Supplementary Materials for:

Placebo responders versus non-responders: A cross-sectional cohort study for psychological determinants

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Fig. S1. Flow chart of the recruitment and enrollment

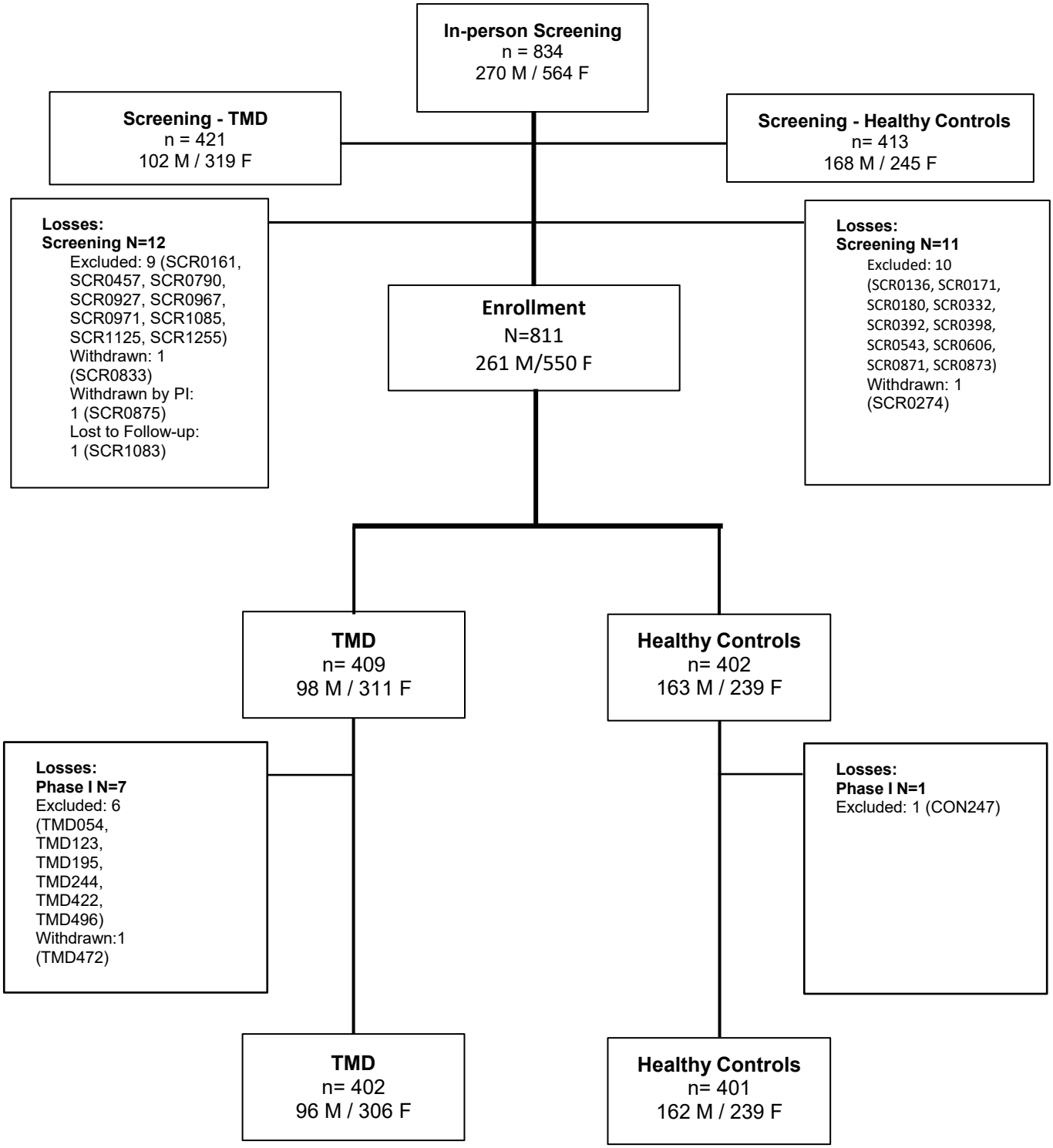

Table S1. Lists of psychological questionnaires to both TMD and HC participants after the experiment.

Category	Questionnaire	Abbreviation	Item	Description	Reference
RDoC Negative Valence Systems	State-Trait Anxiety Inventory (trait)	STAI_y1	20	Measurement of a person's state anxiety level	Spielberger, 2010
	Beck's Depression Inventory	BDI	21	Measurement of characteristics attitudes and symptoms of depression	Beck, Steer, and Brown, 1996
	Depression Anxiety Stress Scales	DASS	21	Measurement of depression, anxiety and stress	Lovibond and Lovibond, 1995
	The Positive and Negative Affect Schedule	PANAS	20	Assessment of the positive and negative affect of an individual during the past week.	Watson et al., 1988
	Mood and Anxiety Symptom Questionnaire	MASQ	62	Assessment of depression and anxiety symptoms. The MASQ contains 4 subscales including Anhedonia Depression (a lack of positive affect), Anxious Arousal (symptoms of somatic arousal), General Distress (non-specific symptoms of distress or negative affect), and general distress depression (negative affect considered depressive).	Watson and Clark, 1991
	Life Orientation Test - Revised	Lot_r	10	Measurement of optimism and pessimism	Scheier, Carver, and Bridges, 1994
RDoC Positive Valence Systems	Behavioral avoidance/inhibition scales	BisBas	24	Assessment of individual differences in the sensitivity of behavioral approach	Carver and White, 1994

				system (BAS) and behavioral avoidance system (BIS). The BisBas includes 4 subscales: behavioral inhibition (BIS), BAS drive, BAS Fun Seeking, and BAS Reward Responsiveness.	
RDoC Social Processes System	Interpersonal Reactivity Index	IRI	28	The IRI assessed reactions of one person to the observed experience of another. It contains 4 subscale including Perspective Taking (the tendency to spontaneously adopt the psychological point of view of others), Fantasy (taps respondent's tendencies to transpose themselves imaginatively into the feeling and action of fictitious characters in books, movies, and plays), Empathic Concern (assesses "other-oriented" feelings of sympathy and concern for unfortunate others), and Personal Distress (measures "self-oriented" feelings of personal anxiety and unease in tense interpersonal settings)	Davis, 1980

General Personality	NEO Five-Factor Inventory	NEO-FFI	60	The NEO-FFI measures five dimensions of personality (i.e., Neuroticism, Extraversion, Openness to experience, Agreeableness, and Conscientiousness)	Costa and McCrae, 2010
Pain related characteristics	Fear of Pain Questionnaire	FPQ	30	Assessment of fear of pain including three subscales: fear of minor pain, fear of medical pain, and fear of severe pain	McNeil and Rainwater, 1998
	Pain Catastrophizing Scale	PCS	13	Measurement of pain catastrophizing with three subscales including Helplessness, Rumination, and Magnification	Sullivan et al., 1997

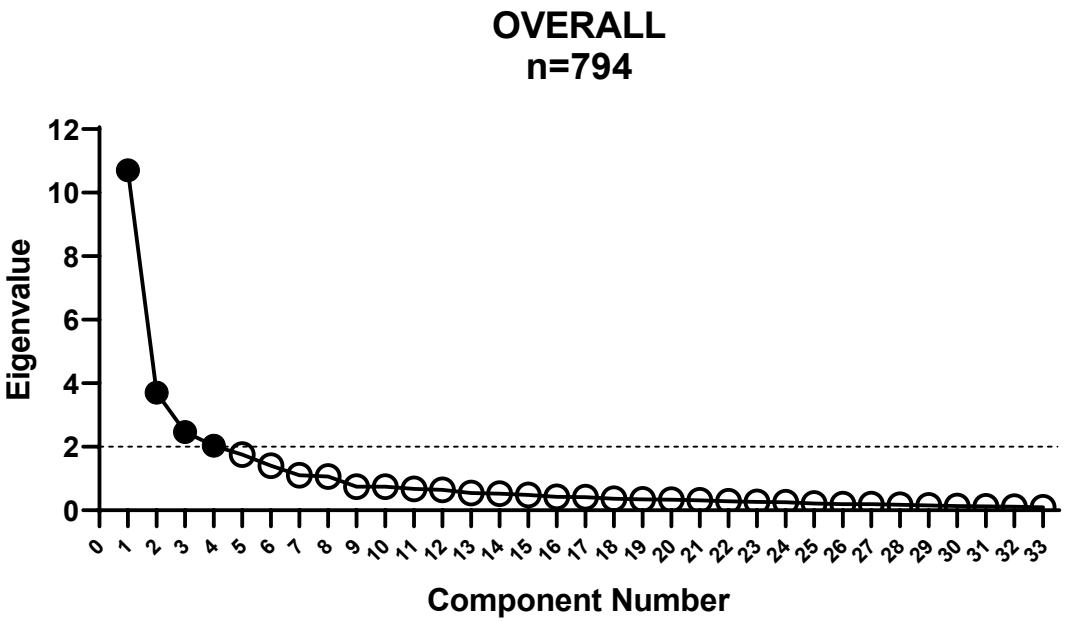

Fig. S2 Elbow scree plot in the overall sample. The principal component analysis (PCA) resulted in 4 components that had the eigenvalue over 2, explaining 54.58% of the total variances of the psychological subscales.

In order to determine 1) if the participants' successful differentiation of red and green trials influenced pain report during the conditioning phase and 2) if the conditioning paradigm elicited significant placebo analgesic effects, we conducted two repeated measure ANCOVAs on individual trial pain intensity ratings during the conditioning phase and the testing phase, respectively. For both ANCOVA models, colors of the screens (red vs. green) and trials (12 trials for conditioning phase, 6 trials for testing phase) were set as within-subject variables. TMD vs. HC participants were set as between-subjects variable. Age, sex, and pain sensitivity (i.e., differences of temperatures in the conditioning phase, and temperature used in testing phase) were set as covariate. Additional repeated ANCOVAs were conducted on conditioning and placebo hypoalgesia with trials (12 trials for conditioning phase, 6 trials for testing phase) as within-subject factors, TMD vs. HC participants as between-subjects factors. This was to *compare conditioning and placebo hypoalgesia* between TMD and HC participants. Greenhouse-Geisser correction was applied when Sphericity assumptions were violated.

Participants with on-going pain showed a similar magnitude of placebo analgesic effects in comparison

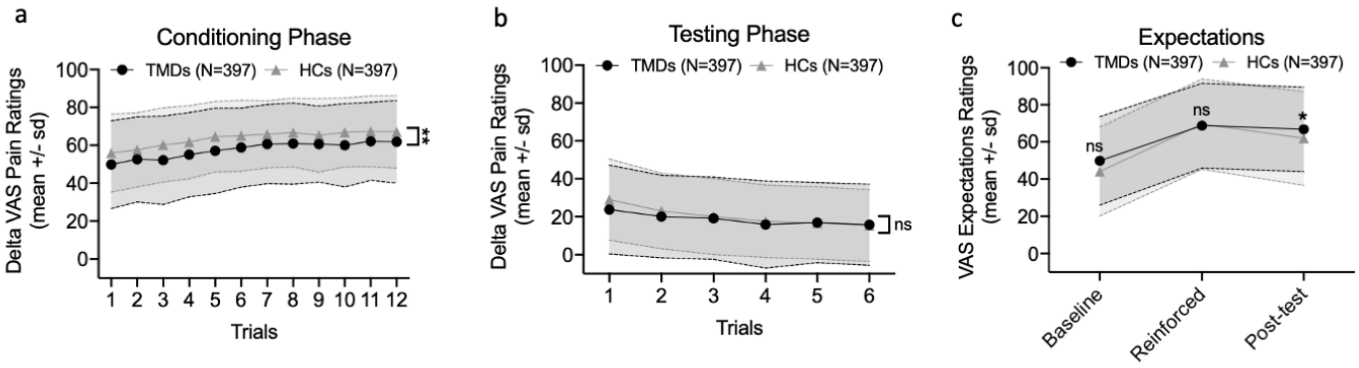

*Fig. S3. (a) Delta VAS pain ratings for TMD and HC participants during the conditioning phase (12 delta scores). TMD participants showed smaller delta scores than HC participants did. The trend of acquisition (slope of the delta scores) did not differ between TMD and HC participants. (b) Magnitudes of placebo hypoalgesia between TMD and HC participants. TMD and HC did not differ in magnitudes of placebo hypoalgesia. TMD participants had a flatter extinction pattern than HC participants did. (c) Assessments of expectations between TMD and HC participants. TMD participants had greater overall expectations than HC participants but did not differ from HC at baseline or after the conditioning phase. Data are displayed with mean and SD. ns=non significance; *p<0.05; **p<0.01*.

with healthy participants. Despite the fact that chronic pain participants experienced lower levels of pain reductions than their healthy counterparts during the conditioning phase, they exhibited comparable levels of *reinforced expectations* on the effectiveness of the intervention. Furthermore, TMD and HC participants were characterized by distinct profiles of psychological features that contributed to the variations in conditioning, expectations, and placebo effects. In a recent parent study [3], we found that verbal suggestion plus classical conditioning induced similar magnitude placebo hypoalgesia in chronic pain participants when compared to healthy controls.

Prior therapeutic experiences of pain reductions drove placebo hypoalgesia [3], regardless of the presence of chronic pain. This is consistent with other clinical studies with chronic pain patients (e.g., patients with irritable bowel syndromes, patients with fibromyalgia, low back pain) where people with ongoing pain showed no different placebo responses than healthy controls [2; 8; 9; 11]. In terms of patterns of acquisition (conditioning phase) and extinction (testing phase), we modeled the rate of the pain rating differences during

the acquisition and the testing phase for each individual. Acquisition, as a process of associative learning, refers to the procedure where the conditioned stimuli (CS) is repeatedly paired with the unconditioned stimuli (US) [1; 6]. After comparing the rates of acquisition processes, we observed no differences in the learning rate between chronic pain and healthy participants, suggesting healthy and chronic pain participants had similar learning efficiency during the conditioning phase. Interestingly, during the testing phase, healthy participants exhibited a *faster* extinction rate of placebo hypoalgesia than TMDs. we found 53.9% and 67.8% of placebo responders in TMD and HC participants, respectively using six repeated measurements via a permutation approach [4; 12]. The permutation calculation accounted for the trial-by-trial variability across self-reported pain ratings during the placebo testing phase.

Recruitment strategy

TMD and HC participants were recruited using the following strategy:

1. Advertising in the Afro-American Newspaper and other local newspapers (e.g. The Baltimore Sun);
2. Advertising at the School of Dentistry clinics and other University of Maryland Baltimore (UMB); student list servers across the campus (e.g. Elm, Dental Digest);
3. Contacting regional orofacial pain primary care providers for participant referrals;
4. Postings in Craigslist, participant recruitment websites such as Just Another Lab Rat, and similar online recruitment resources;
5. Collaborating with the pain management clinics including the University of Maryland Rehabilitation & Orthopaedic Institute;
6. Contacting previous research participants who have provided permission to be re-contacted (e.g. OPPERA studies [5; 7; 10] at SOD and other TMD studies at JHU sending official recruitment letters to previous OPPERA participants);
7. Reaching out to local Blogs and Archives;
8. Posting flyers at local businesses, including at restaurants and stores that have public bulletins or grant permission to us to post about our study;
9. Advertising on public transportation, including the circulator, University of Maryland shuttle, and Baltimore public transportation (buses and trains etc.);
10. Advertising in UMB and public garages, including elevators and common spaces, per the specific garage's policy.
11. Advertising on the UMB Center to Advance Chronic Pain Research (CACPR)website (https://www.umaryland.edu/cacpr/about-cacpr/);
12. Advertising on social media such as Twitter, Instagram and Facebook. A Colloca Lab page was created (colloca.wixsite.com/colloca-lab);
13. Recruiting participants for the study at academic fairs, music and arts festivals, "tabling," health fairs, etc. We requested permission to contact the organizers of the event to include approved advertisements in brochures/handouts for the event and be present in case people were interested in learning more about this research initiative;
14. Sending flyers, information on the study, and other approved advertising materials to forums, informational pages, and support groups other than TMD/TMJ related sources. We noticed that comorbidities such as skeleton-muscular/joint conditions (i.e. Ehlers Danlos Syndrome) are seen in TMD. We have heard from several participants that they participate in online pages such as these that occasionally post studies. We saw this as an opportunity not only to recruit additional participants with TMD, but also to actively involve these communities in research that will improve understanding of their illness and hopefully form the foundation for future research into effective therapies;
15. Searching UM School of Dentistry's patient electronic health record in EPIC and Axium for patients having diagnostic codes related to TMD or co-morbid conditions (i.e. 306.8 (F45.8, F59) bruxism/clenching; 307.8 (F45.41) pain disorder related to psychological disorder; 346.00 (G43.109) migraine with aura; 346.10 (G43.009) migraine w/out aura; 339.00 (G44.009) cluster headache; 339.10 (G44.209) tension-type headache; and 350.2 (G50.1) atypical facial pain.

Psychological factors and TMD

Multiple linear regressions were conducted in the TMD cohort to examine how psychological factors could influence TMD intensity and TMD related interference assessed by Graded Chronic Pain Scale (GCPS [13]). Higher levels of emotional distress were predictive of greater clinical pain intensity (ß=0.14, p=0.012) and pain interference (ß=0.20, p<0.001). Although pain related fear and catastrophizing was not significantly linked with levels of chronic pain intensity (ß=0.10, p=0.058), it was a significant predictor of a higher pain interference (ß=0.11, p=0.035). Moreover, higher reward seeking was linked to a lower level of chronic pain interference (ß=-0.15, p=0.010).

Randomization sequences

	Sequence 1	Sequence 2	Sequence 3	Sequence 4
Conditioning	red	green	green	green
	green	green	red	red
	red	red	green	green
	green	green	red	green
	green	red	green	red
	red	red	red	red
	red	green	green	green
	green	red	red	red
	green	red	green	green
	red	green	red	green
	green	green	green	red
	red	red	red	red
	red	green	green	green
	green	green	red	red
	red	red	green	green
	green	green	red	green
	green	red	green	red
	red	red	red	red
	red	green	green	green
	green	red	red	red
	green	red	green	green
	red	green	red	green
	green	green	green	red
	red	red	red	red
Testing	red	green	green	green
	green	green	red	red
	red	red	green	green
	green	green	red	green
	green	red	green	red
	red	red	red	red
	red	green	green	green
	green	red	red	red
	green	red	green	green
	red	green	red	green
	green	green	green	red
	red	red	red	red

Subject #_____ Protocol # _____ Date_____

Study Exit Form

When you enrolled in the study, we explained that this study uses deception because we were going to provide you with misleading information about parts of the study. When we use deception in a study, we always explain the nature and purpose of the deception after participation.

The purpose of this form is to disclose to you the full nature of the study and to answer any questions that you may have.

You were told that the purpose of the study is to test the role of candidate genes on pain experience (Experiment 1) and brain responses (Experiment 2). You were told that you would receive two levels of painful stimulation – low and high – given immediately after a green and red light, respectively.

However, we did not tell you, that during the last series of stimulations we set the intensity to the same painful level only. Using the same painful stimulation for the green and red lights, allows us to study the way in which pain perception is influenced by expectations. In fact, we can assume that any change in how you experienced pain would be due to your expectations of low and high pain rather than the pain per se.

We were not able to tell you about the change in the intensity of stimulation beforehand, because your knowledge would have affected your responses and perceptions.

Some people do not want to have any further involvement in a study once the deception is described. Please answer the question below to let us know if you would like us to remove your data from the study.

Please check the box and sign below:
You may use my study data: Yes _____

No _____

If you felt concerned or uncomfortable about the fact that you have been intentionally deceived, we will be happy to discuss this with you. Please contact the principal investigator Luana Colloca (Phone 410-706-8422; Floor 7th, Room 729A).

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