

Enhanced Short-Term Sensitization of Facial Compared With Limb Heat Pain

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Abstract: Habituation and sensitization are important features of individual sensitivity to repetitive noxious stimulation and have been investigated in numerous studies. However, it is unclear whether these phenomena vary depending on the site of stimulation. Here we compared short-term and long-term effects of painful heat stimulation on the forehead and limb using an established longitudinal heat pain paradigm performed over 8 consecutive days in 36 healthy volunteers. Participants were randomized into 2 groups; participants received repetitive heat pain stimulation either on the left volar forearm or on the left side of the forehead. Our data show a comparable degree of habituation over the course of 8 days in both groups. However, participants in the trigeminal stimulation group exhibited stronger within-session sensitization (indexed by a higher within-session increase in pain intensity ratings) than those who received the forearm stimulation. Furthermore, over the course of the experiment we found a correlation between habituation and anxiety, showing less habituation in participants with higher trait anxiety scores. Our findings are in line with somatotopic differences in response to painful stimulation and a higher proneness of trigeminal pain to sensitization processes, which might be explained by the biological relevance of the head and facial area for vital functions. The contribution of this sensitivity to the development and maintenance of clinical facial pain and headache disorders warrants further investigation.

Perspective: This study uses psychophysical methods to evaluate the differences in long-term habituation and short-term sensitization to heat pain between the trigeminal and spinal systems. We found stronger sensitization for trigeminal compared with nociceptive stimuli on the forearm. The contribution of this sensitivity to clinical pain states warrants further investigation.

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Key words: Trigeminal pain, heat pain, habituation, sensitization, experimental pain.

The detection of nociceptive information within the head and facial area has a unique biological relevance because of the localization of vital functions such as perception, food intake, and communication in this part of the body. Nociceptive and other salient stimuli perceived within this space might therefore be processed with higher priority and evaluated as more threatening compared with physically identical stimuli applied to the periphery. In line with this notion, Sambo and colleagues³² showed that a defensive reaction (ie, the hand blink reflex) could be elicited with shorter

onset latency, higher amplitude, and higher frequency when a painfully stimulated hand was positioned near the face compared with farther away from the face.

Habituation and sensitization to repetitive noxious stimulation are important features of an individual's sensitivity to pain. Previous behavioral and neuroimaging studies have shown that these responses to repetitive noxious stimulation involve central nervous system mechanisms, such as activity in the descending pain modulatory system,^{4,42} are modulated by both bottom-up and top-down factors, such as expectation,²⁸ and might be associated with the individual's susceptibility to clinical pain disorders.^{11,24,35,40}

However, in most of these studies on habituation and sensitization, painful heat stimuli were applied to the extremities.^{4,6,21,28,39} Only a few studies have investigated habituation to repetitive pain stimuli in the trigeminal system,^{1,36,37} and they did not directly compare habituation and sensitization processes between the trigeminal and spinal systems (limb).

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Here we aimed at exploring potential differences in the response to repetitive painful stimulation between the trigeminal and the spinal systems. To this end, we used an established heat pain paradigm involving a daily session of repetitive thermal painful stimulation over a course of 8 consecutive days^{4,6,21} in 2 groups of healthy volunteers. One group received painful stimulation on the left volar forearm, and the other group was stimulated on the left side of the forehead. Previous studies have shown that this stimulation protocol reliably induces within-session sensitization (WSS) and between-session habituation (BSH).^{4,6,21,28} Given the higher biological relevance of nociceptive signals from the face and head, which should result in increased sensitivity to repetitive stimulation, we hypothesized enhanced WSS for facial stimulation compared with painful limb stimulation. In addition, we expected reduced BSH for facial stimulation compared with stimulation on the forearm, as indicated by a smaller decline of subjective pain ratings over the course of 8 days. Furthermore, we tested for a potential spread of BSH and WSS from the trigeminal nerve to the forearm and vice versa.²⁷ We assessed the influence of expectation, depression, anxiety, and other pain-related psychological processes on potential site-dependent differences in the response to repetitive noxious stimulation.

Methods

Participants

Behavioral data were acquired in 37 healthy local volunteers. One participant had to be excluded from the analyses because of a very low sensitivity to heat pain stimulation. Data from the remaining 36 participants (all right-handed, mean age \pm SD 25.9 ± 4.1 years; 19 men, age 26.42 ± 4.8 years; 17 women, age 25.35 ± 3.08 years) were included in the final analyses. All participants had normal heat pain thresholds³⁰ at the site of stimulus application (see section on Results: Heat Pain Thresholds) and reported normal hearing and normal or corrected-to-normal vision. Considering

Enhanced Sensitization to Trigeminal Heat Pain the influence of depression on pain perception,¹⁴ we included only participants with a depression score below the cutoff of 18 on the General Depression Scale (ADS-K, see Experimental Procedure section). Furthermore, participants reported no history of neurological or psychiatric diseases or recurrent or chronic pain, including head and facial pain syndromes (eg, migraine, temporomandibular joint syndrome). Participants were instructed to refrain from taking any pain medication within the 2 weeks before the experiment and during the experiment. The study was approved by the local ethics committee in accordance with the Declaration of Helsinki. All volunteers gave written informed consent to participate and were free to withdraw from participation at any time.

Experimental Paradigm

The study was performed on 8 consecutive days (see Fig 1) under the same environmental conditions (ie, same room, lighting, temperature, and experimenter). A preparation session 2 or 3 days before the actual experiment was conducted, during which participants provided their written informed consent, completed a number of questionnaires, and were familiarized with the experimental procedure (see later discussion). The experimental paradigm (see Fig 2) used in this study is an established paradigm that has been used previously.^{4,21,27} An identical experimental session was performed on each of the 8 days. First, participants lay on their backs in a 45° upright position facing a computer screen. Pain thresholds at the site of stimulus application (face or arm, depending on the group) were obtained using the method of limits¹³ before participants received 10 blocks of painful thermal stimuli on their left forehead or left volar forearm, respectively. Each pain block consisted of 6 stimuli for 6 seconds duration each, applied without a pause, resulting in a total of 60 heat pain stimuli per day. The intensity of the heat stimulation was individually adjusted to a level of 50 on a visual analog scale (VAS 0–100, with anchors 0 = not painful to 100 = unbearably painful) using an

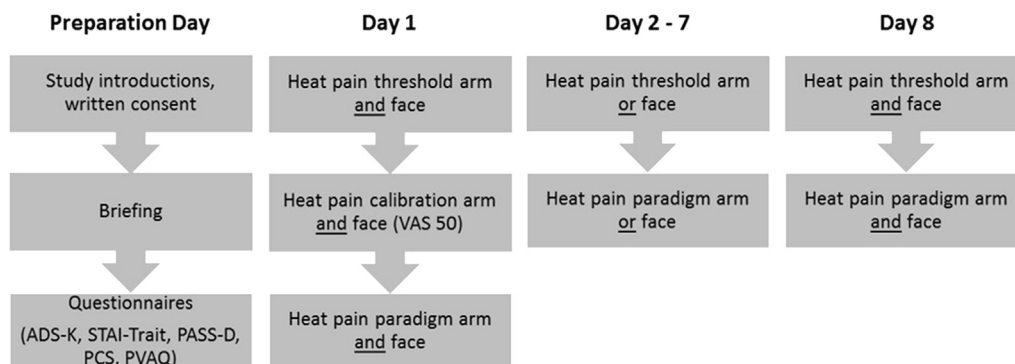


Figure 1. Study design: Participants went through the illustrated procedure on days 1 to 8 of the experiment. On days 1 and 8, participants underwent the heat pain paradigm on the left volar forearm and the left side of the forehead. On days 2 to 7, participants received only heat pain stimulation on one of the stimulation sites depending on their group assignment. Heat pain thresholds were assessed every day. Abbreviations: ADS-K, General Depression Scale–German Version; STAI-Trait, STAI: Trait Scale–German Version; PASS-D, Pain Anxiety Symptoms Scale–German Version; PCS, Pain Catastrophizing Scale–German Version; PSQ, Pain Sensitivity Questionnaire–German Version.

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