

RESEARCH ARTICLE | *Sensory Processing*

Burst-like conditioning electrical stimulation is more efficacious than continuous stimulation for inducing secondary hyperalgesia in humans

S. Gousset, A. Mouraux, and  E. N. van den Broeke

System and Cognition Division, Institute of Neuroscience, Université catholique de Louvain, Brussels, Belgium

Submitted 28 October 2019; accepted in final form 3 December 2019

Gousset S, Mouraux A, van den Broeke EN. Burst-like conditioning electrical stimulation is more efficacious than continuous stimulation for inducing secondary hyperalgesia in humans. *J Neurophysiol* 123: 323–328, 2020. First published December 11, 2019; doi:10.1152/jn.00675.2019.—The aim of the present study was to compare the efficacy of burst-like conditioning electrical stimulation vs. continuous stimulation of cutaneous nociceptors for inducing increased pinprick sensitivity in the surrounding unstimulated skin (a phenomenon referred to as secondary hyperalgesia). In a first experiment ($n = 30$), we compared the increase in mechanical pinprick sensitivity induced by 50-Hz burst-like stimulation ($n = 15$) vs. 5-Hz continuous stimulation ($n = 15$) while maintaining constant the total number of stimuli and the total duration of stimulation. We found a significantly greater increase in mechanical pinprick sensitivity in the surrounding unstimulated skin after 50-Hz burst-like stimulation compared with 5-Hz continuous stimulation ($P = 0.013$, Cohen's $d = 0.970$). Importantly, to control for the different frequency of stimulation, we compared in a second experiment ($n = 40$) 5-Hz continuous stimulation ($n = 20$) vs. 5-Hz burst-like stimulation ($n = 20$), this time while keeping the total number of stimuli as well as the frequency of stimulation identical. Again, we found a significantly greater increase in pinprick sensitivity after 5-Hz burst-like stimulation compared with 5-Hz continuous stimulation ($P = 0.009$, Cohen's $d = 0.868$). To conclude, our data indicate that burst-like conditioning electrical stimulation is more efficacious than continuous stimulation for inducing secondary hyperalgesia.

NEW & NOTEWORTHY Burst-like electrical conditioning stimulation of cutaneous nociceptors is more efficacious than continuous stimulation for inducing heterosynaptic facilitation of mechanical nociceptive input in humans.

burst-like; continuous; electrical stimulation; nociception; secondary hyperalgesia

INTRODUCTION

Long-term potentiation (LTP) refers to a long-lasting activity-dependent increase in synaptic strength and was first demonstrated by Bliss and Lømo (1973) following brief trains of stimulation of the perforant path to dentate granule cells in the hippocampus of anesthetized rabbits. Interestingly, results seem to indicate that burst-like stimulation is more effective for

inducing LTP than continuous stimulation (see Fig. 3 in Larson and Munkácsy 2015).

Activity-dependent LTP can also be induced within spinal nociceptive pathways (Ikeda et al. 2003, 2006). For example, Ikeda et al. (2003) showed that brief trains of high-frequency stimuli (HFS; 100 Hz for 1 s three times at 10-s intervals), further referred to as burst-like stimulation, applied to the rat sciatic nerve triggers homosynaptic LTP at the synapse between peripheral C-fibers and spinal cord lamina I neurons projecting to the parabrachial area in the brain stem. Low-frequency continuous stimulation (2 Hz for 2 min) also triggers homosynaptic LTP, but at the synapse between peripheral C-fibers and spinal cord lamina I neurons projecting to the periaqueductal gray (Ikeda et al. 2006). In addition to homosynaptic LTP, HFS also triggers heterosynaptic LTP at remote C-fibers, which is induced through the activation of spinal glial cells releasing TNF- α and D-serine (Kronschlager et al. 2016). A recent study in rodents suggests that microglia-mediated LTP could be one mechanism responsible for the development of chronic pain (Zhou et al. 2019).

In humans, HFS (100 Hz for 1 s five times at 10-s intervals) delivered to the skin to intensively activate skin nociceptors increases the perception elicited by single weak electrical stimuli delivered through the same electrode at which HFS was delivered. Moreover, it increases the perception elicited by mechanical pinprick stimuli delivered to the surrounding unstimulated skin (Henrich et al. 2015; Klein et al. 2004). It has been suggested that the increase in perception elicited by the weak electrical stimuli after HFS is a perceptual correlate of homosynaptic LTP (also referred to as “homotopic pain LTP”), whereas the increase in mechanical pinprick stimuli is a perceptual correlate of heterosynaptic LTP (also referred to as “heterotopic pain LTP”) (Henrich et al. 2015; Klein et al. 2004). With regard to the pattern of conditioning stimulation, it is at present unclear if burst-like stimulation is more efficacious than continuous stimulation for inducing heterotopic pain LTP.

A previous study in humans compared the heterotopic pain LTP induced by 10-Hz continuous stimulation and 100-Hz burst-like stimulation (HFS) while keeping the total number of stimuli and total duration of stimulation the same for both protocols (Xia et al. 2016). Both conditioning stimuli induced a significant increase in mechanical pinprick sensitivity of the surrounding skin. However, although the average increase in pinprick ratings was greater after burst-like stimulation (49%)

Address for reprint requests and other correspondence: E. N. van den Broeke, System and Cognition Division, Institute of Neuroscience, Université catholique de Louvain, Brussels, Belgium (e-mail: Emanuel.vandenbroeke@Uclouvain.be).

compared with continuous stimulation (27%), these differences were not statistically significant. In contrast to these results, De Col and Maihöfner (2008) found that 20-Hz continuous stimulation resulted in a decreased sensitivity to mechanical pain, i.e., increased mechanical pain thresholds in the area surrounding the stimulated skin, suggesting that continuous stimulation could induce hypoalgesia rather than hyperalgesia. Finally, both Biurrun Manresa et al. (2010) and Vo and Drummond (2014) did not observe any significant changes in pinprick sensitivity after 1-Hz continuous conditioning stimulation.

The aim of the present study was to test if continuous nociceptive conditioning stimulation is more effective than burst-like stimulation in inducing heterotopic pain LTP. To test this, we compared the change in mechanical pinprick sensitivity induced by 50-Hz burst-like stimulation with the change in mechanical pinprick sensitivity induced by 5-Hz continuous stimulation (*experiment 1*). Both protocols have the same total number of stimuli and the same total duration of stimulation. Furthermore, to control for a possible effect of frequency of stimulation, we also compared the change in mechanical pinprick sensitivity induced by 5-Hz continuous stimulation with the change in mechanical pinprick sensitivity induced by 5-Hz burst-like stimulation (*experiment 2*). In this case, both the frequency and the total number of stimuli remained the same, but the total duration was greater for burst-like stimulation.

METHODS AND MATERIALS

Participants

Thirty healthy volunteers took part in *experiment 1*. Participants were randomly assigned to either 5-Hz continuous conditioning stimulation ($n = 15$, 5 men and 10 women; age 19–27 yr, 22.4 ± 2.4 yr, mean $\pm$ SD) or to 50-Hz burst-like conditioning stimulation ($n = 15$, 5 men and 10 women; age 21–36 yr, 23.8 ± 4.0 yr). In *experiment 2*, 40 healthy volunteers were included (5-Hz burst-like stimulation: $n = 20$, 7 men and 13 women; age 18–40 yr, 23.0 ± 4.9 yr; 5-Hz continuous stimulation: $n = 20$, 7 men and 13 women; age 19–27 yr, 22.6 ± 2.3 yr). Parts of the data were reused from the 5-Hz continuous stimulation condition of *experiment 1* ($n = 15$) and the 5-Hz burst-like stimulation condition of our previously collected data set ($n = 15$; van den Broeke et al. 2019). Comparison of these two groups of 15 participants did not reach statistical significance. However, the effect size calculated using the means and SD of the increase in pinprick sensitivity (compared with baseline and control site) was moderate (Cohen's $d = 0.50$), which could indicate that we did not have sufficient power to detect a difference. Therefore, to reduce the risk of making a type II error, we increased the sample from 15 to 20 by collecting data from 5 new participants per group.

The experiment was conducted according to the Declaration of Helsinki (except preregistration of the trial). Approval for the experiments was obtained from the local Ethical Committee (Comité d'Ethique Hospitalo-Facultaire des Cliniques universitaires Saint-Luc-UCLouvain) of UCLouvain (B403201316436). All participants signed an informed consent form and received financial compensation for their participation.

Experimental Design

In all experiments, electrical conditioning stimulation was applied to the dominant or nondominant volar forearm, counterbalanced across participants (10 cm distal to the cubital fossa; Fig. 1). Handedness was assessed using the Flinders Handedness Survey (Nicolls et al. 2013). Before (Pre) and 20 min after (Post) the end of the conditioning stimulation, pinprick sensitivity of the skin was assessed by applying mechanical pinprick stimuli (128 mN) to the skin surrounding the site where the conditioning stimulation was delivered (pinprick test area) and to the corresponding skin area of the contralateral arm serving as control.

Conditioning Stimulation

In all experiments, the conditioning stimulation consisted of biphasic charge-compensated electrical pulses that were delivered to the ventral forearm using a constant-current electrical stimulator (Digitimer DS5, Welwyn Garden City, UK) and a specifically designed electrode built at the Centre for Sensory-Motor Interaction (Aalborg University, Denmark). The biphasic pulses consisted of a 2-ms square-wave pulse followed, after a 0.1 ms delay, by a 4-ms compensation pulse of opposite polarity having half the intensity of the first pulse. The electrode consists of 16 blunt stainless steel pins (diameter: 0.2 mm) protruding 1 mm from the base (Fig. 1). The pins are placed in a 10-mm diameter circle and serve as cathode. A stainless steel anode electrode is concentrically located around the steel pins (inner diameter: 22 mm; outer diameter: 40 mm).

The intensity of conditioning stimulation was individually adjusted to 20 times the detection threshold to a single non-charge-compensated monophasic pulse (pulse width: 2 ms). The electrical detection threshold was determined after the Pre measurement of pinprick sensitivity using a staircase procedure.

In all conditions, the total number of electrical stimuli delivered during the conditioning stimulation was the same (i.e., 500). The 50-Hz burst-like stimulation consisted of 10 trains, each including 50 pulses delivered at 50 Hz. The trains lasted 1 s and were separated by a 10-s intertrain interval (total duration: 100 s). The 5-Hz continuous stimulation consisted of 1 train of 5-Hz stimulation for 100 s. Finally, the 5-Hz burst-like stimulation consisted of 100 trains, each including 5 pulses and lasting for 1 s. The trains were delivered in a 10-s intertrain interval (total duration: ± 17 min).

The electrical pulses were triggered by a National Instruments digital-analog interface (NI, National Instruments, Austin, TX) controlled by custom MATLAB code (MATLAB 2014B, The MathWorks, Natick, MA).

Quantifying Changes in the Perceived Intensity of Mechanical Pinprick Stimuli

To assess changes in pinprick sensitivity, we followed the same method as described in our previous study (van den Broeke et al. 2019), which is summarized here. A calibrated pinprick stimulator exerting a normal force of 128 mN with the use of a 0.25-mm probe (MRC Systems, Heidelberg, Germany) was applied perpendicular to the skin. Before application of the conditioning stimulation and 20 min after application of the conditioning stimulation, a total of three pinprick stimuli were

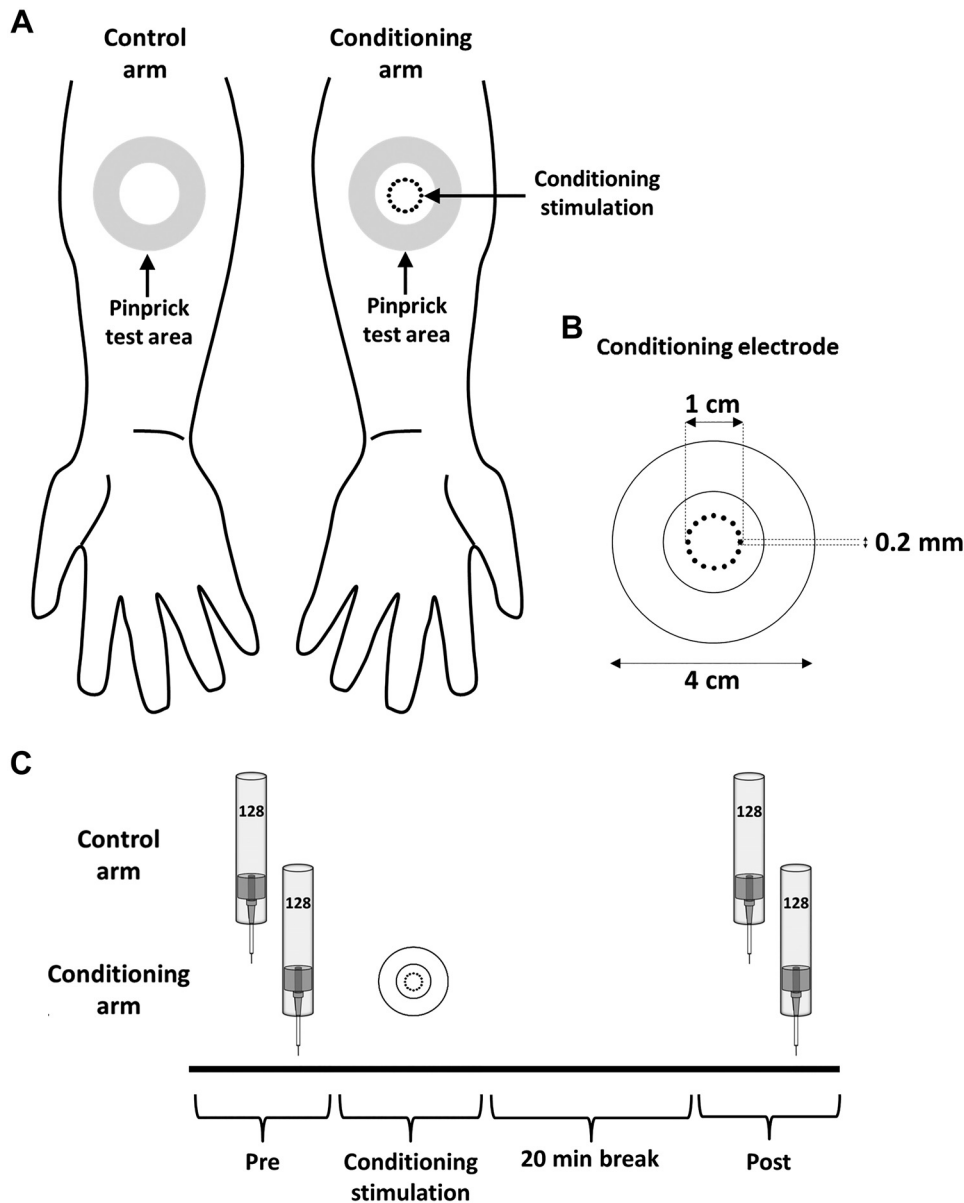


Fig. 1. Experimental setup. *A*: conditioning stimulation is applied to the dominant or nondominant volar forearm. Pinprick stimulation (128 mN) was applied to the skin surrounding the area onto which conditioning stimulation was applied (pinprick test area) as well as to the same skin area on the contralateral control arm. *B*: characteristics of the conditioning electrode. *C*: timeline of the experiment. Perceived intensity elicited by the pinprick stimulation was assessed at two different time points: before conditioning stimulation (Pre) and 20 min after application of conditioning stimulation (Post).

applied inside the pinprick test area of the conditioned arm and the contralateral control arm. The target of each pinprick stimulus was displaced after each stimulus. Participants were asked to report the intensity of perception elicited by the pinprick stimulation on a numerical rating scale (NRS) ranging from 0 (no perception) to 100 (maximal pain), with 50 representing the transition from nonpainful to painful domains of sensation.

Statistical Analysis

Statistical analyses were performed using SPSS Statistics 24 (IBM Corp., Armonk, NY). In *experiment 1*, the change in perceived pinprick intensity induced by the 5-Hz continuous stimulation and the 50-Hz burst-like stimulation was compared using a mixed two-way repeated-measures ANOVA with arm (HFS vs. control) and time (post vs. pre) as within-subject factors and condition (5-Hz continuous vs. 50-Hz burst-like) as between-subject factor. Post hoc, an independent *t* test was used to test for differences in the increase in pinprick sensitiv-

ity (compared with baseline and control site) between the 5-Hz continuous stimulation and the 50-Hz burst-like stimulation. In *experiment 2*, the change in perceived pinprick intensity induced by the 5-Hz continuous stimulation and the 5-Hz burst-like stimulation was compared using a mixed two-way repeated-measures ANOVA with arm (HFS vs. control) and time (post vs. pre) as within-subject factors and condition (5-Hz continuous vs. 5-Hz burst-like) as between-subject factor. Post hoc, an independent *t* test was used to test for differences in the increase in pinprick sensitivity (compared with baseline and control site) between the 5-Hz continuous stimulation and the 5-Hz burst-like stimulation. In all tests, the level of significance was set at $P < 0.05$.

RESULTS

Electrical Detection Thresholds

Experiment 1. The electrical detection thresholds to a single monophasic non-charge-compensated pulse were 0.29 ± 0.08

mA (mean $\pm$ SD) for the 5-Hz continuous stimulation and 0.26 ± 0.07 mA for the 50-Hz burst-like stimulation. An independent t test revealed no statistically significant difference in electrical detection thresholds.

Experiment 2. The electrical detection thresholds to a single monophasic non-charge-compensated pulse were 0.26 ± 0.09 mA for the 5-Hz burst-like stimulation and 0.30 ± 0.08 mA for the 5-Hz continuous stimulation. An independent t test revealed no statistically significant difference in electrical detection thresholds.

Changes in Mechanical Pinprick Sensitivity

Experiment 1: 5-Hz continuous stimulation vs. 50-Hz burst-like stimulation. The means and SD of the intensity of perception elicited by pinprick stimuli delivered before and after conditioning stimulation at both arms (control vs. conditioned) in both conditions (5-Hz continuous stimulation vs. 50-Hz burst-like stimulation) are shown in Fig. 2. The mixed repeated-measures ANOVA revealed a significant time $\times$ arm $\times$ condition interaction [$F(1,28) = 7.062$, $P = 0.013$, $\eta^2 = 0.201$]. Separate repeated-measures ANOVAs for the 5-Hz continuous stimulation and the 50-Hz burst-like stimulation revealed a significant time $\times$ arm interaction for both protocols [5-Hz continuous: $F(1,14) = 13.883$, $P = 0.002$, $\eta^2 = 0.498$; 50-Hz burst-like stimulation: $F(1,14) = 32.859$, $P < 0.001$, $\eta^2 = 0.701$]. The increase in perceived intensity was significantly greater for the 50-Hz burst-like stimulation compared with the 5-Hz continuous stimulation [$t(28) = 2.658$, $P = 0.013$, Cohen's $d = 0.970$; Fig. 2].

Experiment 2: 5-Hz continuous stimulation vs. 5-Hz burst-like stimulation. The means and SD of the intensity of perception elicited by pinprick stimuli delivered before and after conditioning stimulation at both arms (control vs. conditioned) for both the 5-Hz burst-like stimulation and the 5-Hz continuous stimulation are shown in Fig. 3. The mixed repeated-measures ANOVA revealed a significant time $\times$ arm $\times$ condition interaction [$F(1,38) = 7.543$, $P = 0.009$, $\eta^2 = 0.166$]. Separate repeated-measures ANOVAs for the 5-Hz continuous stimulation and the 5-Hz burst-like stimulation revealed a significant time $\times$ arm interaction for both protocols [5-Hz burst-like stimulation: $F(1,19) = 37.421$, $P < 0.001$, $\eta^2 = 0.663$; 5-Hz continuous stimulation: $F(1,19) = 20.519$, $P < 0.001$, $\eta^2 = 0.519$]. The increase in perceived intensity was significantly greater for the 5-Hz burst-like stimulation compared with the 5-Hz continuous stimulation [$t(38) = 2.746$, $P = 0.009$, Cohen's $d = 0.868$; Fig. 3].

DISCUSSION

The aim of the present study was to compare the efficacy of continuous vs. burst-like electrical stimulation of cutaneous nociceptors for the induction of heterotopic pain LTP. Our data shows that, when controlled for frequency of stimulation, burst-like conditioning stimulation induces a significantly greater increase in pinprick sensitivity than continuous stimulation.

In *experiment 1*, we showed that the increase in mechanical pinprick sensitivity induced after 50-Hz burst-like stimulation was significantly greater compared with the increase in mechanical pain sensitivity induced after 5-Hz continuous stimulation. In this experiment, the total duration of the conditioning

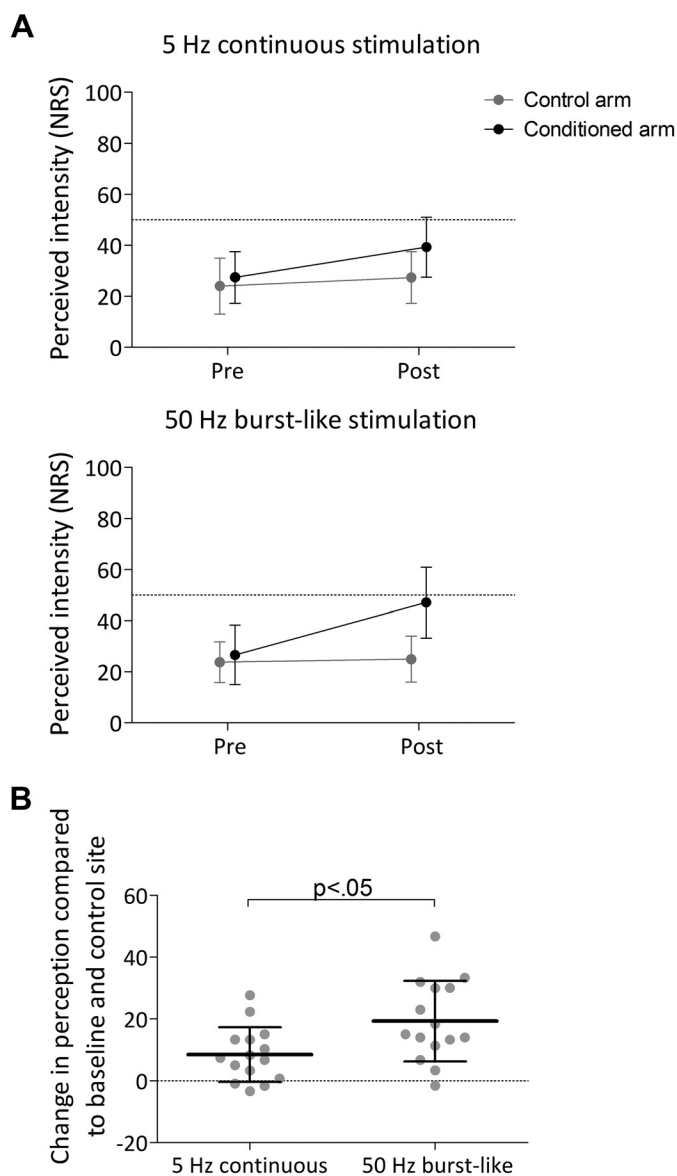


Fig. 2. *Experiment 1.* A: intensity of perception elicited by the mechanical pinprick stimulation (128 mN) before (Pre) and 20 min after (Post) application of 5-Hz continuous conditioning electrical stimulation (top) or 50-Hz burst-like stimulation (bottom). Shown are the group-level average and SD of the numerical rating scale (NRS) scores. B: group-level average and SD increase in NRS compared with baseline and control site. P value shows the result of the independent t test on the individual changes in perception.

stimulation and the total number of applied stimuli were identical, but the stimuli were delivered at different frequencies. Hence, differences between the two conditions could have been related to differences in stimulation frequency (van den Broeke et al. 2019) rather than the use of burst-like vs. continuous patterns of stimulation. For this reason, we conducted a second experiment in which we compared the increase in mechanical pinprick sensitivity induced by 5-Hz continuous stimulation and 5-Hz burst-like stimulation. In this experiment, frequency of stimulation and total number of stimuli were identical across conditions. Again, we found that 5-Hz burst-like stimulation induced a greater increase in pinprick sensitivity compared with 5-Hz continuous stimulation.

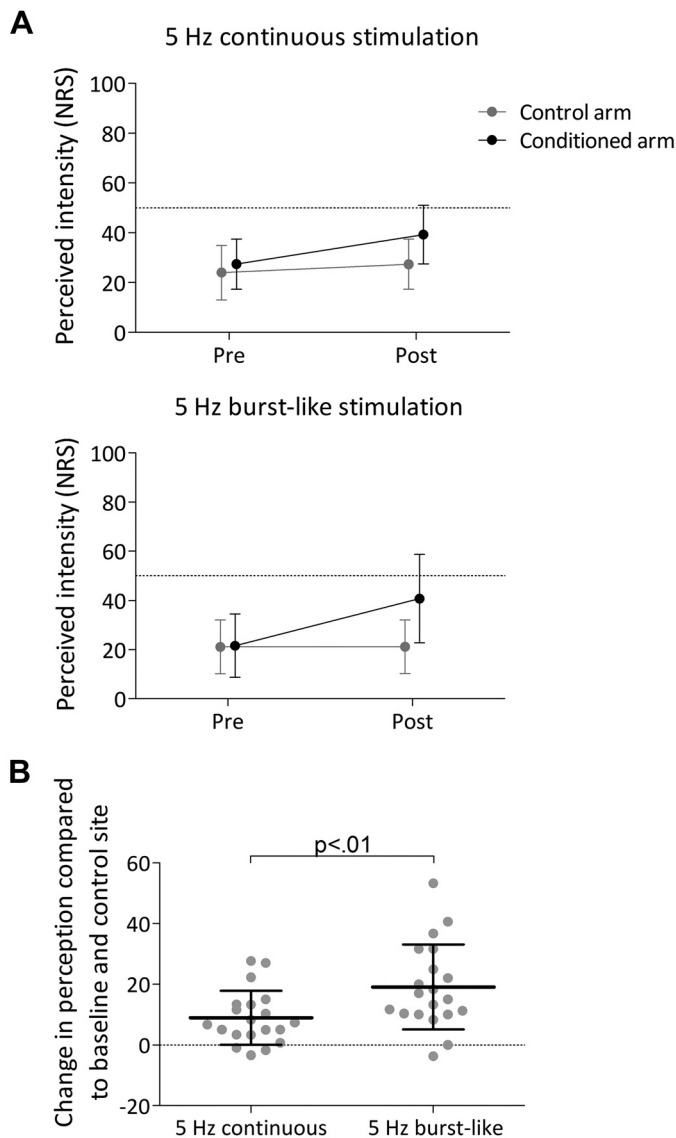


Fig. 3. *Experiment 2.* A: intensity of perception elicited by the mechanical pinprick stimulation (128 mN) before (Pre) and 20 min after (Post) application of 5-Hz continuous conditioning electrical stimulation (*top*) or 5-Hz burst-like stimulation (*bottom*). Shown are the group-level average and SD of the numerical rating scale (NRS) scores. B: group-level average and SD increase in NRS compared with baseline and control site. *P* value shows the result of the independent *t* test on the individual changes in perception.

When studying LTP in the hippocampus, Larson and Munkácsy (2015) found that burst-like stimulation induced a relatively larger homosynaptic LTP than continuous tetanic stimulation. If heterotopic pain LTP is indeed a manifestation of heterosynaptic LTP, our results suggest that burst-like stimulation is more efficacious than continuous stimulation in inducing spinal heterosynaptic LTP. Studies conducted in rodents have shown that high-frequency burst-like stimulation of the sciatic nerve can activate microglia (Kronschläger et al. 2016) and that activated microglia can release brain-derived neurotrophic factor (BDNF; Zhou et al. 2019). The release of BDNF is thought to contribute to central sensitization (Retamal et al. 2018; Zhou et al. 2019) and may decrease the activity of the potassium-chloride cotransporter (KCC2), which would result in an increase in intracellular chloride concentration

leading to a loss of inhibition and, as a consequence, increased excitation (Coull et al. 2003; Dedek et al. 2019). Interestingly, studies in rats have shown that unlike burst-like stimulation, continuous stimulation does not lead to the release of BDNF (Lever et al. 2001).

Xia et al. (2016) also compared changes in pinprick sensitivity induced by continuous stimulation and burst-like stimulation in humans. Specifically, they compared 10-Hz continuous stimulation with 100-Hz burst-like stimulation while keeping the total number of stimuli and total duration of stimulation the same. They observed a significant increase in pinprick sensitivity after both stimulation protocols, however, and in contrast to our results, no statistically significant difference was observed, although the increases were not the same (10 Hz: 27%; 100 Hz: 49%). Xia et al. used an intensity of stimulation corresponding to 10 times the detection threshold, whereas in the present study we used an intensity of 20 times the detection threshold. Moreover, in the present study we compared the two conditions (5 Hz vs. 50 Hz) with respect to baseline and contralateral control arm, whereas in the study of Xia et al., they compared three conditions (10-Hz continuous, 100-Hz burst-like, and 200-Hz burst-like stimulation) with respect to baseline and a control condition in which the electrode was attached to the skin but no stimulation was delivered.

We also show that continuous stimulation induces an increase in mechanical pinprick sensitivity. Klein et al. (2004) also observed hyperalgesia to pinprick stimulation in surrounding unstimulated skin after 1-Hz continuous conditioning stimulation, but only when the intensity of stimulation was 20 times the detection threshold. The total duration of their conditioning stimulation was around 16 min, and the stimulation was applied to the ventral forearm. Also Torta et al. (2019) showed an increase in pinprick sensitivity of the skin after 2 min of 2-Hz continuous stimulation at the forearm.

In contrast, De Col and Maihöfner (2008) showed that 20-Hz continuous stimulation applied to the ventral forearm induced hypoalgesia rather than hyperalgesia of the skin surrounding the site at which the conditioning stimulation was delivered. However, there are differences between the present study and their study. In the study of De Col and Maihöfner, the continuous stimulation lasted for 35 min, whereas our continuous conditioning stimulation lasted 100 s only. Moreover, the electrode those authors used to deliver the conditioning stimulation is different from ours. Whereas their electrode had only two pins, our electrode has 16 pins. It is likely that our stimulation activated a larger number of afferents. Furthermore, the frequency of stimulation is different: whereas it was 20 Hz in their study, it was 5 Hz in the present study. Finally, the intensity of stimulation was different. In the study of De Col and Maihöfner, the intensity was continuously adjusted during the conditioning stimulation to a pain intensity of 5 on a numeric rating scale ranging from 0 (no pain) to 10 (worst imaginable pain), whereas in our study the intensity of stimulation was set at 20 times the detection threshold.

Finally, Biurrun Manresa et al. (2010) and Vo and Drummond (2014) also used 1-Hz continuous conditioning stimulation but did not observe any significant changes in pinprick perception in the unstimulated surrounding skin. In both studies, their conditioning stimulation was delivered at 10 times detection threshold. Moreover, in the study of Biurrun Manresa

et al., they applied the conditioning stimulation to the dorsum of the foot instead of the forearm.

To conclude, the present study provides evidence that burst-like conditioning stimulation is more efficacious in inducing increased pinprick sensitivity in the surrounding unstimulated skin than continuous stimulation. These results show that the pattern of peripheral nociceptive input (i.e., not only the total amount of input) is an important determinant of how much central sensitization will be induced. Our results may have important implications for neurostimulation in the context of pain therapy.

GRANTS

E. N. van den Broeke is supported by the Fonds de Recherche Clinique provided by UCLouvain, Belgium. A. Mouraux is supported by an European Research Council “Starting Grant” (PROBING PAIN 336130).

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

S.G. performed experiments; S.G., A.M., and E.N.V.D.B. interpreted results of experiments; S.G., A.M., and E.N.V.D.B. drafted manuscript; S.G., A.M., and E.N.V.D.B. approved final version of manuscript; A.M. and E.N.V.D.B. conceived and designed research; A.M. and E.N.V.D.B. prepared figures; E.N.V.D.B. analyzed data.

REFERENCES

- Biurrun Manresa JA, Mørch CD, Andersen OK. Long-term facilitation of nociceptive withdrawal reflexes following low-frequency conditioning electrical stimulation: a new model for central sensitization in humans. *Eur J Pain* 14: 822–831, 2010. doi:10.1016/j.ejpain.2009.12.008.
- Bliss TV, Lømo T. Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path. *J Physiol* 232: 331–356, 1973. doi:10.1113/jphysiol.1973.sp010273.
- Coull JA, Boudreau D, Bachand K, Prescott SA, Nault F, Sîk A, De Koninck P, De Koninck Y. Trans-synaptic shift in anion gradient in spinal lamina I neurons as a mechanism of neuropathic pain. *Nature* 424: 938–942, 2003. doi:10.1038/nature01868.
- De Col R, Maihöfner C. Centrally mediated sensory decline induced by differential C-fiber stimulation. *Pain* 138: 556–564, 2008. doi:10.1016/j.pain.2008.02.005.
- Dedek A, Xu J, Kandegedara CM, Lorenzo LÉ, Godin AG, De Koninck Y, Lombroso PJ, Tsai EC, Hildebrand ME. Loss of STEP61 couples disinhibition to *N*-methyl-D-aspartate receptor potentiation in rodent and human spinal pain processing. *Brain* 142: 1535–1546, 2019. doi:10.1093/brain/awz105.
- Henrich F, Magerl W, Klein T, Greffrath W, Treede RD. Capsaicin-sensitive C- and A-fibre nociceptors control long-term potentiation-like pain amplification in humans. *Brain* 138: 2505–2520, 2015. doi:10.1093/brain/awv108.
- Ikeda H, Heinke B, Ruscheweyh R, Sandkühler J. Synaptic plasticity in spinal lamina I projection neurons that mediate hyperalgesia. *Science* 299: 1237–1240, 2003. doi:10.1126/science.1080659.
- Ikeda H, Stark J, Fischer H, Wagner M, Drdla R, Jäger T, Sandkühler J. Synaptic amplifier of inflammatory pain in the spinal dorsal horn. *Science* 312: 1659–1662, 2006. doi:10.1126/science.1127233.
- Klein T, Magerl W, Hopf HC, Sandkühler J, Treede RD. Perceptual correlates of nociceptive long-term potentiation and long-term depression in humans. *J Neurosci* 24: 964–971, 2004. doi:10.1523/JNEUROSCI.1222-03.2004.
- Kronschläger MT, Drdla-Schutting R, Gassner M, Honsek SD, Teuchmann HL, Sandkühler J. Gliogenic LTP spreads widely in nociceptive pathways. *Science* 354: 1144–1148, 2016. doi:10.1126/science.aah5715.
- Larson J, Munkácsy E. Theta-burst LTP. *Brain Res* 1621: 38–50, 2015. doi:10.1016/j.brainres.2014.10.034.
- Lever IJ, Bradbury EJ, Cunningham JR, Adelson DW, Jones MG, McMahon SB, Marvizón JC, Malcangio M. Brain-derived neurotrophic factor is released in the dorsal horn by distinctive patterns of afferent fiber stimulation. *J Neurosci* 21: 4469–4477, 2001. doi:10.1523/JNEUROSCI.21-12-04469.2001.
- Nicholls ME, Thomas NA, Loetscher T, Grimshaw GM. The Flinders Handedness survey (FLANDERS): a brief measure of skilled hand preference. *Cortex* 49: 2914–2926, 2013. doi:10.1016/j.cortex.2013.02.002.
- Retamal J, Reyes A, Ramirez P, Bravo D, Hernandez A, Pelissier T, Villanueva L, Constandil L. Burst-like subcutaneous electrical stimulation induces BDNF-mediated, cyclothraxin B-sensitive central sensitization in rat spinal cord. *Front Pharmacol* 9: 1143, 2018. doi:10.3389/fphar.2018.01143.
- Torta D, De Laurentis M, Eichin KN, von Leupoldt A, van den Broeke E, Vlaeyen J. High cognitive load may prevent the development of nociceptive hypersensitivity (Preprint). *PsyArXiv* 2019. doi:10.31234/osf.io/zq5sx.
- van den Broeke EN, Gousset S, Bouvy J, Stouffs A, Lebrun L, van Neerven SG, Mouraux A. Heterosynaptic facilitation of mechanical nociceptive input is dependent on the frequency of conditioning stimulation. *J Neurophysiol* 122: 994–1001, 2019. doi:10.1152/jn.00274.2019.
- Vo L, Drummond PD. Analgesia to pressure-pain develops in the ipsilateral forehead after high- and low-frequency electrical stimulation of the forearm. *Exp Brain Res* 232: 685–693, 2014. doi:10.1007/s00221-013-3776-x.
- Xia W, Mørch CD, Andersen OK. Exploration of the conditioning electrical stimulation frequencies for induction of long-term potentiation-like pain amplification in humans. *Exp Brain Res* 234: 2479–2489, 2016. doi:10.1007/s00221-016-4653-1.
- Zhou LJ, Peng J, Xu YN, Zeng WJ, Zhang J, Wei X, Mai CL, Lin ZJ, Liu Y, Murugan M, Eyo UB, Umpierre AD, Xin WJ, Chen T, Li M, Wang H, Richardson JR, Tan Z, Liu XG, Wu LJ. Microglia are indispensable for synaptic plasticity in the spinal dorsal horn and chronic pain. *Cell Reports* 27: 3844–3859.e6, 2019. doi:10.1016/j.celrep.2019.05.087.