ORIGINAL ARTICLE

Somatic Symptom Perception From a Predictive Processing Perspective: An Empirical Test Using the Thermal Grill Illusion

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ABSTRACT

Objective: In a predictive processing perspective, symptom perceptions result from an integration of preexisting information in memory with sensory input. Physical symptoms can therefore reflect the relative predominance of either sensory input or preexisting information. In this study, we used the thermal grill illusion (TGI), which applies interlaced warm and cool temperatures to the skin to create a paradoxical heat-pain experience. Assuming that the TGI compared with single-temperature stimulation relies more importantly on an active integration process of the brain to create this paradoxical sensation, we tested the hypothesis whether a manipulation of the expectations during TGI would have more impact than during single-temperature stimulation.

Methods: Sixty-four participants received different temperature combinations (16/16°C, 40/40°C, 16/40°C) with neutral, positive ("placebo"), and negative ("nocebo") instructions. Subjective stimulus intensity was rated, and neuroticism and absorption (openness to absorbing and self-altering experiences) served as potential moderating factors.

Results: The TGI condition was rated highest. Overall, negative instructions increased ($p < .001$, $d = 0.58$), whereas positive instructions did not significantly change the TGI intensity perception (versus neutral; $p = .144$, $d = 0.19$). In the TGI condition, increased modulation of pain was observed with higher neuroticism ($\beta = 0.33$, $p = .005$) and absorption ($\beta = 0.30$, $p = .010$).

Conclusions: Whereas negative instructions induced a nocebo effect, no placebo effect emerged after positive instructions. The findings are in line with the predictive processing model of symptom perception for participants with higher levels of neuroticism and absorption.

Key words: thermal grill illusion of pain, predictive coding, expectation, thermal stimulation, nocebo effect.

INTRODUCTION

Chronic pain may persist even after the original source (e.g., injury) has elapsed (1). Although acknowledging that pain does not equal nociception, a clear model of pathogenetic processes of chronic pain is still lacking. Predictive processing (2,3) provides a general framework of perceptual processes (4,5) and might help explaining the paradox of pain without noxious stimulation (6–8).

According to predictive processing, our brain constantly predicts sensory inputs by generating and updating hypotheses via recurrent hierarchical processing (9). By comparing predictions (priors) with actual sensory inputs at each hierarchical level, the emerging prediction error can either revise or strengthen former predictions, thus leading to new, ideally more adaptive predictions. Predictions can therefore strongly influence the eventual perception (posterior). Placebo effects, for instance, have been explained within a predictive processing framework as resulting from successful manipulation of the prior (9). Expectations of low/high pain, for example, by verbal suggestions, can shift the perception into the direction of the respective prior, resulting in placebo hypoalgesia/nocebo hyperalgesia. The more precise the prior, that is, the more confident the expectation, the larger its influence on the posterior (10,11). The precision of sensory inputs, as well, can vary (bee sting versus gastric spasm) and is an equally important parameter (9). It is assumed that the eventual percept is shifted relatively more into the direction of the prior with less precise/more ambiguous sensory input (12). To our knowledge, this prediction has not yet been tested empirically in the realm of somatic symptom perception.

In the framework of predictive processing as well as placebo and nocebo effects, personality traits are discussed to serve as moderating factors (12). Specifically, trait negative affect (neuroticism) and absorption (i.e., the tendency to become involved in imaginative and sensory experiences [13]) might play important roles in altered somatic symptom perception. Neuroticism possibly leads to more precise priors (14) as well as less detailed sensory-perceptual processing (15) and is known to moderate symptom report (16–18). Absorption has been related to suggestibility and responsiveness to placebo effects (19,20) and might lead to low precision in negative affective states (15).

CI = confidence interval, **HPC** = heat-pinch-cold, **M** = mean, **SD** = standard deviation, **TGI** = thermal grill illusion

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This study used the thermal grill illusion (TGI) (21) emerging from integrating interlaced innocuous warm and cool stimulation. It leads to a paradoxical increased (sometimes painful) perception compared with the perception of single temperatures, possibly due to unmasking (disinhibition theory [22]) or summation effects (additivity theory [23]). Assumedly, during the TGI, the brain receives unusual (unexpected) and ambiguous information, implying from a predictive processing perspective that the neural distributions representing this input are less precise compared with single temperatures. The illusory experience seems to reflect the brain's integrative work to create a meaningful stimulus experience. Accordingly, the role of top-down prior expectations in creating the eventual percept is greater in the TGI than in unambiguous single-temperature conditions. If so, this suggests that manipulations of these prior expectations should have a stronger impact for TGI compared with single-temperature conditions. To test this prediction, we gave positive and negative verbal instructions concerning different thermal stimuli. Furthermore, the moderating effect of neuroticism and absorption was assessed. Participants high in neuroticism and absorption were expected to display a stronger modulation of the heat perception by the verbal suggestions in the TGI condition.

METHODS

Sample

An a priori power analysis with G-power (24) indicated a required sample size of 68 participants to obtain a power of 80% for detecting a medium-sized effect in a multiple linear regression with two predictors when using a criterion of 5% for statistical significance. Participants were recruited with a note on the local university campus, via e-mail, and Facebook. Exclusion criteria were chronic or acute pain, intake of painkillers or psychopharmacological medication, use of illegal drugs, chronic diseases as diabetes, high blood pressure, coronary heart disease, tachycardia, cardiac arrhythmia, cardiac arrest, kidney failure, liver dysfunction, epilepsy, stroke, Parkinson disease, and multiple sclerosis. Exclusion criteria were checked via a questionnaire.

Altogether, 68 individuals participated in the study, from which 4 were excluded because they did not complete both parts of the study (questionnaires and laboratory session). The final sample (mean [standard deviation], or M [SD] = 24.00 [4.46] years, 42 women [66%]) consisted of 64 participants. All participants were white; 57 (89%) were students and 7 (11%) were employed.

All participants signed an informed consent form before starting the experiment. After completing the study, all participants were fully informed about the purpose of the study and about deceptive parts (expectation induction) and signed a second informed consent form. Participants were compensated monetarily (5€ at every beginning of half an hour). The local ethics committee (Ethics Committee of the Psychological Institute of the University of Mainz, Germany) granted ethical approval for the study (2017-JGU-psychEK-008).

Experimental Procedure

After screening for exclusion criteria, participants filled in the questionnaires (see hereinafter) regarding personality traits at home via SoSci Survey (25). Experimental testing took place in a laboratory of the University of Mainz between September 2017 and January 2018 and lasted approximately 2 hours. Participants were told that the purpose of the study was to explore the perception of different temperature stimuli. Every participant received the same three temperature stimuli (cool, 16/16°C; warm, 40/40°C; and TGI, 16/40°C) in a randomized sequence after neutral, positive, and negative instruction, respectively (3 × 3 within-subject design). The chosen temperatures were close to but actually below the often-reported thresholds for heat pain (approximately 45°C) and cold pain (approximately 13°C) (26,27) and based on previous studies using the same TGI device (28). The neutral instruction always came first and did not include any specific instruction beyond explanation of the rating task. The sequence of the positive and negative instructions was randomized. Specifically, before the positive condition, the participants received the following instruction to induce a positive expectation: "From previous studies we know that the following temperature settings are usually perceived as very pleasant and mild." Specifically, before the negative condition, the participants received the following instruction to induce a negative expectation: "From previous studies we know that the following temperature settings are usually perceived as very unpleasant and painful." In each condition (neutral, positive, negative), every temperature stimulus was applied twice for 30 seconds each (Figure 1). After changing the temperature, participants were shortly reminded of the instruction (e.g., "now, another temperature setting will be applied, which most participants describe as very pleasant and mild") because it took on average 7.5 minutes to switch to the next temperature.

After both 15 and 30 seconds during each thermal stimulation, participants were prompted to rate their subjective intensity perception (Figure 1). The scale ranged from 0 ("no sensation") to 200 ("most intense sensation imaginable"), with an additional anchor at 100 ("just above pain threshold") that indicated the pain threshold (29). This scale was used to enable a description of the sensation in the painful and nonpainful range and has been successfully used in previous studies (29,30). Before testing, participants were familiarized with the scale, and during the experiment, they were instructed to call out numbers according to their sensation while a scale lay in front of them for visual reference.

Assessment of Personality Traits

We assessed absorption, described as "openness to absorbing and self-altering experiences," with the 34-item Tellegen Absorption Scale (31) (German version by Ritz and Dahme (32); Cronbach α in this study: α = .94). Absorption has been shown to be related to hypnotizability and imaginative involvement, a facet of openness (33,34) and placebo responsiveness (19,20).

Neuroticism was assessed with the respective six-item subscale of the NEO Five-Factor Inventory (35) (German short version by Korner et al. (36); Cronbach α of the neuroticism subscale in this study: α = .79). Neuroticism correlates with negative affect and with the experience of bodily symptoms (16,17,37).

Thermal Grill Device

A custom-built and water bath–driven thermal grill device was used to apply the thermal stimuli (I. Curio, PhD, Medical Electronics, Bonn, Germany; (28,38,39)). The thermal grill (Figure 2) consisted of eight pipes made of borosilicate glass. The temperature of alternating pipes could be regulated separately (e.g., cold and warm). The glass pipes were spaced at a distance of 7.5 mm. In order to prevent any heat transfer between pipes, bars made of 5 mm hollow (thickness, 0.5 mm) polyvinyl chloride with negligible thermal conductivity were placed between the pipes. Temperatures were regulated with two separate thermoelectric recirculating chillers (T255P; ThermoTek Inc.) delivering the water to the pipes through separate flexible and insulated plastic conduits. The flow rate of the pump was 3.86 L/min, approximately 15 mL/s per glass pipe. The volume of one glass pipe was approximately 16.5 cm^3. The fluid content of each pipe was exchanged at a rate of approximately 1 second. The fluid temperature was continuously controlled with a digital thermometer (PL-120 T2, Voltcraft; visual display of T1–T2 temperatures in degrees Celsius; basic accuracy 1°C) attached to the borosilicate tubes and covered against ambient temperature with silicone rubber. The real temperature at the stimulated surface is hard to estimate, as it depends, for example, on thickness of the skin, contact pressure and area, and properties of the skin (wet or dry), but mainly from the capillary perfusion of the skin (for further information, please refer to the Supplemental Digital Content of Ref. (28)).

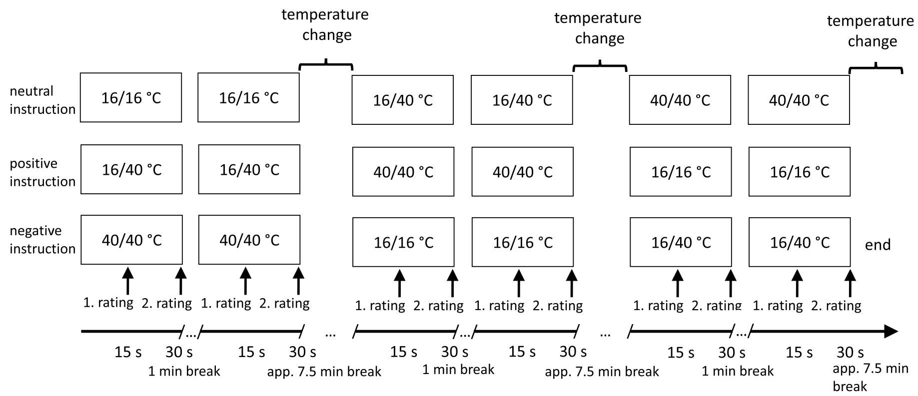

FIGURE 1. Experimental design. Starting with the neutral instruction, participants received one of the three temperature combinations (randomized) twice for 30 seconds each (separated by a break of 1 minute) and rated subjective intensity after 15 and 30 seconds, respectively. Then, the temperature setting was changed, with the transition taking approximately 7.5 minutes. After receiving all three temperature combinations, the procedure was repeated under a positive and a negative instruction (randomized sequence).

Statistical Analysis

Subjective intensity ratings of the different TGI conditions served as the primary outcome. Repeated ratings of the same temperature within the same condition were averaged (reliability of the ratings was excellent, with Cronbach α ranging between $\alpha = .91$ and $\alpha = .99$ for the different conditions). A repeated-measures analysis of variance with the within-factor "temperature" (cool, warm, TGI) and "instruction" (neutral, positive, negative) and one between-factor "sequence" (positive instruction first, negative instruction first) was used to analyze intensity ratings (basic model). Greenhouse-Geisser corrections were performed where applicable. Post hoc tests were Bonferroni-corrected.

For the subsequent analysis, both control temperatures (warm and cool temperature) were averaged because they did not differ significantly, and the positive instruction condition was omitted because it did not prove effective. A multiple linear regression analysis was performed using neuroticism and absorption as predictors. The criterion variable (the TGI nocebo effect) was generated by calculating the difference between neutral and negative ratings of the control temperatures and TGI, respectively, and then calculating the difference of the resulting values, to specifically test the hypotheses of increased modulation of the TGI compared with the control temperatures.

Measures of effect sizes are reported, and a level of significance of 5% was applied. Data were analyzed with IBM SPSS Statistics (Version 23) and JASP 0.9.0.1 (40).

RESULTS

Basic Model

In a repeated-measures analysis of variance, a significant main effect of temperature was observed ($F(1.73,107.38) = 69.52$, $p < .001$, $\eta^2 = 0.53$). Post hoc tests indicated that cool and warm temperatures were perceived similarly intense ($p = .23$, $d = 0.22$), whereas the perceived intensity of TGI was increased compared with cool ($p < .001$, $d = 1.12$) and warm stimuli ($p < .001$, $d = 1.23$), indicating that the TGI was successfully induced (Figure 3). Furthermore, a main effect of instruction appeared ($F(1.80,111.35) = 14.29$, $p < .001$; $\eta^2 = 0.19$). Post hoc tests suggested that compared with the neutral instruction, the negative instruction led to an increase in intensity perception ($p < .001$, $d = 0.58$), whereas the positive instruction did not modulate the perceived intensity ($p = .40$, $d = 0.19$). A main effect of sequence ($F(1,62) = 4.89$, $p = .031$; $\eta^2 = 0.07$) indicated increased intensity ratings when the negative instruction and decreased intensity rating when the positive instruction was received first. No interaction effect with sequence was significant. Contrary to the hypothesis, no significant interaction between temperature and instruction was observed ($F(3.48,215.70) = 2.14$, $p = .087$; $\eta^2 = 0.03$).

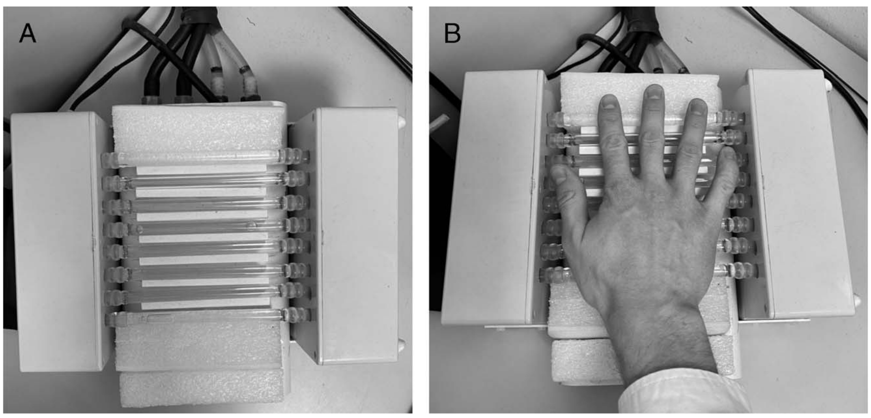

FIGURE 2. Thermal grill device. A, The glass pipes were connected to one of two thermoelectric recirculating chillers (ordered alternately) to separately regulate the temperature. B, Participants we instructed to put their dominant hand on the glass pipes and to keep good contact throughout the stimulation.

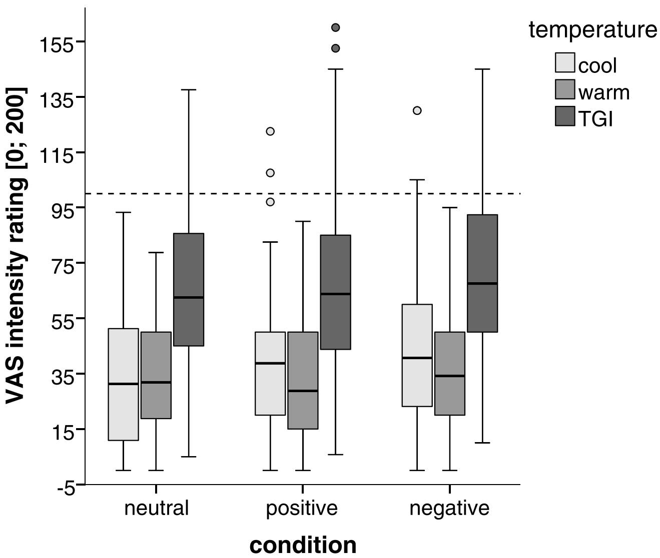

FIGURE 3. Box plots of subjective intensity ratings of the thermal stimuli (cool, warm, thermal grill) after neutral, positive, and negative instructions. The dashed line at an intensity rating of 100 represents the "just above pain threshold" anchor of the visual analog scale, which ranged from 0 ("no sensation") to 200 ("most intense sensation imaginable").

Although TGI was perceived as more intense than the cool and warm control temperatures, only few participants evaluated the sensation caused by the TGI as painful (i.e., exceeding the "just painful" anchor on the visual analog scale). There were 5 (7.8%) participants (*M* [SD] = 113.75 [16.25]) in the neutral condition, 10 (15.6%) participants (*M* [SD] = 126.88 [21.82]) in the positive condition, and 15 (23.4%) participants (*M* [SD] = 117.83 [15.39]) in the negative condition who reported values higher than 100.

Regression Analysis

Neuroticism (r = 0.35, 95% confidence interval [CI] = 0.11 to 0.54, p = .005) and absorption (r = 0.32, 95% CI = 0.108 to 0.52, p = .010) positively correlated with the TGI nocebo effect (i.e., the double difference between neutral and negative ratings of the control temperatures and TGI; Figure 4), whereas neuroticism and absorption did not correlate (r = 0.05, 95% CI = −0.20 to 0.29, p = .69). A multiple linear regression indicated that neuroticism (β = 0.36, 95% CI = 0.13 to 0.59], p = .002) and absorption (β = 0.30, 95% CI = 0.108 to 0.53, p = .010; interaction: β = 0.17, 95% CI = −0.06 to 0.40, p = .14) simultaneously predicted the TGI nocebo effect significantly (R^2 = 0.24, $F(3,63)$ = 6.31, p = .001), indicating that the TGI compared with the control temperatures increased with higher levels of neuroticism and absorption.

DISCUSSION

Predictive processing provides an innovative, powerful, and empirically testable theoretical framework for somatic symptom perception (12,41,42). The aim of this study was to test predictions based on predictive processing by using the TGI, a paradoxical sensory percept often used in research on hypersensitivity in chronic pain that cannot be relayed to physiological dysfunction. Because illusory perceptions can be expected to rely more heavily on central integrative processes of the brain, our primary hypothesis was that a TGI condition would be more sensitive to manipulations of prior expectations (i.e., positive and negative expectations in the sense of placebo and nocebo effects) compared with single thermal grill temperatures. In addition, we expected that this effect would be moderated by neuroticism and absorption as central

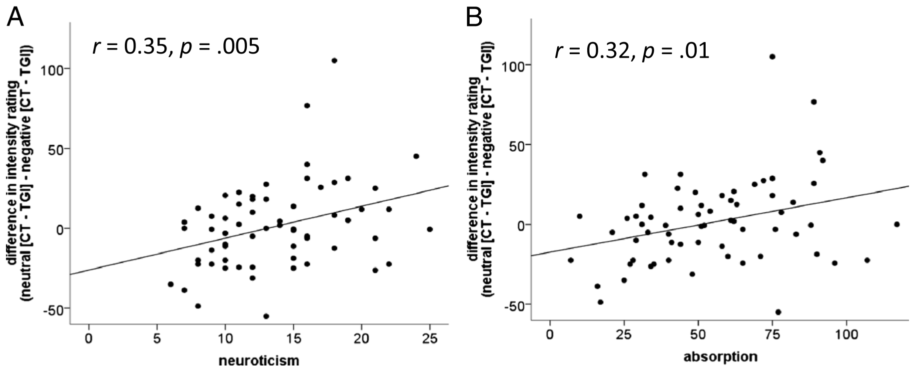

FIGURE 4. Scatterplots showing that the modulation of the TGI nocebo effect is related to neuroticism (A) and absorption (B); that is, the nocebo effect for the TGI condition is stronger in participants with higher neuroticism or absorption. TGI = thermal grill illusion.

neural dispositions known to influence somatic perception. In support of our primary hypotheses, we observed an increased impact of our expectation manipulation in the TGI condition compared with the single temperatures. However, this was only true when negative expectations were induced and the effect was moderated by neuroticism and absorption. Our hypothesis was based on the assumption that paradoxical pain perceptions in response to unusual thermal grill input implying simultaneous stimulation with two innocuous, interlaced warm and cool temperatures, reflect the integrative work of the brain to create a meaningful experience to a higher degree compared with simultaneous stimulation with two identical warm or cool stimuli. Supporting this assumption, a qualitative study showed that the TGI is perceived as a complex, ambiguous percept integrating various perceptual qualities (43,44). Along these lines, in a post hoc calculation comparing the equality of coefficients of variation (45), we observed the largest SDs for the intensity ratings in the TGI condition compared with both control conditions (cool versus TGI, $p < .001$; warm versus TGI, $p = .003$; cool versus warm, $p = .45$), speaking in favor of a lower precision. Therefore, if the sensation during the TGI condition relies relatively more on the integrative work of the nervous system, it should be influenced more strongly by manipulations of the prior beliefs.

Neuroticism and absorption can be considered relatively stable neural dispositions to process information and have theoretically and empirically been linked to increased perception of somatic symptoms (13,46,47). Absorption reflects the tendency to become involved in imaginative and sensory experiences (13) and is related to hypnotizability and responsiveness to placebo effects (19,20). The increased TGI nocebo effect in participants high in absorption could therefore be due to their greater susceptibility to verbal suggestions or their predisposition to get more absorbed in a noxious sensation (46). In the context of predictive processing, absorption has been discussed to enhance the perceived overlap between affective and somatic prediction and lead to low precision when negative states are activated (15), thus facilitating the perception of symptoms. Neuroticism has been suggested to constitute a moderator of symptom perception in a predictive processing framework, influencing the correspondence between prediction error, prior, and their respective precision (12). Possibly, it leads to oversimplification and increases perceived homogeneity of sensation categories, which in turn could lead to more precise priors (14) and possibly less detailed sensory-perceptual processing (15). It is thus conceivable that especially participants high in neuroticism display a stronger modulation of the perception by negative verbal suggestions. Altogether, this suggests that predictive processing could provide a theoretical background to explain symptom development in patients with symptoms unrelated to observable physiological dysfunction (48), because they are known to have higher levels of neuroticism and the influence of top-down processes on symptoms seems to be more pronounced compared with healthy individuals (49).

Relatively weak negative verbal instructions led to an increase in temperature perception, suggesting a successful manipulation of the prior and induction of a nocebo effect. Contrary to our hypothesis, the positive instruction did not decrease temperature perception. Different explanations could account for this discrepancy, including a general asymmetry of positive and negative events (50,51). Against the background of evolutionary advantages that might be associated with the nocebo effect (e.g., harm avoidance; (52)), previous studies show that nocebo effects are more easily established by verbal suggestions only, whereas placebo effects oftentimes fail to develop after verbal suggestions and more heavily depend on previous experience and learning (53). Consequently, this result could mirror the fact that placebo and nocebo effects are not just the same with reversed sign (52). Another possible explanation concerns the measure used. Different scales have been used to assess the TGI, for example, visual analog scale pain scales (28), thermal color bars (54), verbal-numerical rating scales (38), or numerical rating scales of thermal intensity (55). The descriptive labels of most scales, including the one we used (e.g., "maximum pain tolerable"), might lead participants to categorically classify their sensations as symptoms (56). Accordingly, the placebo instruction "pleasant and mild temperature settings" in this context might seem counterintuitive to the participants, rendering the positive instruction unsuccessful.

The TGI (21) was successfully induced; that is, participants perceived the interlaced stimulation with two innocuous temperatures as more intense than stimulation with the single temperatures. At least two prominent theories exist that try to explain the thermal grill phenomenon. According to the disinhibition theory (22), warm stimulation inhibits cold-sensitive neurons in the spinothalamic tract, which unmasks activity in the nociceptive pathway caused by stimulation of C-polymodal nociceptors (heat-pinch-cold, or HPC). The additivity theory (23), on the other hand, states that afferent activity in warm and cold fibers converges on nonspecific neurons in the spinothalamic tract (wide dynamic range or HPC), and summation could lead to activation levels usually produced by more intense heating or cooling. Simultaneous activity in warm-specific neurons and inhibition of cold input could lead to activity normally produced by stronger (nonpainful) heating. The authors propose that pain sensations could arise when the stimuli are sufficiently intense to activate temperature-sensitive nociceptors, which unmasks input from HPC neurons, as suggested by the disinhibition theory.

In the present study, only few participants rated the TGI as painful. Although this is in accordance with accounts of "synthetic heat," as described by the additivity theory (23,57), the stimulus intensity of the cool stimulus (16°C) was low enough to activate HPC neurons (<22°C, (58); <19°C, (59)). The nonpainful reports might therefore be due to the scale used; whereas most studies on the TGI use pure pain scales (26), we used a scale that allowed for differentiation in the painful and nonpainful range. Using a scale without specifying a nonpainful range possibly biases the reports because there is no possibility to indicate a more intense but nonpainful sensation and ratings above zero (oftentimes representing "no pain") are interpreted to indicate a painful sensation.

Strengths and Limitations

By combining placebo and nocebo inductions and the TGI for the first time, this study empirically tested the modulation of heat-pain perception by simultaneously varying the level of ambiguity of the sensory stimulation from which the brain creates a meaningful percept and the specific prior beliefs regarding the stimulation. Based on the predictive processing model, we tested the assumption that manipulating prior beliefs would have more impact in conditions where the eventual experience relies more on integrative processes by the brain. Although our hypothesis was confirmed for negative expectations, a placebo effect was not induced when using a positive verbal suggestion. This result warrants further investigation but could indicate a relatively larger responsiveness concerning negative versus positive instructions. We did not observe a significant interaction between the temperature conditions and the instruction, that is, our hypothesis was only confirmed when considering participants high in neuroticism and absorption. Furthermore, besides the quality of the sensation, the thermal grill sensation differs from the single temperatures because of the increased perceived intensity, which constitutes a confounding factor and limits the comparability of the TGI condition and the single temperatures. The used within-design facilitated carryover effects of the different instructions, indicated by the significant sequence effect. Future studies should therefore counterbalance the order of all conditions. The thermal grill was constructed from borosilicate glass (to be compatible with functional magnetic resonance imaging), which does not have optimal thermal conductivity; thus, the actual temperatures delivered to the skin might have been less extreme than intended (cf. [28]). Because of dropout, our sample consisted only of 64 participants and might therefore be underpowered (planned sample size, 68 participants). Finally, the presented results are based on a healthy student-based sample rendering future studies with clinical samples (e.g., patients with chronic pain or somatic symptom disorder) necessary.

CONCLUSIONS

In summary, the TGI proved valuable as an experimental model to investigate the relative contribution of central versus peripheral input to the eventual somatic percept. The ambiguous TGI stimuli were more vulnerable for induced negative expectations than clearly defined temperature stimuli for persons with higher levels of neuroticism and absorption. This observation is in line with predictions derived from the predictive processing approach to symptom perception, rendering predictive processing promising in the future investigation of pathogenetic mechanisms in patient groups where symptoms do not completely match physiological dysfunction.

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Author contributions: A.-K.B., S.S., R.S., and M.W. developed the study concept and contributed to the study design. Testing and data collection were performed under the supervision of A.-K.B. A.-K.B. performed the data analysis. A.-K.B., M.W., and O.V.d.B. interpreted the data. A.-K.B. drafted the manuscript, and S.S., R.S., O.V.d.B., and M.W. provided critical revisions. All authors approved the final version of the article for submission.

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