

# Cortical stimulation and tooth pulp evoked potentials in rats: A model of direct anti-nociception

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While the effect of cortex stimulation on pain control is widely accepted, its physiological basis remains poorly understood. We chose an animal model of pain to study the influence of sensorimotor cortex stimulation on tooth pulp stimulation evoked potentials (TPEPs). Fifteen awake rats implanted with tooth pulp, cerebral cortex, and digastric muscle electrodes were divided into three groups, receiving 60 Hz, 40 Hz and no cortical stimulation, respectively. TPEPs were recorded before, one, three and five hours after continuous stimulation. We observed an inverse relationship between TPEP amplitude and latency with increasing tooth pulp stimulation. The amplitudes of the early components of TPEPs increased and their latency decreased with increasing tooth pulp stimulation intensity. Cortical stimulation decreased the amplitude of TPEPs; however, neither the latencies of TPEPs nor the jaw-opening reflex were changed after cortical stimulation. The decrease in amplitude of TPEPs after cortical stimulation may reflect its anti-nociceptive effect.

Key words: pain, sensorimotor cortex stimulation, TPEP, rats

## INTRODUCTION

Chronic pain remains a challenging field for investigation and development of further therapeutic approaches. Pain control, and methods to achieve it, have been topics of study for many years. In contrast to pharmacotherapy, which is not always efficient, there is less data available regarding non-pharmacological management of chronic pain, in particular regarding electrophysiological methods.

Clinical research, in humans, has provided data demonstrating the efficiency of long-term motor cortex stimulation (MCS) in the treatment of trigeminal neuropathic pain (Boucher et al. 1993, Meyerson et al. 1993, Nguyen et al. 1997, Lefaucheur et al. 2004), deafferentation pain (Tsubokawa et al. 1991), and thalamic, post-herpetic and phantom pain (Meyerson et al. 1993, Nguyen et al. 1999). Although the therapeutic benefit of motor cortex stimulation has become widely

accepted, the underlying physiological mechanisms and determinant factors of its analgesic effect remain poorly understood.

To date, few papers have dealt with the effect and mechanisms of cortical stimulation in animals. The pain model of cortical stimulation in awake rats has shown weak anti-nociception efficacy in the formalin test (Kuroda et al. 2000), and the effect of anti-nociception has been shown to be suppressed by spinal administration of nitric oxide synthase (NOS) inhibitors (Kuroda et al. 2001). Cortical stimulation has also been shown to transiently inhibit the responses of spinal cord dorsal horn neurons to nociceptive stimuli (Senapati et al. 2005), while rhizotomized animals (central pain model) (Rusina et al. 2005) and animals with ligated sciatic nerves (causalgia model) (Vaculin et al. 2008) recovered pain thresholds to normal levels after cortical stimulation. Somatosensory cortical stimulation in rats has been shown to decrease upregulated expression of c-Fos, an immediate early gene protein product sensible to noxious stimulation in medullary dorsal horn neurons (Gojyo et al. 2002).

Despite several controversies, it is generally accept-

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ed that in rats, tooth pulp stimulation (TPS) represents a valuable pain model (Morita et al. 1977, Toda et al. 1980, Chapman et al. 1986, Sugimoto et al. 1988, Alantar et al. 1997); moreover, TPS has been proposed as a model for trigeminal pain (Chapman et al. 1986).

Tooth pulp stimulation evokes the jaw-opening reflex (JOR) in rats, considered to be a correlate of pain, which is mediated by C fibers – the only pain conducting fibers present directly within the tooth pulp. Low intensity TPS elicit a long latency JOR (15 ms). When TPS intensity is increased, the long latency component of the JOR decreases and finally disappears, while a short latency component of the JOR (6 ms) appears. This is elicited by activation of more distant periodontal afferents and fast conducting A fibers (Azerad and Woda 1976, Jiffry and Matthews 1977, Hayashi 1980, Jiffry 1981, Toda et al. 1981, Engstrand et al. 1983, Carter and Matthews 1989, Kowler 1990).

Tooth pulp cortical evoked potentials (TPEP) are considered to be a useful tool for investigation of analgesic drug action (Cox et al. 1998). TPEP amplitude decrease and latency increase demonstrated a drug induced antinociceptive effect (Dannemann 1994). To our knowledge there is no study showing similar changes in TPEP latency and/or amplitude in a non-pharmacological setting.

The aim of our study was to analyze modifications of TPEPs following cortical stimulation as a marker of non-pharmacologically induced antinociception. We used tooth pulp stimulation (TPS) as a painful stimulus. Concomitant TPEP and JOR recordings allowed a more precise identification of pulp stimulation induced nociception and its analysis. We evaluated the influence of cortex stimulation on TPEP amplitude and latency in awake and freely moving rats. Our hypothesis is that this arrangement would allow us to establish a useful model for the explanation of the complicated effect of motor cortex stimulation.

## METHODS

Experiments were carried out on fifteen adult male Sprague-Dawley rats (body weight 300–350 g), obtained from the Animal Facilities of Paris VII University. The experiment was conducted in accordance with the guidelines of the International Association for the Study of Pain (Zimmermann 1983) and the principles of laboratory animal care (NIH publication

No. 86–23, revised 1985). The study was approved by the local animal care study committee.

Prior to electrode positioning surgery, the animals were anaesthetized with an intraperitoneal injection of ketamine (Imalgene® 500, Rhône Merieux – France) (100 mg/kg) and the implantation procedures were performed on a heat controlled operating table.

Three types of electrodes were implanted: (1) tooth pulp stimulating electrodes, (2) jaw opening reflex recording electrodes, and (3) cortical electrodes for both evoked potential recording and sensorimotor cortex stimulation (contrarily to humans, in rats there is no distinct division between the sensory and motor cortex (Kolb 1990, Starr et al. 1991, Paxinos and Watson 2007)).

The left mandibular incisor was carefully prepared and peripheral bipolar stimulation electrodes, made of Teflon coated 125 µm platinum wires, were implanted into the tooth pulp and sealed. Correct electrode placement was confirmed by evoking a JOR. The electrode wires led to a common, subcutaneously implanted, contact board located on the skull. Tooth pulp stimulation was delivered using a stimulation unit (302-T, WPI, UK). Stimulating parameters of the rectangular impulses were as follows: duration 1 ms, frequency 0.5 Hz; intensity was manually adjusted within the range 0.01 to 10 mA in order to evoke three types of JOR latencies: (1) long latency alone (low intensity), (2) both long and short latency (moderate intensity), and (3) short latency JOR (high intensity).

Two 170 µm silver Teflon coated electrodes were exposed and placed over the anterior belly of the left digastric muscle in order to record EMG responses. The wires from this electrode led subcutaneously to the common contact board. After amplification, the signal was visualized on an oscilloscope so that JOR latencies could be set using electromyography.

Lastly, two cortical electrodes made of inox wire, to measure cortical evoked potentials and provide sensorimotor cortex stimulation, were inserted, after craniotomy, and cemented to the skull with 4META resin (Superbond, C&B, Japan). Cortical epidural electrodes were placed (1) 1 mm rostral and 1 mm right, and (2) 1 mm caudal and 2 mm lateral to bregma. The ground reference electrode was inserted in the nasal bone.

Anesthesia was used only for implantation of electrodes. All other study procedures (TPS, TPEP recording, cortical stimulation) were done on awake freely moving rats.

A pulse generator, (Medtronic-3625, Medtronic, Inc. Minneapolis, USA) was used to deliver rectangular impulses 0.2 ms in duration at a frequency of 60 Hz (Group 60) or 40 Hz (Group 40). Stimulation frequencies of 40 Hz and 60 Hz were chosen on the basis of a pilot study (unpublished data). The intensity was set between 80–90% of the intensity that evoked facial muscles twitches (the range of stimulation was from 0.27–0.150 mA). Conscious test animals received continuous sensorimotor cortex stimulation for periods of 1, 3, and 5 hours.

TPEP recordings utilized the same electrodes used for cortical stimulation. In order to analyze TPEPs, the signals obtained from the electrodes were amplified (AI417 and AI 405; Cyberamp 380, Axon instrument, USA) and digitized using a sampling rate of 2 kHz (Digidata 1200 A, Axon instruments) for off-line signal processing.

Following a recovery period (5–7 days) after electrode implantation, TPEPs were recorded for three different intensities of tooth pulp stimulation (no sensorimotor cortex stimulation; START – Figs 1 and 2).

Each animal was stimulated separately; the stimulus intensity was adapted following the slow and rapid component of the JOR in order to obtain well designed curves which confirmed that periodontal A and/or pulpar C fibers, respectively, were actually stimulated. That means that stimulation intensities showed an important inter/individual variability and therefore cannot be displayed in a simple table

The animals were then divided into three groups. The first group (Group 60) received 5 hours of 60 Hz cortical stimulation. TPS induced TPEPs were recorded at one, three, and five hours (time 1, 3, 5 – Figs 1 and 2) after the start of stimulation. The second group (Group 40) received 40 Hz cortical stimulation following the same experimental paradigm. The third control group did not receive any cortical stimulation but underwent TPEP recordings following the same time intervals.

We analyzed 128 TPEP records of 250 ms duration using multi-resolution-based noise reduction using a protocol detailed by Bertrand and coauthors (1994). This method used a time-scale transformation of the signal similar to the time-frequency transformation used in FFT (Fast Fourier Transform). The coefficients of this time-scale transformation were adjusted in such a way as to cancel the non Gaussian white noise present in the TPEP, subsequently the inverse transform was computed in such a way as to return the de-noised TPEP. Because

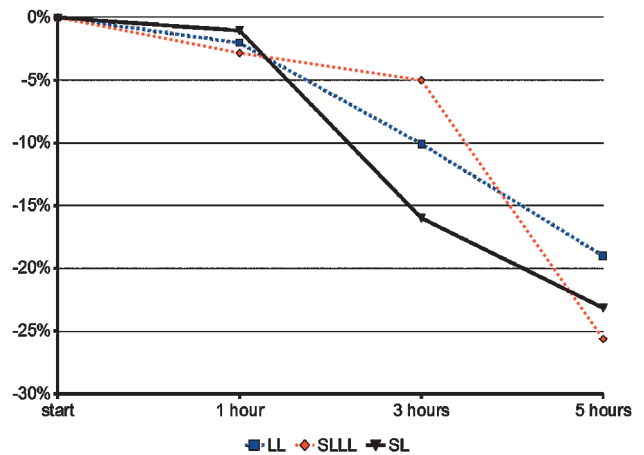


Fig. 1. Variation and SD of the maximum amplitude value of TPEPs after stimulation in percents; recorded over the sensorimotor cortex after 1 hour, 3 and 5 hours of cortical stimulation at 60 Hz (Group 60) for the different components of the jaw-opening reflex [(LL) long latency JOR; (SLLL) short and long latency JOR; (SL) short latency JOR] following tooth pulp stimulation. Significant differences appear after 5 hours of continuous cortical stimulation in contrast to non significant results after 1 hour and 3 hours of stimulation

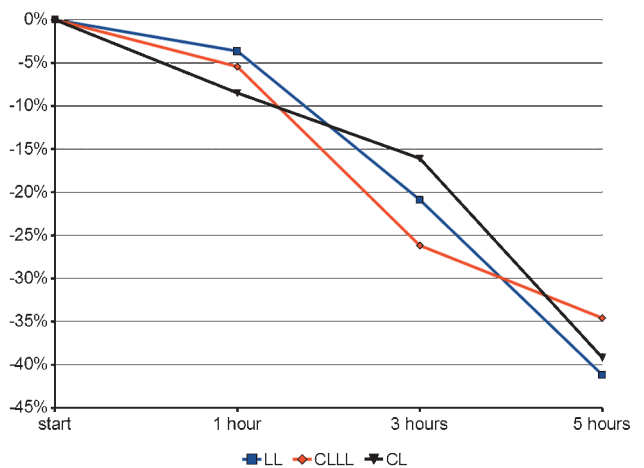


Fig. 2. Variation and SD of the integration of TPEPs after stimulation in percents; recorded over the sensorimotor cortex after 1, 3 and 5 hours of cortical stimulation at 60 Hz (Group 60) for the different components of the jaw-opening reflex [(LL) long latency JOR; (SLLL) short and long latency JOR; (SL) short latency JOR] following tooth pulp stimulation. Significant differences appear after 5 hours of continuous cortical stimulation in contrast to non significant results after 1 hour and 3 hours of stimulation

of fluctuant inter-individual variations of the TPEP curve, a normalization process was employed in this study to compare animals with noteworthy inter-individual differences (Shigenaga et al. 1974, Falinower et al. 1994, Grass et al. 2003, You et al. 2003).

Results are presented as a mean percentage of the variation observed between individual steps of cortical stimulation. Two parameters were calculated for every TPEP: (1) the maximal amplitude of the main wave (appearing between 20 and 30 ms), and (2) the integration of the whole evoked curve.

The data were compared in order to determine if there were statistical differences in observed parameters of TPEPs after 1 hour, 3 hours or 5 hours of cortical stimulation at 60 Hz or 40 Hz. Due to the small sample and uncertain data normality, the Kruskal-Wallis non parametric test was carried out, followed by the Dunn test for multiple comparisons. Statistical analysis was performed using XLSTAT software v 2007.1 (Addinsoft, USA).

## RESULTS

Depending on the tooth-pulp-stimulation intensity, different response patterns could be observed at the level of the digastric muscle (JOR) and at the cortical (TPEPs) level (Fig. 3). Low intensity TPS evoked long latency JORs (mean latency 16 ms), moderate intensity TPS evoked both long and short latency JORs, and high intensity TPS evoked short latency JORs (mean latency 6 ms).

The TPEPs consisted of a first component including the stimulation artifact and recorded between 0 and 17 ms. This component was followed by either a triphasic component (N27, P53, N69) at low intensity TPS, or a biphasic early component (N23, P48) and (N22, P51) at medium and high TPS intensities. Regardless the TPS intensity, those components were followed by a late polyphasic component composed of a complex set of peaks having variable amplitudes (Fig. 4).

We assessed the latency and amplitude of the first negative peak (N27 for low intensity TPS and N23 for higher intensity TPS, respectively) as a marker of nociception, accordingly to previously published reports (Danneman 1994).

The maximal amplitude of TPEP was recorded at 27 ms for low intensity TPS, at 23 ms for medium intensity TPS and at 22 ms for high intensity TPS. The maximal amplitude ranged 75–250  $\mu$ V. The average

value of the maximal amplitude was 87  $\mu$ V, 150  $\mu$ V and 210  $\mu$ V for low, medium, and high TPS, respectively.

The distribution and amplitude of the peaks correlated with TPS stimulation intensity ( $r=0.96$ ,  $P<0.01$ ).

### Effect of cortex stimulation on TPEP

Results are given for both stimulated groups after one hour, 3 hours and 5 hours of continuous cortical stimulation and compared to the values obtained in the same animal before cortical stimulation ( $T_0$ ) (Figs 1, 2).

### Cortex stimulation and latency of TPEP

Regardless of TPS intensity, no statistically significant variation of TPEP latency was observed. Accordingly, no significant latency differences were observed in relation to the frequency or the duration of cortical stimulation.

### Cortex stimulation and maximal amplitude of TPEP

For low intensity TPS (evoking long-latency JORs) a progressive decrease in the component of maximal amplitude was observed in both experimental groups after cortex stimulation (Fig. 1). In both experimental groups (Group 60 and 40), the decrease became significant,  $-19\% \pm 2.26$  and  $-6.34\% \pm 2.16$  respectively, after 5 hours of continuous cortical stimulation.

For the medium intensity TPS (evoking both short and long-latency JOR) similar results were obtained. In Group 60, a significant decrease ( $-25.62\% \pm 5.03$ ) in the early component maximal amplitude was found after 3 hours of continuous cortex stimulation. In Group 40, a significant decrease ( $-7.99\% \pm 4.07$ ) for the peak of the maximal amplitude of P23 was observed after 5 hours of continuous cortical stimulation.

Similar results were also obtained for the high intensity TPS (evoking only short-latency JORs). In both experimental groups (Group 60 and 40), a significant decrease,  $-23.15\% \pm 7.03$  and  $-9.66\% \pm 4.96$ , respectively, was found in the maximal amplitude of the P22, after 5 hours of continuous cortical stimulation.

In the control group, no significant changes were found in the latency or in the amplitude of TPEP, regardless of TPS intensity.

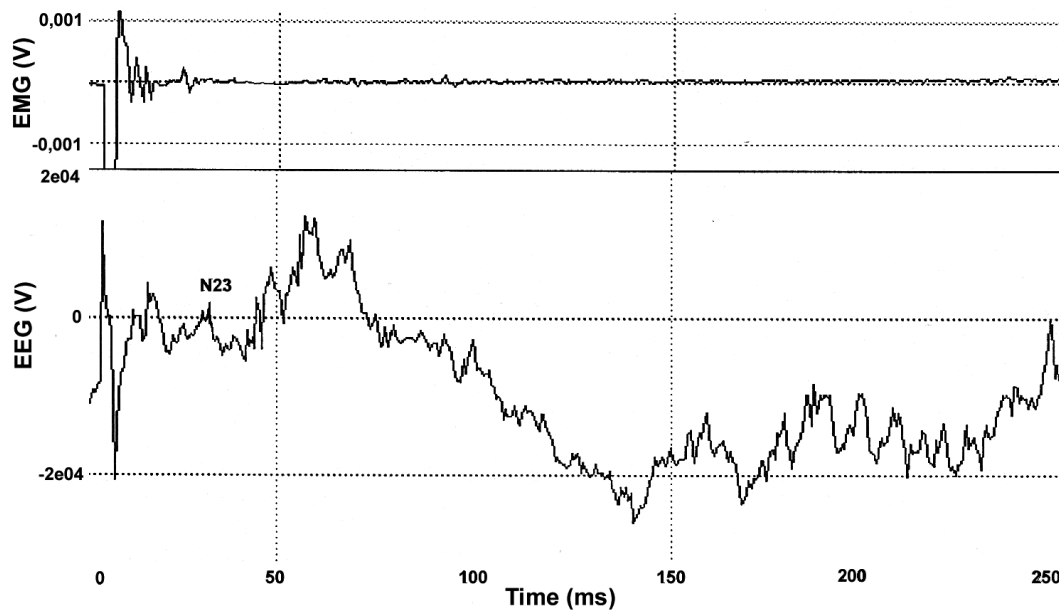


Fig. 3. Responses evoked after a single tooth pulp stimulation at the digastric level (jaw opening reflex – EMG recording channel) and at the cortical level (tooth pulp evoked potentials – EEG recording channel). JOR and TPEP are recorded at the same time for a duration of 250 ms. Amplitude scale is in V for both EMG and EEG recording channels.

### Cortex stimulation and integration of the TPEP curve

In the analysis of TPEP integration, a trend similar to that described for the maximal amplitudes, could be seen. Regardless of TPS intensity and cortical stimulation frequency, TPEP integration decreased significantly after 5 hours of continuous cortical stimulation (Fig. 2).

In controls, no significant changes were found in the integration of TPEP regardless of TPS intensity.

### DISCUSSION

A key point in our study methodology was to ensure that during tooth pulp stimulation (TPS) we stimulated nociceptive C fibers and not other surrounding structures, and that concomitantly recorded evoked potentials over the sensorimotor cortex really reflected induced nociception.

For this purpose we rigorously analyzed the jaw-opening reflex (JOR) obtained by pulp stimulation and recorded over the digastric muscle to reassure that our experimental tooth pulp stimulation activated nociceptive fibers.

The jaw opening reflex – as previously described (Carter and Matthews 1989), consists of two different responses which are dependent on stimulation intensity.

Low intensity TPS evokes long-latency JORs resulting from stimulation of slow conducting non-myelinated

C-fibers, which are the only fibers present in the rat incisor tooth pulp that we stimulated (Jiffry 1981). Only a higher intensity TPS evokes short-latency JORs because it spreads toward the more distant periodontal tissue and also activates fast conducting periodontal myelinated A fibers (Azerad and Woda 1976).

These anatomical conditions explain why – with increasing intensity stimulation - we recorded the long latency component of JOR reflex prior to the short latency component. Therefore our findings are not in contradiction with basic neurophysiological principles that A fibers have a lower threshold than C fibers when exposed to electrical stimulation (You et al. 2003).

The amplitude of the JOR is not directly related to nociception and pain in such a way that more the painful the stimulus the more intense the JOR response. We included the JOR into our study protocol with the aim to control that tooth pulp stimulation really stimulated the periodontal A fibers and pulpal C fibers. Our study enhanced three main findings in Figs 1 and 2: (1) the amplitudes of the early component of tooth pulp evoked potentials (TPEPs) increased and latencies decreased with increasing tooth pulp stimulation intensity, (2) cortical stimulation decreased both the amplitude of TPEP waves and curve integration (possible analgesic effect), and, (3) cortex stimulation did not significantly change the latencies of the TPEP waves or the appearance of the jaw-opening reflex.

First, in our study, TPS induced evoked potentials recordable over the sensorimotor cortex. The pattern of the TPEP curve consists of an early and a late component. The early component in the 0 ms to 17 ms range included a large stimulation artifact. Because of the conduction time between the tooth pulp and the somatosensory cortex, this early component could not be considered to be of pulpal origin (Barek et al. 2007). So we analyzed only the part of the cortical evoked potential in the 20 ms to 250 ms range. Regarding previous results and the results of this study the first negative peak of the early component (appearing between 22 and 27 ms after TPS – Figs 3 and 4) considered to be a correlate of nociception (Shigenaga et al. 1974, Danneman 1994, Barek et al. 2007).

Both TPEP latency and amplitude were dependent on the intensity of TPS: the greater the intensity of TPS, the higher the amplitude, and the lower the latency of the analyzed wave.

In other words, at lower stimulus intensities, slow conducting tooth pulp C-fibers were activated – resulting in longer TPEP latencies; when the stimulus intensity (TPS) was increased, both C-fibers and periodontal A-fibers were recruited, resulting in a shorting of TPEP latencies and an increase of the TPEP amplitude. Therefore, we believe that the waves appearing at 27,

23 and 22 ms, at different TPS intensities, were variations of the same wave.

Second, the increase in amplitude and decrease in latency of the analyzed TPEP wave (with increasing TPS intensity) were observed in animals prior to continuous cortical stimulation. The same procedure consisting of TPEP recording with concomitant JOR monitoring was repeated following continuous stimulation of the sensorimotor cortex.

In our study, the maximal amplitude of the early TPEP component tended to consistently decrease with the duration of cortex stimulation. In the current literature (Danneman 1994, Logginidou et al. 2003), decreases in the amplitude of tooth pulp evoked potentials are considered to be a correlate of analgesic effects in both humans and animals.

Most available data about this topic are based on pharmacological studies. Cortical evoked potentials after TPS, in human volunteers, were observed to decrease after codeine administration (Suri et al. 1996). A study involving TPS in rats (Cox et al. 1998) found a decrease in the amplitude of the early component after alfentanil administration, although the latency of the wave was unchanged. It was shown (Logginidou et al. 2003) that propofol (drug with no analgesic effect) produced a dose-dependent depression of somatosensory

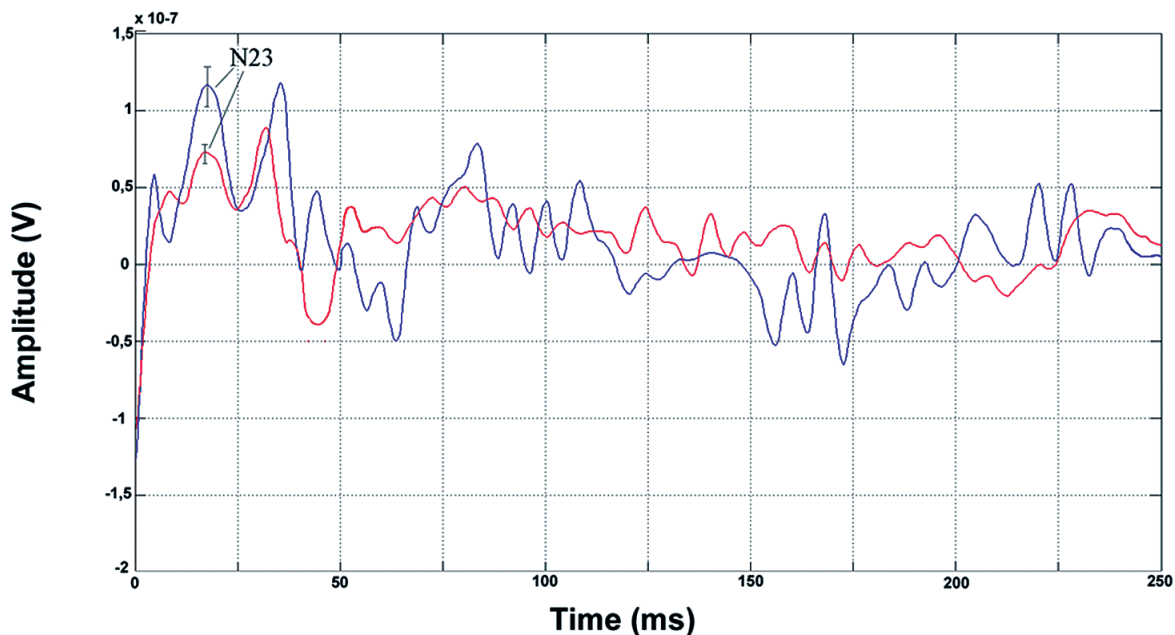


Fig. 4. Mean of 128 multi-resolution enhanced TPEPs recorded for medium intensity TPS before (blue) and after five hours (red) of stimulation at 60Hz (Group 60) and showing noteworthy attenuation of the evoked potential. Standardized error of main peak is presented on the peak.

evoked potentials and prolonged the response latency. Another study using TPEP in rats (Danneman 1994) showed that morphine decreased the maximal amplitude, while droperidol had no effect. Consequently Danneman suggested that the decreased amplitude of the early component of TPEP could be considered as a marker of anti-nociception rather than a general reduction of cortical excitability (Dannemann 1994). Similarly, the decrease in the maximal amplitude of the early component observed in our study suggests an anti-nociceptive effect produced by cortical stimulation.

Due to the TPEP shape variability following motor cortex stimulation (Fig. 4), analysis of the early maximal amplitude component alone might be an insufficient marker, as such we preferred to analyze the area under the curve using TPEP integration.

The results of integration are in good agreement with amplitude evolution: in both stimulated groups the integration decreased significantly after 5 hours of stimulation, the results were more evident in the highest stimulation frequency group (Group 60). We consider data from integration evaluation to be more reliable if compared to amplitude analysis alone. Thus, in the 60 Hz group there was a significant decrease in the maximal amplitude at both 3 hours and 5 hours, however, a significant decrease in integration was only observed at 5 hours – demonstrating the greater benefit of a longer periods of continuous sensorimotor cortex stimulation.

Third, in our study, continuous sensorimotor cortex stimulation neither prolonged the latency of the analyzed TPEP wave nor did modify JOR patterns. These findings indirectly suggest that cortical stimulation acts by a direct antinociceptive mechanism rather than impact on cortical excitability and/or arousal. Mechanisms responsible for anti-nociceptive effects are still quite poorly understood. Cortical activity is influenced by both duration and frequency of cortical stimulation inducing temporary inhibition probably with a distant effect on subcortical regions.

In a similar way, cortical stimulation in Parkinson's disease is thought to be effective at cortico-striatal circuits pathways by activation of neuromodulatory inputs on the basal ganglia-cortex loops (Gutierrez et al. 2009). Moreover, cortical stimulation could proceed to liberation of neurotrophic factors with a distant effect on nociceptive transmission in subcortical areas. Cortical stimulation may act by rebalancing the control of non-nociceptive sensory inputs over nociceptive afferents at cortical, thalamic, brainstem and spinal

levels. In addition, it may interfere with the emotional component of nociceptive perception. Biochemical processes involving endorphins and GABA may also be implicated in the mechanism of motor cortex stimulation (Cioni and Meglis 2007).

The main limitation of our study was the small number of animals involved – which is the general problem of all experiments with implanted animals and the clinical observations of implanted humans. Another difficulty could have been the influence of stress and anxiety in animals with implanted electrodes. Nevertheless the behavior of implanted animals did not differ from other rats in our laboratory. It is worth noting that for continuous cortical stimulation we used the same epidural electrodes as for TPEP recording. We considered this process to be less traumatic than implantation of two electrodes and without influence on the final results. It has been demonstrated (Rusina et al. 2005, Barek et al. 2007) that cortical stimulation modifies the pain threshold in deafferented animals and the effect of cortical stimulation disappears within 24 hours.

Therefore we conclude that the observed changes in this study are directly related to cortical stimulation itself, rather than to eventual changes in the impedance of the electrode or any damage/inflammation to the underlying brain tissue.

## CONCLUSION

In the present study, we used the jaw-opening reflex to investigate the effect of sensorimotor cortex stimulation on TPEPs – a non-pharmacologic pain control model. The concomitant use of TPEP analysis together with JOR recordings allowed a more precise identification of tooth pulp stimulation. Mathematical processing with signal purification and the analysis of TPEP integration added more precision to our results. Therefore, our protocol enables us to differentiate analgesic effects of continuous cortical stimulation on C and A afferents.

Since continuous cortical stimulation led to a decrease in TPEP amplitude, but did not reduce nor prolonged the latency of the maximal amplitude, cortical stimulation using the TPS models suggests a direct anti-nociception effect.

This hypothesis is supported by (1) the decrease in the early component maximal amplitude (present study) and (2) similar results showing at least slight anti-nociception from cortical stimulation in other acute pain models (Kuroda et al. 2000, Rusina et al.

2005). However, due to the small sample size, our results should be interpreted with care. Further research i.e. in cellular mechanisms would be beneficial for better understanding of the underlying processes induced by cortical stimulation.

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