (PSS).

In all analyses significance level was set at $p < .05$ for ease of comparison with the norms of Cohen (1988), we calculated effect sizes for independent samples using the formula of Dunlap et

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this is problematic because you are doing so many tests and you are maximising the effect of chance...please either justify this or change p values.

al. (1996). We determined whether Cohen's d was small (≤ 0.20), medium (≤ 0.50), or large (≤ 0.80). We also report the 95% confidence intervals (95% CI) of the effect sizes.

Results

TOJ

The JND was not significantly different between the TMD group ($M = 73.87$, $SD = 20.84$) and the control group ($M = 64.42$, $SD = 15.42$), $t(38) = 1.63$, $p = .11$. Analysis of the PSS values in the TMD group showed that tactile stimuli delivered to the non-painful side of the jaw had to be delivered before tactile stimuli at the painful side, for both stimuli to be perceived as occurring at the same time ($M = 17.59$, $SD = 41.5$). This was the case in 13 out of 20 patients. However, the difference with the actual point of simultaneity (0 ms) failed to reach statistical significance, $t(19) = 1.90$, $p = .07$ ($d = 0.42$, [95% CI: -0.19, 1.03]). There was no significant difference in PSS values between patients with left joint pain ($M = 7.15$, $SD = 41.89$) and patients with right joint pain ($M = 28.02$, $SD = 40.51$), $t(18) = 1.13$, $p = .27$. In the control group, the PSS approached zero ($M = -0.12$, $SD = 27.40$), and did not differ from the actual point of simultaneity, $t(19) = -0.02$, $p = 0.98$. Mean PSS values in both samples are shown in Figure 1.

Insert Fig. 1 about here

Perceived tactile intensity

Perceived intensity of tactile stimuli (across sides and blocks) was significantly higher in the TMD group ($M = 5.44$, $SD = 2.03$) than in the control group ($M = 3.98$, $SD = 1.99$), $t(38) = 2.29$, $p = .028$ ($d = 0.71$ [95% CI 0.07-1.35]). Furthermore, no significant difference in perceived

 Number: 1 Author: Reviewer Subject: Sticky Note Date: 21/9/17, 4:53:54 pm
please state 95% CI to support that the PSS was different to zero and thus support your statement.

 Number: 2 Author: Reviewer Subject: Sticky Note Date: 21/9/17, 4:54:04 pm
it is not clear to me that you mean by 'this was the case in 13/20. do you mean that the mean and sd you have just stated was drawn from just 13 of them or this was drawn from the whole sample but 7/20 of the sample had a pss that was negative?

 Number: 3 Author: Reviewer Subject: Sticky Note Date: 21/9/17, 4:54:13 pm
this is intriguing because you established the intensity based on a perceived score of 3. did you expect this? is this why you hypothesised that they would sensitise over time? or have i misunderstood this?

intensity between tactile stimuli presented on the painful side ($M = 5.56$, $SD = 2.02$) and tactile stimuli presented on the non-painful side ($M = 5.31$, $SD = 2.27$) was found, $t(19) = 0.80$, $p = 0.44$

When considering the results on perceived tactile intensity it is important to note that the actual intensity of administered tactile stimuli was not different between the TMD group ($M = 22.78$, $SD = 3.47$) and the control group ($M = 21.93$, $SD = 3.10$), $t(38) = 0.82$, $p = .419$, and that in the TMD group there was no significant difference in actual tactile intensity between the painful joint ($M = 23.05$, $SD = 4.85$) and the non-painful joint ($M = 22.50$, $SD = 3.86$), $t(19) = 0.46$, $p = 0.651$.

Self-report data

Table 2 represents the average scores and standard deviations for the self-report questionnaires in the TMD group and the control group (except for TSK-TMD). Scores on the MPI were quite similar as those found in a large ($N = 491$) sample of TMD patients (Reissman et al., 2008), except for the pain severity subscale, which was almost 1 standard deviation lower in the current sample. The mean score for the TSK-TMD ($M = 24.75$, $SD = 6.44$, range 14-40) was highly similar to the score obtained in a large sample of TMD patients ($N = 301$, $M = 24.2$, $SD = 6.9$) in the validation study of the TSK-TMD (Visscher et al., 2010)

With regard to the MPI, independent samples t -tests revealed that the TMD group had significantly higher scores as compared to the control group (pain severity: $t(38) = 3.33$, $p = .002$; pain interference: $t(38) = 2.67$, $p = .011$). For the PVAQ, independent samples t -tests revealed that the TMD group had significantly higher scores as compared to the control group, $t(38) = 2.62$, $p = .01$. No significant differences between both groups were found on the Pain Catastrophizing Scale ($t(38) = 0.55$, $p = 0.58$).

 Number: 1 Author: Reviewer Subject: Sticky Note Date: 21/9/17, 4:54:26 pm
so that is very interesting isn't it! they sensitised bilaterality from calibration to testing phase.

 Number: 2 Author: Reviewer Subject: Sticky Note Date: 21/9/17, 4:54:35 pm
this would seem appropriate for the discussion not results

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Insert Table 2 about here

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Discussion

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Pearson Correlations between questionnaire scores and the spatial bias measure (PSS) in the TMD group are shown in Table 3. Most correlations did not reach significance, but there was a significant positive correlation between the PSS and the somatic focus subscale of the TSK-TMD ($r = .50, p = .025$) suggesting that higher scores on this scale were associated with a tactile processing bias toward the painful side of the jaw. Given the small sample size, we verified the robustness of this association by additionally calculating a non-parametric correlation (Spearman's rho), and obtained a very similar effect ($r = .49, p = .030$).

Insert Table 3 about here

We investigated spatial bias in tactile processing at the orofacial region in chronic unilateral TMD patients. Based upon two research lines in the literature, either slower (Moseley et al., 2012) or faster (Van Damme et al., 2016) processing of tactile stimuli at the painful temporomandibular joint might be hypothesized in TMD patients. While the average PSS in healthy controls was approximately zero, it was positive (about 18 ms) in the TMD group, suggesting enhanced rather than attenuated tactile processing at the painful joint in these patients. Nevertheless, it should be emphasized that the difference with the actual point of simultaneity (0 ms) just failed to reach statistical significance ($p = .07$) and that there was considerable

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this is highly problematic considering how many analyses you did all up - you are almost bound to get a false positive somewhere

 Number: 2 Author: Reviewer Subject: Sticky Note Date: 21/9/17, 4:54:50 pm
but it wasn't significant.....so it does not suggest enhanced processing, but no bias.

individual variability, with only 13 out of 20 patients displaying this effect. Note that the study was sufficiently powered to detect previously reported effect sizes with similar paradigm¹

To gain² further insight in this individual variability, we examined the correlations between the PSS values and the self-report questionnaire scores regarding pain cognitions in the TMD group. Cognitive-affective pain models would predict threatening appraisal of pain (e.g., fear-avoidance beliefs, pain catastrophizing, hypervigilance) to be associated with enhanced top-down prioritization of pain-related information (Crombez, Van Damme & Eccleston, 2005; Eccleston & Crombez, 1999; Van Damme et al., 2010; Vlaeyen & Linton, 2000).³ Yet, it might be possible that enhanced tactile processing on the painful joint might especially emerge in patients who have a stronger tendency to experience negative pain cognitions.⁴ We found partial support for this idea. Specifically, we observed a significant positive association between the "somatic focus" subscale of the TSK-TMD, suggesting that those who tend to appraise somatic sensations in their jaw in a threatening way, show a stronger spatial bias in tactile processing to the painful side of the jaw. Although the importance of this significant correlation should not be overstated, given the rather small sample, it fits well with previous findings showing that levels of pain-related fear are associated with self-reported jaw activity limitations and disability in TMD patients (Turner et al., 2001; Visscher et al., 2010) and faster detection of innocuous electrical stimuli in chronic low back pain patients (Peters et al., 2002). It may thus be well worth further exploring the possible effect of TMD-specific pain-related fear on somatosensory processing in future studies. The lack of significant correlation between PSS and self-reported pain catastrophizing and pain vigilance may be somewhat surprising, but it should be noted that, contrary to the TSK-TMD, both PCS and PVAQ assess general pain cognitions that are not specifically related to TMD.

 Number: 1 Author: Reviewer Subject: Sticky Note Date: 21/9/17, 4:54:58 pm

thus, it would seem you should conclude that your hypothesis was not supported.

 Number: 2 Author: Reviewer Subject: Sticky Note Date: 21/9/17, 4:55:05 pm

i think this might be a semantic bias....

 Number: 3 Author: Reviewer Subject: Sticky Note Date: 21/9/17, 4:55:13 pm

why then would you hypothesise a bias in TACTILE processing, which is not pain related information?

 Number: 4 Author: Reviewer Subject: Sticky Note Date: 21/9/17, 4:55:28 pm

but you mainly found no support for it.

364 Our results seem to contradict previous findings in patients with unilateral pain complaints.
 365 Studies using tactile TOJ methodology have shown that in patients with both unilateral chronic
 366 low back pain and complex regional pain syndrome, tactile processing at the painful side
 367 appeared be attenuated (Moseley et al., 2009, 2012a, 2012b; but see Van der Biest et al.,
 368 unpublished data¹ or a failed replication in a complex regional pain syndrome sample). More
 369 specific, these authors found shifts in PSS so that tactile stimuli at the affected side had to be
 370 presented before stimuli at the other side, in order to be perceived as simultaneous. Why we were
 371 not able to replicate this in patients with chronic unilateral TMD, and even found indications for
 372 the opposite effect, is puzzling. It has been argued that impaired tactile processing at the affected
 373 body part may be a consequence of disrupted spatial representation (Moseley et al., 2009).
 374 Perhaps such disruption is a characteristic of only specific subpopulations of chronic pain
 375 patients, and is this feature not present in (our sample of) patients with TMD² should also be
 376 noted that there are minor methodological differences between our study and other experiments,
 377 especially with regard to the SOAs used in the tactile TOJ. More specific, we used SOAs
 378 between 10 and 200 ms, whereas in the studies of Moseley and colleagues, the range was
 379 between 10 and 240 ms. It is unlikely, though, that these small differences would be responsible
 380 for obtaining opposite effects. Anyway, our findings show that we should be cautious in
 381 generalizing the idea of disrupted tactile processing in painful body parts to the entire population
 382 of unilateral chronic pain patients (Van Damme et al., 2016). More research with more diverse
 383 and larger samples of chronic pain patients (e.g., Van Damme et al., 2014, 2015), allowing
 384 identification of moderating factors of enhanced versus attenuated tactile processing, is highly
 385 recommended.

 Number: 1 Author: Reviewer Subject: Sticky Note Date: 21/9/17, 4:55:35 pm

how does the reader see this? i don't think it is in the reference list. also cite bultitude including co authors here for visual toj data that support the moseley papers.

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indeed this perspective has already been argued in subsequent papers.

386 A number of issues deserve further discussion. First, we may speculate that the (non-
 387 significant) spatial processing bias to tactile stimuli in the painful joint might be due to
 388 heightened tactile sensitivity at that location in TMD patient¹ however, we individually
 389 calibrated and matched tactile stimuli across both joints to be perceived as equally intense, and
 390 that was also confirmed by self-reports during the experiments. More specific, both actual and
 391 perceived intensity of tactile stimuli did not differ between the affected and the non-affected jaw
 392 in our TMD sample, so spatial bias to the painful joint cannot be explained by differences in
 393 tactile sensitivity. Second, an interesting observation is that the overall perceived intensity of
 394 tactile stimuli (across both sides) was higher in the TMD group than in the control group,
 395 whereas actual objective intensity was not different between groups. This may suggest some
 396 form of sensitization to somatosensory input in TMD patients. However, because this amplified
 397 perception was not specific to the painful side, it cannot explain any spatial bias. Also, this
 398 overall heightened tactile intensity in TMD patients had no impact upon their ability to perform
 399 the TOJ task, as the JND measure did not significantly differ between the TMD group and the
 400 control group. Third, we already mentioned that the spatial bias in TMD patients was small, and
 401 that individual variability was high, with strongest bias in those patients characterized by
 402 threatening appraisal of bodily signals in the jaw. An interesting avenue for future research
 403 would be to investigate the effect of contextual factors on spatial bias² should be noted that in
 404 this study, there was no induction of any bodily threat. It might be that situations in which
 405 patients actively anticipate pain would increase spatial bias to the painful jaw. It could be
 406 recommended that future studies examine tactile processing while anticipating a painful dental
 407 procedure, or after experimentally inducing orofacial pain or pain anticipation by requiring TMD
 408 patients to perform certain movements with their jaw (Moore et al., 2013). Such experimental

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this is highly problematic - to argue that you had non significant bias is not in keeping with the data.

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the authors have in fact investigated this in a previous study that is relevant here and perhaps should be cited.

manipulation of bodily threat has proven successful in inducing spatial bias in tactile processing in non-clinical samples (Durnez & Van Damme, 2015; Vanden Bulcke et al., 2013; Van Hulle et al., 2015). Fourth, it must be emphasized that we should be cautious in generalizing the results to populations experiencing other forms of unilateral pain, and call for further research in these populations.

Conclusions

Our findings add to existing evidence that TMD patients show alterations in tactile processing, i.e., we replicated previous studies showing that TMD patients perceived tactile stimuli at the jaw as more intense compared with healthy controls. In addition, for the first time, indications were found that unilateral TMD patients, especially those who are characterized by fear-avoidance beliefs, show a tactile processing bias toward the painful side of the jaw. This finding suggests a potential role of hypervigilance, and is in line within recent cognitive-affective theories of chronic pain.

Acknowledgements

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 Number: 1 Author: Reviewer Subject: Sticky Note Date: 21/9/17, 4:56:08 pm
i believe your results do not support this conclusion.

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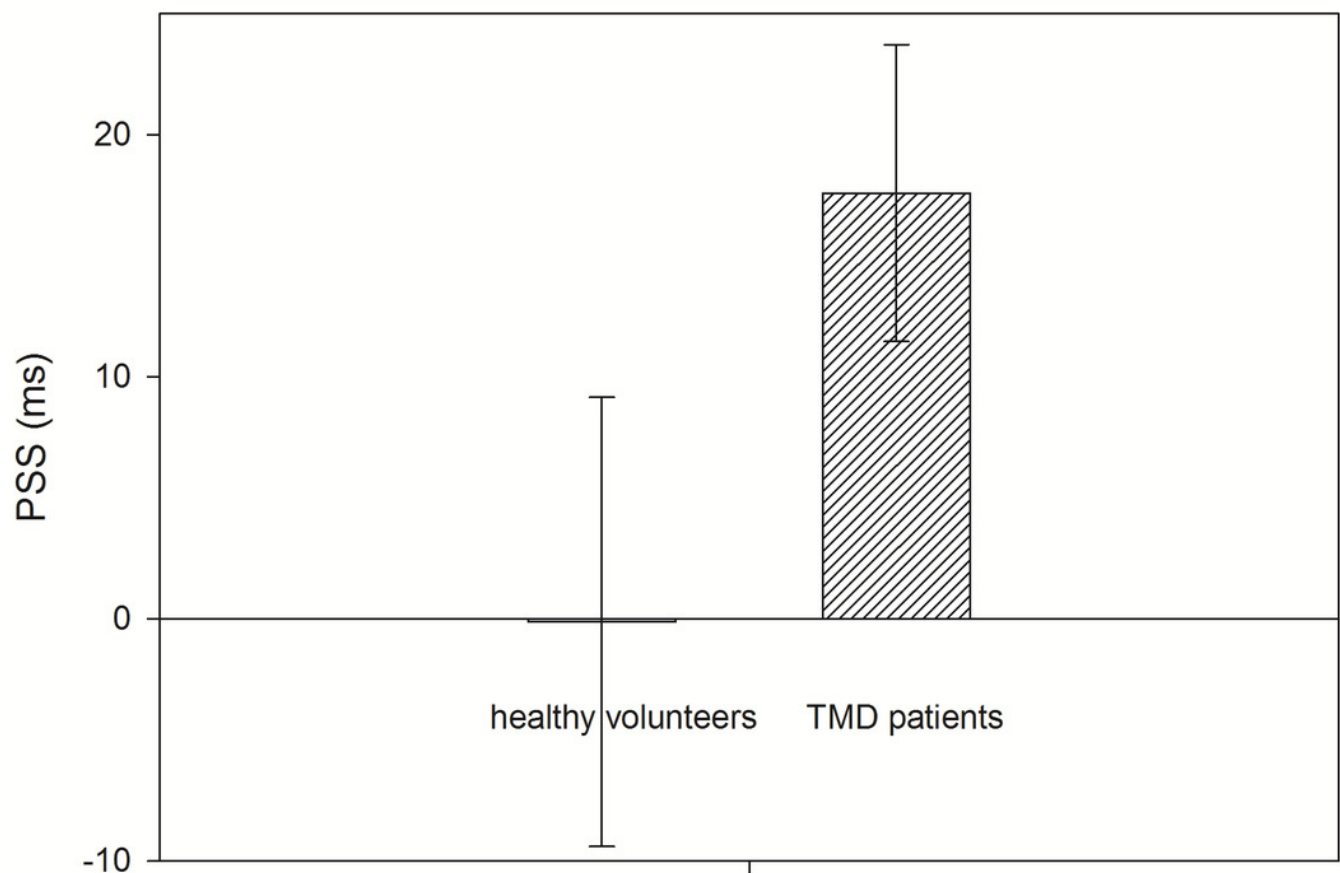
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Figure 1

Index for spatial bias (PSS) (in ms and with standard errors) for healthy volunteers and TMD patient 



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please use standard deviations here or 95% confidence intervals so that the reader can intepret it

Table 1 (on next page)

Demographic data

Demographic characteristics of TMD group and control group

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1 Table 1
2 *Demographic characteristics of the patient and control group*

	TMD patients		Control group	
	M ± SD	N (%)	M ± SD	N (%)
Men		3 (15%)		2 (10%)
Women		17 (85%)		18 (90%)
Age (in years)	36.8 ± 11.66 (range 22-59)		36.9 ± 13.90 (range 20-63)	
Family situation				
single		4 (20%)		12 (60%)
living together		5 (25%)		4 (20%)
married		8 (40%)		4 (20%)
widow(er)		3 (15%)		0
Educational level				
primary education		0		0
lower secondary education		2 (10%)		1 (5%)
higher secondary education		6 (30%)		8 (40%)
higher education		4 (20%)		4 (20%)
higher education: university		8 (40%)		7 (35%)
Profession				
housemen/housewife		1 (5%)		1 (5%)
laborer		2 (10%)		0
employee		10 (50%)		10 (50%)
professional		0		0
senior manager		0		1 (5%)
disabled		3 (15%)		1 (5%)
student		4 (20%)		5 (25%)
job seeker		0		2 (10%)

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Table 2(on next page)

Self-report data

Average and standard deviation of self-report measures among participants for each group

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1 Table 2

2 *Means and standard deviations of self-report questionnaires in both groups*

	TMD group	Control group
MPI: pain severity	1.9 (1.1)	0.9 (0.9)
MPI: interference	2.0 (1.9)	0.8 (1.0)
TSK-TMD: total	24.8 (6.4)	-
TSK-TMD: activity avoidance	16.5 (4.7)	-
TSK-TMD: somatic focus	8.3 (2.6)	-
PVAQ: total	45.1 (15.5)	32.3 (13.1)
PVAQ: attention to pain	26.0 (9.8)	16.3 (7.4)
PVAQ: attention to changes in pain	19.1 (6.8)	16.1 (8.9)
PCS: total	18.4 (13.0)	16.3 (11.0)
PCS: rumination	6.7 (4.2)	6.9 (4.2)
PCS: magnification	3.8 (3.3)	3.5 (2.7)
PCS: helplessness	7.9 (6.2)	6.0 (5.3)

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Table 3(on next page)

Correlation data

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1 Table 3

2 *Correlations between self-report measures and the TOJ outcome measure (PSS) for the TMD group*

	1	2	3	4	5	6	7	8	9	10
1. PSS	-									
2. TSK-TMD (TOT)	.31	-								
3. TSK-TMD (AA)	.15	.94 ^c	-							
4. TSK-TMD (SF)	.50^a	.78 ^c	.53 ^a	-						
5. PVAQ (TOT)	.17	.29	.10	.55 ^a	-					
6. PVAQ (PAIN)	.16	.27	.05	.59 ^b	.95 ^c	-				
7. PVAQ (CHANGES)	.15	.27	.14	.41	.90 ^c	.73 ^c	-			
8. PCS (TOT)	.09	.43	.45 ^a	.26	.40	.37	.38	-		
9. PCS (RUM)	-.13	.27	.31	.10	.44	.42	.39	.93 ^c	-	
10. PCS (MAG)	.29	.50 ^a	.47 ^a	.38	.37	.36	.32	.93 ^c	.76 ^c	-
11. PCS (HELP)	.11	.46 ^a	.48 ^a	.27	.35	.31	.36	.98 ^c	.87 ^c	.90 ^c

3 ^a $p < .05$, ^b $p < .01$, ^c $p < .001$

4 Note: TOT = total score; AA = Activity Avoidance; SF = Somatic Focus; PAIN = Attention to pain; CHANGES = Attention to pain
 5 changes; RUM = rumination; MAG = magnification; HELP = Helplessness

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