Pain-related and negative semantic priming enhances perceived pain intensity

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BACKGROUND: Negative affective and pain-related cues, such as pictures or words, have been shown to act as primes and enhance the perceived intensity of subsequent painful events. For pain-related semantic primes, it remains unclear whether this effect depends on negative valence itself or, specifically, on the pain-relatedness of the words.

OBJECTIVES: To investigate the effect of pain-related, negative affective (pain-unrelated) and neutral semantic primes on the perception of subsequent noxious target stimuli.

METHODS: Pain ratings in response to noxious electrical stimulation of light and moderate intensity were examined in 39 healthy subjects after subjects were exposed to semantic primes of different meaning and valence (pain-related, negative, positive and neutral adjectives) presented with different interstimulus intervals (0 ms, 500 ms and 1500 ms).

RESULTS: Increased pain ratings of noxious stimuli were observed following pain-related and negative compared with neutral primes.

DISCUSSION: The results support the motivational priming theory for semantic stimuli, indicating that affectively negative semantic primes increase subjective pain intensity. However, a specific pain-related priming effect was not reliably demonstrated. Additionally, it is shown that experimental parameters (ie, stimulus intensity and interstimulus interval) modify the extent of negative and pain-related semantic priming.

CONCLUSIONS: Verbal priming plays a role for the perception of noxious stimuli in a time-dependent manner.

Key Words: Affective words; Electrical stimulation; Pain ratings; Pain words; Semantic priming

L’amorçage sémantique lié à la douleur et négatif favorise l’intensité perçue de la douleur

HISTORIQUE: Il est démontré que des indices affectifs négatifs et liés à la douleur, tels que des images ou des mots, agissent comme des amoncels et accroissent l’intensité perçue d’événements douloureux subseqents. Pour ce qui est des amoncels sémantiques liés à la douleur, on ne sait pas si cet effet dépend d’une valence négative ou, plus précisément, du lien des mots avec la douleur.

OBJECTIFS: Examinier l’effet d’amoncels sémantiques liés à la douleur, affectives négatives (sans lien avec la douleur) et neutres sur la perception de stimuli ciblés douloureux administrés par la suite.

MÉTHODOLOGIE: Les chercheurs ont examiné les évaluations de la douleur en réponse à une stimulation électrique douloureuse d’intensité légère à modérée chez 39 sujets en santé après les avoir exposés à un amorçage sémantique aux diverses significations et valences (adjectifs liés à la douleur, négatifs, positifs et neutres), présenté à divers intervalles entre les stimuli (0 ms, 500 ms et 1 500 ms).

RÉSULTATS: Les chercheurs ont observé des évaluations plus élevées de la douleur après des amoncels liés à la douleur ou des amoncels négatives par rapport à des amoncels neutres.


CONCLUSIONS: L’amorçage verbal joue un rôle dans la perception des stimuli douloureux en fonction du temps.

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processing in memory structures and the organization of behavioural responses to word stimuli have been suggested (31,33,34). Thus, the prime is stressing working memory and initiates response selection. Given that the central processing of visually presented semantic stimuli involves several distinct steps, the priming effect of those stimuli on the processing of the succeeding noxious stimulus may critically depend on the ISI between presented word and noxious stimulus.

Furthermore, the intensity of the noxious stimulus appears to be an important moderator for the interaction between prime and stimulus. Godinho et al (27) showed a distinct negative priming effect for clearly painful electrical stimulation but not for lower stimulation intensities slightly beyond the pain threshold. Kenntner-Mabiala and Pauli (9) presented a significant affective priming effect of negative pictures, compared with neutral pictures, for mild painful electrical stimulation.

We hypothesized that both pain-related and negative pain-unrelated primes increase the pain rating in response to subsequent noxious stimuli compared with neutral primes. Furthermore, we hypothesized that pain-related semantic primes compared with pain-unrelated, negative primes further increase those pain ratings. We also aimed to investigate whether these effects depend on the intensity of noxious stimulation and on the duration of the ISI between prime and noxious stimulus.

METHODS

Subjects
Thirty-nine right-handed healthy volunteers (19 female and 20 male, mean ± SD age 21.1±2.1 years) participated in the present experiment. Participants were students recruited via announcements on university billboards and mailing lists. All subjects were native German speakers and provided informed consent for participation, in accordance with the Declaration of Helsinki. Subjects were free of pain medication and were not experiencing any type of acute or chronic pain. The Beck Depression Inventory (BDI-2) (35) was used to assess depressive symptoms and a life pain questionnaire with Likert scales (scores of 0 to 10) was used to assess participants’ previous pain experience. None of the subjects was excluded because of fulfilling the a priori criteria of BDI-2 scores >18 or previous critical pain experiences (eg, traumatic injuries or indices for chronic pain experiences). The mean BDI-2 score was 6.65±3.07 and, according to an additional clinical interview, none of the subjects showed depressive symptoms.

Pain stimuli
Electrical stimuli consisted of rectangular pulses (20 ms duration) generated by a constant current stimulator (DS7H; Digitimer, United Kingdom). Intracutaneous stimuli were applied to the tip of the middle finger of the left hand (3,5,36,37); an isolated golden pin electrode (diameter 0.95 mm; length 1 mm) was inserted into a small epidermal cavity of 1 mm diameter and approximately 1 mm depth and fixed with adhesive tape. Care was taken not to cause any bleeding. The purpose of this preparation was to reduce skin resistance and, thus, to increase the current necessary to elicit a pain sensation. A flexible stainless steel electrode, fixed loosely around the first finger joint, served as a reference electrode.

Study design
Individual stimulus-response curves were determined before the experiment by applying five series of electrical stimuli with ascending and descending intensity in increments of 0.5 mA. Maximum stimulation intensity before starting the descending series was fixed to a rating of ≥50, indicating strong pain. The intensity was then reduced until the participant rated the stimulus as not perceived (0). Participants were asked to rate each stimulus on a modified Ellermeier scale (0, no sensation; 1 to 10, just perceived but not painful; 11 to 20, clearly perceived but not painful; 21 to 30, very mildly painful; 31 to 40, mildly painful, 41 to 50, moderately painful; 51 to 60, strongly painful, 61 to 70 very strongly painful; and ≥71, not tolerable; this part of the scale is open at its upper end) (38). The scale was presented on the same computer screen on which adjectives were presented each time after noxious stimulation (Figure 1). According to Ellermeier et al (38), subjects have first to choose a verbal categorization of stimulation (eg, mildly painful) followed by a more fine-graded numerical decision within the range belonging to the verbal categorization (ie, for the verbal category ‘mildly painful’ in the range between 31 and 40). This scale has been shown to be valid, reliable and even equidistant concerning physical stimuli (38,39). Subjects were prompted to give only the numerical rating verbally. Mean stimulus intensities rated as very mildly painful (Int1 = 25) and moderately painful (Int2 = 45) were chosen for the experiment. Usually, short phasic noxious stimuli tend to habituate (40); however, there are rare cases of sensitization. To protect subjects from strong stimulations, an algorithm that finished the experiment whenever participants consecutively rated three stimuli ≥50 was introduced. According to this criterion, one subject showing sensitization effects was not included in the analyses.

Based on a previous study, a total of 40 adjectives were used as semantic primes: 10 pain related, 10 negative, 10 positive and 10 neutral (23). Words between categories were matched according to their word frequencies (using Cosmus Version 3.6.1, www.ids-mannheim.de/cosmas2) and lengths. For this purpose, groups of four words (one of each category) were constructed. Within these groups, word length and number of syllables were matched. Furthermore, word frequency was matched by the number of citations in German publications according to the COSMAS program. In rare cases, where matching was not perfect, care was taken that there was no statistical difference between categories in any of the matched parameters. Finally, pain- and negative related words were balanced according to their valence and arousal qualities. For this reason, the words were rated regarding valance and arousal on Likert scales (scored from 0 to 10) by 28 subjects during a preliminary study. Subsequently, matching pairs of words were selected as described in Richter et al (23). Positive adjectives were presented to counteract an affective bias toward negative mood during the experiment.

Subjects were paid €6/h for participation. To increase participants’ mental effort to attend to and process the semantic primes and to minimize error rates, subjects were informed that they could earn an extra €10 if they correctly repeated >90% of the words presented during the experiment. This additional payment was announced at the beginning of the experiment to ensure that the participants attentively processed the semantic stimuli. Primes were presented in a pseudorandomized order for 300 ms each, and each prime was followed by one of another descriptor category to prevent summation effects. Subjects were instructed to silently read the word primes on a computer screen. Coincident with switching off the prime (ISI 0 ms) or shortly after the end of representation of the prime on the screen (ISI 500 ms or 1500 ms), an electrical stimulus of predetermined pain intensity (‘mildly painful’ [Int1] or ‘moderately painful’ [Int2]) was applied (Figure 1). A maximum of three stimuli of the same intensity were presented consecutively to reduce possible anchor effects. The ISI between primes and noxious target stimuli was varied randomly among the three ISIs. After each noxious stimulus, the rating scale presented on the computer screen and subjects were asked to rate the intensity of the stimulus verbally. Therefore, they were requested to repeat the prime verbally (Figure 1). After 3 s, the next trial started. During this time, the experimenter entered the rating and the correctness of the prime repetition on the keyboard. A total of 240 trials were conducted (ie, each prime was repeated six times throughout the experiment). The whole experiment was controlled by the software Presentation (version 14.5, Neurobehavioral Systems Inc, USA).

Data analysis
To test the two main hypotheses, a repeated-measures ANOVA with three within-subject factors (Category × Intensity × ISI) was applied. When appropriate, degrees of freedom were corrected by the Greenhouse-Geisser procedure to account for violations of sphericity.
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The ‘Category’ factor included four types of adjectives used as primes (pain-related, negative, neutral and positive); ‘Intensity’ included the two intensities of the electrical stimulation (Int1 and Int2); and ‘ISI’ comprised three levels (ISI 0 [0 ms], ISI 500 [500 ms] and ISI 1500 [1500 ms]). For significant main effects, post hoc t-tests for paired samples were calculated according to the hypotheses (two-tailed, Bonferroni corrected). These analyses were followed by contrast analyses modelling simple interaction and second-order simple main effects. Finally, t-tests for paired samples were used to test relevant differences between categories as a function of ISI and Intensity (two-tailed, Bonferroni corrected). In addition, the number of false prime repetitions during the experiment was also compared among word categories using an ANOVA for repeated measures.

RESULTS

ANOVA revealed significant main effects for Category (F[3, 114]=2.99; P=0.034; $\eta^2$=0.07) and Intensity (F[1, 38]=167.18; P<0.001; $\eta^2$=0.82) as well as significant interactions for Category × Intensity (F[3, 114]=8.39; P=0.001; $\eta^2$=0.18), Category × ISI (F[6, 228]=4.28; P<0.001; $\eta^2$=0.11) and Category × Intensity × ISI (F[6, 228]=2.47; P=0.043; $\eta^2$=0.06).

Main effects

T-tests between the levels of factor Category showed significant differences for pain versus neutral (t=3.18; P=0.009) and negative versus neutral (t=2.54; P=0.046) (Figure 2). Mean (± SE) intensity rating scores of noxious stimuli were 31.11±1.09 following pain-related primes, 30.94±1.08 following negative, 30.45±1.05 following neutral and 30.96±1.05 following positive primes. Factor Intensity has only two levels; therefore, the main effect reported above indicates a significant contrast in Int2 versus Int1, with a mean intensity of 25.64±1.09 for Int1 and 36.09±1.18 for Int2 (Figure 3).

With regard to factor ISI, no significant difference of intensity ratings were found.

Interactions

With respect to the threefold interaction, simple interaction effect analyses were first conducted. Therefore, the simple interaction effect Category × ISI were analyzed for each of the two levels of Intensity. For Int1, this effect was not significant. In contrast, the analysis for Int2 revealed a significant simple interaction effect between these two factors (F[6, 36]=9.32; P<0.001; $\eta^2$=0.63). To further investigate this simple interaction effect, second-order simple main effect analyses of the factor Category were conducted for each level of ISI within Int2. A significant second-order simple main effect was found for ISI 0 (F[3, 36]=5.67; P=0.007; $\eta^2$=0.33) and ISI 500 (F[3, 36]=16.81; P<0.001; $\eta^2$=0.58), but not for ISI 1500. The differences between categories were analysed by separate post hoc t-tests for Int2 as a function of ISI. For ISI 0, significant differences between pain versus neutral (t=2.90; P=0.038), negative versus neutral (t=2.85; P=0.042) and pain versus positive (t=4.28; P<0.001) were observed. For ISI 500, significant differences for pain versus neutral (t=4.50; P=0.001) and neutral versus positive (t=0.73; P=0.001) were revealed. The contrast in pain versus negative failed to reach significance for all ISIs. Means and SDs for all conditions are listed in Table 1. Figure 4 presents means and SEs for the above-mentioned triple interaction.

During the experiment, a relatively low number of false prime repetitions occurred with mean (± SE) of 3.15±0.50 for pain primes, 3.33±0.50 for negative, 1.46±0.30 for neutral and 3.02±0.43 for positive primes, indicating that the task was feasible for all participants.

ANOVA of false repetitions revealed a significant main effect for Category (F[3, 114]=7.15; P=0.001). t-tests indicated a significant differences between pain versus neutral (t=4.96; P<0.001), negative versus neutral (t=4.00; P=0.002) and neutral versus positive (t=3.59; P=0.006).
TABLE 1
Mean pain ratings depending on the factors Intensity, word Category and interstimulus interval (ISI)

<table>
<thead>
<tr>
<th>Word category</th>
<th>ISI</th>
<th>0 ms</th>
<th>500 ms</th>
<th>1500 ms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intensity 1 = 25</td>
<td>Pain-related</td>
<td>25.93±7.15</td>
<td>25.55±7.08</td>
<td>25.40±7.50</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>25.37±7.38</td>
<td>25.16±6.67</td>
<td>25.92±7.64</td>
</tr>
<tr>
<td></td>
<td>Neutral</td>
<td>26.77±7.71</td>
<td>25.09±7.29</td>
<td>25.14±5.96</td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>25.87±6.55</td>
<td>26.21±7.35</td>
<td>25.27±7.15</td>
</tr>
<tr>
<td>Intensity 2 = 45</td>
<td>Pain-related</td>
<td>37.13±8.36</td>
<td>35.98±7.44</td>
<td>36.66±7.57</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>36.96±7.82</td>
<td>36.20±7.70</td>
<td>36.41±7.70</td>
</tr>
<tr>
<td></td>
<td>Neutral</td>
<td>35.30±7.61</td>
<td>34.41±7.28</td>
<td>36.00±7.35</td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>35.40±7.77</td>
<td>36.96±7.75</td>
<td>36.06±7.04</td>
</tr>
</tbody>
</table>

Data presented as mean ± SD

DISCUSSION

We hypothesized that semantic priming with pain-related and negative word primes would result in stronger pain ratings to subsequent noxious target stimuli than priming with neutral words. Furthermore, we hypothesized that priming with pain-related words increases pain ratings to subsequent noxious target stimuli compared with priming with negative words. These hypotheses were investigated with respect to varying ISIs and pain intensities.

Main effects of factors Category and Intensity

In accordance with our expectations, an overall negative priming effect of pain-related and negative primes for the processing of subsequent noxious stimuli compared with neutral primes appeared as a main effect of factor Category. This finding is consistent with studies showing a negative emotional priming effect induced by unpleasant visual stimuli (8-10,41). According to the present study, we conclude that semantic stimuli with distinct negative valence exert negative priming on the processing of succeeding painful stimuli. According to the motivational priming theory, this may be due to the activation of neural structures associated with negative affect (13).

Concerning hypothesis 2, we did not find a main effect indicating a significant difference in pain ratings following pain-related compared with negative primes.

The main effect for Intensity indicates that the establishment of two distinct pain intensities, one mild and one medium pain intensity, during the experiment was successful.

Interaction effects among the factors Category, Intensity and ISI

In the ANOVA, we found an interaction among all three factors. The following simple interaction effect analyses, one for each Intensity, revealed an interaction for Category × ISI only during the condition in which noxious stimuli were of moderate pain intensity (Int2), but not when intensity was mild (Int1). Thus, word stimuli describing pain-related adjectives appear to affect the processing of painful stimuli only when the stimulus is clearly painful. This finding is in accordance with results of a study performed by Godinho et al (27). These authors also found priming effects for clearly painful electrical stimulation, but no influence for intensities lightly beyond the pain threshold. Taking these data as well as a study from Kenntner-Mabiala and Pauli (9) also demonstrating a priming effect of negative pictures (compared with neutral pictures) for painful electrical stimulation, priming effects of context must be considered for painful electrical stimuli. These effects may be stronger the higher the pain intensity.

Additionally, a negative priming effect for Int2 was found when the ISI between verbal prime and electrical stimulus was short (ISI 500) or when the prime was immediately followed by the stimulus (ISI 0), supporting our first hypothesis. Previous studies also found distinct priming effects when the target pain stimulus was presented immediately after or during prime presentation (10,27,28,40).

Similarly, studies investigating semantic priming indicate that the semantic priming effect loses magnitude during prolonged time intervals between prime and target (42,43). In a study investigating the affective priming effect of pain-related pictures on reaction times during categorization of subsequent negative words (44), the priming effect was only present when target stimulus was presented 300 ms after onset of the prime, but not after 500 ms or 1000 ms. At least in part, our results support the assumption of these authors, concluding that affective priming is a rapid and automatic cognitive process that may be alleviated by higher cognitive processes such as working memory or resting-state processes commencing quickly after prime onset.

The priming effect for ISI 0 may be affected by processes investigated under the term of attentional blink. In a series of experiments, it was demonstrated that the processing and recognition of a second target stimulus that follows a first target stimulus becomes significantly disturbed within a time window of approximately 500 ms after onset of the first stimulus (45,46). During ISI 0, the noxious target stimulus was presented during the time interval of the attentional blink; more precisely, 300 ms after onset of the prime stimulus. The processing of the noxious stimulus may, therefore, be impaired by this process. However, it has been shown that the attentional blink is attenuated when the second stimulus is of negative affective valence (47) or semantically related to the first stimulus (48,49). Consequently, this effect may be reduced when the previously presented prime is of the same affective quality or is associated semantically with the noxious stimulus. The higher pain ratings we found during negative and pain-related priming compared with neutral priming may, therefore, be related to a weakened attentional blink effect. However, during ISI 500 as compared with ISI 0, we found reduced pain ratings beyond all categories (except for the positive words) and a similar significant difference between pain ratings following negative affective and neutral primes. During ISI 500 (i.e., 800 ms after prime onset, processes related to the attentional blink ought to be completed). Therefore, the attentional blink appears to play a minor role for the explanation of our results.

As expected, pain intensity ratings were significantly lower after neutral and positive primes versus negative and pain-related primes for ISI 0. However, for ISI 500, pain ratings after positive primes were elevated compared with neutral primes. For this ISI, positive primes appeared to have a negative priming effect similar to negative and pain-related primes, resulting in increased pain ratings compared with neutral stimuli. The N400, occurring between 300 ms and 500 ms after the presentation of a linguistic stimulus, is assumed to reflect semantic processing of the stimulus (50). According to Li et al (51), the N400 amplitude is increased after the presentation of incongruent verbal stimuli. It is assumed that this N400 increase is due to the semantic processing of the primes with the particular category in comparison with neutral adjectives; asterisks indicate significant changes compared with neutral adjectives.
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conflict between the primes. In our study, a semantic conflict may emerge between the positive valence of the prime and the expectation of a negative pain stimulus for the ISI of 500 ms. This cognitive conflict may itself serve as a negative prime during ISI 500 and, therefore, elevate the following pain rating, similar to the negative and pain-related primes.

As mentioned above, we did not find a main effect indicating a significant difference in pain ratings following pain-related compared with negative primes. For ISI 0 ms, the assumed effect is shown descriptively but failed to reach statistical significance. Previous studies investigating healthy subjects during priming with affective pictures reported a larger effect for pain-related primes compared with negative, pain-unrelated primes on intensity ratings of succeeding electrical stimuli (27,28) or on pain tolerance threshold measured by the cold pressor test (14). Regarding the fact that mean pain rating for Int2 indicated that intensity was perceived to be relatively mild, we presume that the priming effect of pain-related words may have been more pronounced for higher pain intensities, as indicated by a previous study (27).

Limitations and future directions
Our study demonstrated very systematic effects of priming. However, the effect sizes were relatively small. Participants of the present study were healthy young individuals. It appears that the category of the primes plays a minor role in modulating the perception of noxious stimuli in this particular group. There are clues indicating that the priming effects of pain-related primes versus negative, pain-unrelated primes are more pronounced in chronic pain patients compared with healthy controls (21,28). It appears that subjects with repeated pain experiences, such as subjects with a chronic pain disease, have developed stronger associative learning networks during incremental experiences and, therefore, show larger priming effects after receiving pain-related primes versus negative, pain-unrelated primes. Investigation of priming in chronic pain patients should clarify this issue.

In the present study, four categories of words were used, each consisting of 10 different adjectives. The acquisition of a greater variety of different matching primes could support the generalization of the findings. Furthermore, priming may be more potent for images. We did not find a significant difference in pain ratings for pain-related versus negative pain-unrelated stimuli, in contrast to de Wied and Verbaten (14) and Ogino et al (15). Therefore, emotional and pain-related pictures may be better for the investigation of principle mechanisms of priming in humans. However, this does not preclude the necessity of investigating the extent of verbal priming in chronic pain patients. There are already hints that the effects are stronger than in healthy subjects (21).

Although two distinct pain intensities were successfully established, the manipulation of the moderate pain intensity resulted in a relatively mild average pain rating. This could be one of the reasons why some of the assumed effects for the differences between negative and pain-related adjectives failed to reach statistical significance. It may be a challenge for future research on electrical pain stimulation to solidly apply moderate pain intensities to clearly distinguish them from mild or no pain intensities. One way of doing so may be a bio-adaptive approach, as proposed previously (26).

CONCLUSION
Semantic priming was investigated by using negative and pain-related stimuli that were matched for valence and arousal. In accordance with the motivational priming theory, we found stronger pain ratings for subsequent electrical stimuli after negative and pain-related priming compared with neutral priming. These effects were especially apparent for stronger intensities of the painful stimulation and when the interval between prime and target stimulus was ≤500 ms. Further studies are necessary to examine whether this trend indicates a specific effect according to the theory of associative neural networks.

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