

**Szent István University**  
**Postgraduate School of Veterinary**  
**Sciences**

**Evaluation of trigeminal nociceptive**  
**processing in horses**

Theses of PhD Dissertation

Kata Orsolya Veres-Nyéki

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Szent István University  
Postgraduate School of Veterinary Sciences

Supervisor and member of field committee:

.....

**Gábor Bodó**, DVM, Dr. vet. med, PhD, habil., DipECVS  
Supervisor

Head of Equine Clinic  
Faculty of Veterinary Medicine  
Szent István University

**Claudia Spadavecchia**, Prof, DVM, Dr.med.vet, PhD,  
DipECVAA  
Consultant

Anaesthesiology Division  
Department of Clinical Veterinary Medicine  
Vetsuisse Faculty, University of Bern

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Kata Orsolya Veres-Nyéki DVM, Dr.med.vet, DipECVAA,  
MRCVS

## **1. Introduction**

In the last decade successful pain management became one of the main goals of the veterinarians. Fortunately equine clinicians recognized that the benefits of analgesia surmount the side effects of the treatment (Taylor, Pascoe et al. 2002). Untreated pain has several undesirable consequences as it provokes sympathetic stimulation, alterations in the neuroendocrine system and development of pathological pain conditions. All these factors lead to increased stress level and even distress, leading to a deterioration of the patient's quality of life which raises welfare issues (Stafford and Mellor 2007; Lerche and Muir 2008).

Consequently, the necessity of proper pain management is beyond doubt and continuous research helps to understand the underlying mechanisms of different types of pain. This enables mechanism-based treatment approaches (Vinuela-Fernandez, Jones et al. 2007), although equine studies are still lacking in this field (Muir 2010). Besides the tools to alleviate pain, the second cornerstone of successful pain management is the effective and accurate pain assessment (Stafford and Mellor 2007). Recognition and assessment of pain in horses is challenging as they are nonverbal prey animals hiding their symptoms. Furthermore, pain is known to be a subjective,

multidimensional experience with high individual variability lacking objective measures (Taylor, Pascoe et al. 2002; Lerche and Muir 2008).

Equine idiopathic headshaking is one of those syndromes where pathologic pain conditions could be responsible for the clinical signs. The symptoms of the disease, including nasal rubbing, snorting and sudden flipping of the head, may deteriorate during exercise and make the horse unrideable. Many affected animals are euthanized on humanitarian grounds as they are in enormous distress and evidently suffering. Although the pathophysiology behind the clinical signs is not known (Newton, 2005) neuropathic pain originating from the trigeminal nerve could be responsible for the symptoms observed (Newton et al., 2000; Roberts et al., 2009). Further, success in the treatment of headshaking in some horses has been obtained using a therapeutic regimen that is commonly used to treat trigeminal neuralgia in humans (Newton et al., 2000).

To investigate the physiology and pathophysiology of the trigeminal system in humans, electrically induced reflexes can be used. As a trigeminal neuropathic disorder is suspected in headshaking horses, investigating the trigeminal nerve function with electrophysiological methods might disclose new

perspective into the understanding of the pathophysiology of this disease.

To the best of our knowledge, the trigemino-cervical reflex (TCR) has not yet been described in horses and the blink reflex (BR) has only been described in sedated horses, although assessment of the related electrophysiological parameters may provide a diagnostic tool for diseases affecting the trigeminal system in non-sedated horses. A better understanding of the trigeminal nociceptive physiology could facilitate the treatment of diseases associated with trigeminal nerve dysfunction, too.

Therefore, the aims of this thesis were as follows: (1) to assess if noxious transcutaneous electrical stimulation of the supraorbital or infraorbital nerves (ION or SON) would be suitable to evoke TCR in horses as in humans; (2) to describe its electrophysiological characteristics and stimulus–response function in non-sedated horses; (3) to evaluate the BR while eliciting the TCR; (4) to define the trigeminal temporal summation threshold, and (5) to evaluate the electrophysiological properties of trigeminal nociceptive reflexes evoked by repeated electrical stimulation in non-medicated horses.

## **2. Material and methods**

### 2.1 Animals

Ten adult Warmblood horses (6 geldings, 4 mares; 7 Swiss Warmblood, 2 Freiberger and 1 Hanoverian) were included in the study. The horses, aged 14–23 years and weighing 540–640 kg, were judged to be clinically healthy with no known neurological disorders. The experiments were performed between the 2<sup>nd</sup> and 28<sup>th</sup> of February 2009 with the approval of the Bernese Committee for Animal Experimentation, Switzerland (Tierversuche/Bewilligung 92/08). The measurements were taken either at the Vetsuisse Faculty of the University of Bern or at the National Equine Centre in Bern (NPZ Bern - Nationales Pferdezentrum Bern)

### 2.2 Definitions of experimental objectives

The BR is the response of OO muscles to the stimulation of the cutaneous area innervated by the trigeminal nerve. Its afferent pathway is formed by the sensory branches of the trigeminal nerve and the efferent arch is provided by the facial nerve motor fibres. According to Anor et al. (1996) the BR in horses consists of three components, called R1, R2 and R3. The TCR is the response of the neck muscles to the stimulation of the cutaneous area innervated by the trigeminal nerve. Its afferent pathway is formed by the sensory branches

of the trigeminal nerve and the efferent arch is provided by cervical nerve motor fibres. In human studies, the reflex induced by superficial noxious electrical stimulation occurs quite late after stimulation onset, in the mean range of 40–50 ms (C3) (Ertekin et al., 1996, 2001; Serrao et al., 2003), whereas the earlier components (C1, C2) are usually elicited only by mechanical, percutaneous or non-noxious electrical stimulation (Di Lazzaro et al., 1996; Ertekin et al., 2001; Leandri et al., 2001).

### 2.3 Instrumentation

Experiments were performed between two feeding times and after daily exercise to reduce the stress for the animals and in order to standardise the procedure. A venous catheter was placed into the left jugular vein to allow prompt sedation if necessary since the horses were restrained in stocks for stimulation and recording. The same investigators (CS and KV-Ny) performed the electro-physiological recordings and scored the behavioural reactions. The nerve stimulator was a purpose-built battery-powered optoisolated constant-current stimulator with a maximum voltage of 200 V.

### 2.4 Scoring the behavioural reactions

One observer (KV-Ny) judged the behavioural reaction to stimulation using a numerical rating scale (NRS) (Table 1) and a visual analogue scale (VAS). The VAS was consisting of a

100 mm line, where no reaction corresponded to the zero on the left end and worst possible reaction on the right end of the line. Measuring the distance in millimetres of the assigned score on the scale from its left end gave a measure of the intensity of the reaction observed.

**Table 1**

*Numerical rating scale (NRS) to evaluate behavioural reaction to stimulation*

| Score | Observed behaviour  |
|-------|---|
| 0     | no reaction   |
| 1     | blinking, but no other reaction                           |
| 2     | blinking and mild retraction of the head                  |
| 3     | blinking and powerful retraction of the head              |
| 4     | sudden violent reaction of the whole body to the stimulus |
| 5     | unmanageable reaction of the whole body                   |

### 2.5 Stimulating technique

In order to evoke the TCR and the BR, either the SON or the ION was transcutaneously stimulated using two pairs of self-adhesive electrodes (Ambu 700 05-J). The electrode sites above the left supraorbital and infraorbital foramens were shaved and cleaned with alcohol (Softasept N, B. Braun

Medical). The stimulating electrodes were applied with the cathode over the respective foramen and the anode 20 mm dorsally.

#### 2.6 Recording technique

In order to simplify the experiments as far as possible, and to provide the minimum discomfort for the horses, both BR and TCR were only recorded ipsilateral to the stimulus. To record the BR from the OO muscle, one pair of self-adhesive electrodes was placed on the shaved and degreased skin of the lateral canthus of the left eye over the OO. To record the TCR, two 7.5 cm long purpose-made stainless steel un-insulated needle electrodes (0.35 mm diameter) were placed approximately 5 cm apart subcutaneously above the middle of the left SPL while another pair was placed above the middle of the left CM as perpendicular to the muscle fibres as possible. The ground electrode was fixed on the left side behind the withers on previously moistened hair. Flexible leads were connected to the electrodes and secured to the skin and the mane to prevent displacement of the electrodes and disturbances of the horses. The distances between electrodes and the base of the ear, considered as the projection of the trigeminal nerve origin on the skull surface, were measured for estimation of conduction time. The resistance of the

stimulating electrodes had to be lower than 5 k $\Omega$  during the whole experiment.

## 2.7 Electrical stimulation

### 2.7.1 Single stimulus (SS) to define TCR reflex threshold and evaluate stimulus-response curve

The stimulator was activated manually when the behaviour of the horse and the position of the head were deemed adequate, i.e. when there were no movements, a straight neck and minimal background activity of the SPL. Electromyographic activity was recorded from 100 ms before (background activity) to 400 ms after stimulation started. Inter-stimulus intervals were random within the range of 30–60 ms to prevent habituation. A standard SS consisted of a 1 ms train-of-five constant current square wave pulses delivered at the frequency of 200 Hz. Stimulation was always started at the lowest intensity of 1 mA. Then, in order to define the TCR threshold, the current was gradually increased in steps of 0.5 mA until a clear aversive backward movement of the head was elicited, which corresponded to behavioural score of 3. Adjustments were made by increasing the stimulation intensity in steps of 0.1 mA from the last sub-threshold stimulation to the point at which threshold intensity ( $T_{SS}$ ) for the TCR was confirmed. To be considered a threshold reflex, the amplitude

of the EMG activity burst recorded from the neck muscles had to be at least three times the background activity. A second stimulation at  $T_{SS}$  was performed to verify reproducibility of the response. Once the threshold was defined, intensities of 0.9, 1, 1.1, 1.2, 1.3, 1.4 and 1.5 x  $T_{SS}$  were applied, with a minimum interval of 30 s between stimulations, to evaluate the stimulus–response curve. Stimulations were stopped if NRS score of 4 was reached.

#### 2.7.2 Repeated stimulation (RS) to evaluate temporal summation

In order to perform the repeated stimulation, the standard SS consisting of 1 ms train-of-five (200 Hz) constant current square wave pulses previously used to define  $T_{SS}$  was delivered 10 times with a frequency of 5 Hz over 2 s. Each RS was delivered at progressively increasing intensities, in particular at 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2 and 1.3 times the previously defined  $T_{SS}$  intensity. To rule out relevant changes of the reflex threshold, each RS was evaluated shortly after the assessment of  $T_{SS}$  in the same experimental session. To avoid habituation, at least 30 s were allowed between each RS.

## 2.8 Definition of variables and signal analysis

### 2.8.1 Single stimulation

The latency of the reflex or of its individual components was defined as the time measured from the start of electrical stimulation to the onset of the muscle response. The duration of the reflex or of its individual components was measured as the interval from the beginning of the first deflection to its final return to the baseline. The peak-to-peak amplitude (PTP) was calculated as a difference between the highest and lowest peak of the evoked EMG burst. Moreover, the root mean square amplitude (RMS) of the EMG activity was calculated for the 100 ms epoch before stimulation, and over the individual reflex bursts.

### 2.8.2 Repeated stimulation

The total electromyographic (EMG) recording time was 4000 ms, including 500 ms before stimulation onset. The 500–2500 ms interval was analysed during RS and was divided into ten 200 ms sections to investigate the response to each stimulus separately. The epochs of the reflex components were determined according to the reference values acquired by SS: (1) 10–40 ms and 40–140 ms after the onset of each stimulus to analyse the early (BR early) and late components (BR late) of the blink reflex, and (2) 50–200 ms interval after the onset of

each stimulus to analyse the trigemino-cervical reflex (TCR SPL and TCR CM). The root-mean-square (RMS) amplitudes of these epochs were calculated to quantify the magnitude of the electromyographic responses. To reduce the inter-individual variability, the reflex size was normalised to the baseline activity of muscle. The post-stimulation activity was recorded for the interval 2500–4000 ms. The reflex threshold was defined as the intensity of each SS necessary to elicit electromyographic reflex activity with amplitude of at least three times the baseline activity and a behavioural score of BR = 1 and TCR = 3. Reflex threshold of TCR SPL, TCR CM, BR early and BR late ( $T_{RS}$ ) were defined for each nerve and the reported values were normalised to the single stimulation threshold ( $T_{SS}$ ) of the TCR. In addition, the stimulus number able to evoke the first reflex and the maximal reflex response were recorded.

## 2.9 Analysis of the data

### 2.9.1 Single stimulation

In order to describe the reflex characteristics when stimulating at  $T_{SS}$ , medians and interquartile ranges (IQR) were calculated for reflex latency, duration, PTP, RMS, stimulation intensity, NRS and VAS scores. Three EMG records per horse were analysed both in case of ION and SON stimulation. Wilcoxon

Signed Rank Test was used to compare the records obtained while stimulating the two nerves (ION and SON) from each muscle and from the two muscles (SPL and CM) for each stimulated nerve. To evaluate the stimulus–response curve, the Friedman Repeated Measures Analysis of Variance on Ranks was applied. The Spearman Rank Order Correlation was used to evaluate correlation between parameters.

#### 2.9.2 Repeated stimulation

Non-parametric tests were used for statistical evaluation of the data. Descriptive statistics were used to define individual reflex threshold to repeated stimulation. One sided exact Wilcoxon Signed Rank Test was applied to investigate the effect of repeated stimulation on the reflex threshold intensity. The Brunner–Langer model was used to analyse the effect of different stimulation intensities on trigeminal reflexes evoked by repeated stimulations. The Mann–Whitney Rank Sum Test was used to compare the electrophysiological characteristics of the two nerves.

### **3. Results**

All horses tolerated the experimental procedure easily and without discomfort. Stimulation sites were regularly inspected after the experiment but no signs of skin reaction or damage were detected.

#### 3.1 Reflexes at $T_{SS}$ after single stimulation

Surface electrical stimulation of the trigeminal afferents ION or SON evoked clear EMG reflex responses in the OO, SPL and CM. The horses tolerated the stimulation series without any sign of discomfort or need for additional sedation until  $T_{SS}$  was reached. Technical problems (computer failed to record the measurement) were responsible for the loss of 1 out of 3 threshold EMG recordings from one horse for ION and SON stimulation, so only 29 sets of data at  $T_{SS}$  for each nerve could be analysed. The occurrence of the different components of BR (Anor et al., 1996) was inconsistent when stimulating at  $T_{SS}$ . The R1 component (BR early) was recorded in 14 cases (48%) after SON stimulation and 20 cases (69%) after ION stimulation. The R2 and R3 components (BR late) were present in 19 (66%) and 25 (86%) cases after SON stimulation and in 19 (66%) and 27 (93%) cases after ION stimulation. Blink reflex evoked by stimulating either the ION or the SON showed similar PTP and RMS, latency and duration.

Higher current was necessary to elicit the TCR while stimulating the ION compared to the SON ( $P < 0.001$ ), but similar VAS and NRS scores were attributed at  $T_{SS}$  stimulation for the two nerves. No significant difference was found in the TCR latency, duration and size when the two nerves were compared except that the duration of the reflex recorded from CM was longer after ION stimulation compared to SON ( $P = 0.018$ ). No reflex EMG activity was observed in the first 30 ms epoch after stimulation onset where C1 and C2 component would have been expected, which suggested that the TCR recorded in our study probably corresponded to the human C3. After stimulation of the SON, the evoked muscle potentials recorded from the SPL were comparable to those recorded from the CM as to latency and duration. However, reflex amplitudes were significantly different, with records from the SPL having approximately double RMS and triple PTP than those from the CM ( $P < 0.001$  for both parameters). Evaluating responses to ION stimulation resulted in similar observations. In particular, both RMS and PTP from the SPL were higher than those from the CM ( $P = 0.001$  and  $P = 0.004$  respectively). The amplitude of the background activity recorded from the SPL was higher than the one recorded from the CM while stimulating both nerves ( $P < 0.001$ ).

### 3.2 Stimulus–response curve after single stimulation

While stimulating at supra-threshold intensity to describe the stimulus–response curve, a NRS score of 4, that determined interruption of the experiment, was reached in two horses after  $1.3 \times T_{SS}$  SON stimulation, in three horses after  $1.3 \times T_{SS}$  and in two horses after  $1.4 \times T_{SS}$  ION stimulation. At  $0.9 \times T_{SS}$  the BR was missing in five horses when stimulating the SON and in three horses when stimulating the ION. None of the measured parameters was affected by increasing stimulation intensity. A significant negative correlation was found between R1 latency and intensity for SON stimulation ( $r = 0.29$ ;  $P = 0.041$ ).

Because some of the data were missing (6/10 at  $0.9 \times T_{SS}$  and 5/10 at  $1.5 \times T_{SS}$  ION stimulation and 8/10 at  $0.9 \times T_{SS}$  SON stimulation), we only performed statistical analysis of the TCR stimulus–response curve in the range of  $1–1.4 \times T_{SS}$  after ION stimulation and  $1–1.5 \times T_{SS}$  after SON stimulation. When the stimulus intensity was increased both TCR latencies in the SPL (SON:  $P < 0.001$ ; ION:  $P = 0.008$ ) and the CM (SON:  $P = 0.007$ ; ION:  $P = 0.002$ ) decreased.

This was also confirmed by a significant negative correlation between intensity and latency (SON:  $r = 0.57$ ;  $P < 0.001$  [SPL] and  $r = 0.47$ ;  $P < 0.001$  [CM]; ION:  $r = 0.32$ ;  $P = 0.02$  [SPL] and  $r = 0.33$ ;  $P = 0.01$  [CM]). On the other hand PTP (SON:  $P =$

0.005 [SPL],  $P = 0.026$  [CM]; ION:  $P = 0.036$  [SPL],  $P = 0.036$  [CM]) and RMS (SON:  $P = 0.001$  [SPL],  $P = 0.017$  [CM]; ION:  $P = 0.015$  [SPL],  $P = 0.013$  [CM]) increased parallel with the stimulation intensity.

These later results are reinforced by the positive correlation found between the amplitudes and intensity (SON:  $r = 0.47$ ;  $P < 0.001$  for RMS,  $r = 0.49$ ;  $P < 0.001$  for PTP [SPL],  $r = 0.39$ ;  $P = 0.003$  for RMS,  $r = 0.45$ ;  $P < 0.001$  for PTP [CM]; ION:  $r = 0.45$ ;  $P < 0.001$  for RMS,  $r = 0.42$ ;  $P = 0.001$  for PTP [SPL],  $r = 0.48$ ;  $P < 0.001$  for RMS,  $r = 0.49$ ;  $P < 0.001$  for PTP [CM]).

Reflex duration was not significantly affected by the stimulus intensity, even if a positive significant correlation was found between most of them (SON:  $r = 0.28$ ;  $P = 0.03$  [SPL]; ION:  $r = 0.33$ ;  $P = 0.01$  [SPL];  $r = 0.29$ ;  $P = 0.03$  [CM]). The VAS scores showed a significant increase in the magnitude of the behavioural responses as stimulation intensity increased (SON:  $P < 0.001$ , ION:  $P = 0.002$ ) with strong positive correlation (SON:  $r = 0.73$ ;  $P < 0.001$ , ION  $r = 0.81$ ;  $P < 0.001$ ). No significant intensity effect was found on NRS scores despite that strong positive correlation was detected between them (SON:  $r = 0.74$ ;  $P < 0.001$ , ION:  $r = 0.75$ ;  $P < 0.001$ ).

### 3.3 Repeated stimulation

The TCR was not evoked by subthreshold intensity RS and temporal summation of afferent trigeminal inputs could not therefore be observed ( $P = 0.5$ ). The stimulus number evoking the first and the maximal reflex response was noted to check whether temporal summation has occurred.

Our data clearly demonstrate that the first reflex was evoked by the first stimulus in the sequence and this had the highest RMS amplitude. Only the early, non-nociceptive component of the BR had a tendency to increase in size with the stimulus number.

The median RMS amplitude for the 10 horses showed a tendency to decline over the stimulation sequence.

Reflex activity increased significantly with increasing stimulation intensities (ION BR,  $P < 0.001$ ; SON BR,  $P = 0.039$ ; ION SPL,  $P = 0.024$ ; SON SPL,  $P < 0.001$ ; ION CM,  $P < 0.001$ ; SON CM,  $P = 0.002$ ). To exclude long-term effects of RS on muscular function, baseline activity of all muscles was evaluated with respect to increasing stimulation intensity and was found to be stable (ION BR,  $P = 0.721$ ; SON BR,  $P = 0.07$ ; ION SPL,  $P = 0.926$ ; SON SPL,  $P = 0.744$ ; ION CM,  $P = 0.635$ ; SON CM,  $P = 0.591$ ). Behavioural scores increased significantly ( $P < 0.001$ ) with increasing stimulation intensity.

Behavioural score 3, corresponding to TCR reflex criteria, was attributed at reflex threshold level in the majority of horses.

#### **4. New scientific results**

I. We have found that surface electrical stimulation of the infraorbital (ION) or supraorbital (SON) nerve induces reproducible reflex responses that could be recorded by electromyography from cervical muscles in horses as trigemino-cervical reflex (TCR).

II. We have found that higher current is necessary to elicit the TCR while stimulating the ION compared to the SON.

III. We have found that the TCR evoked by SON or ION stimulation shows similar features regardless of the nerve that had been stimulated.

IV. Stimulations of increasing intensity elicited reflexes of increasing amplitude and decreasing latency, accompanied by stronger behavioural reactions, therefore we could have confirm the nociceptive nature of the TCR.

V. We have found that reflexes recorded from the SPL were significantly larger in amplitude than from the CM, possibly reflecting their different function in the organization of the final aversive movement or to the higher background activity of the SPL, due to its antigravity function that facilitates the reflex.

VI. We have found identical psychophysical (behavioural score) and electrophysiological thresholds.

VII. We found that the nociceptive late component of the BR and the TCR were not elicited by sub-threshold intensity repeated transcutaneous electrical stimulation, so temporal summation of afferent trigeminal inputs could not be observed. Therefore, the modulation of trigeminal nociceptive processing attributable to repeated A $\delta$  fibre stimulations seems to differ from spinal processing of similar inputs as it seems to have an inhibitory rather than facilitatory effect.

## **5. Conclusions**

Improper pain assessment in animals leads to either extra use of drugs with all their side effects or a suffering patient. Unfortunately, no golden standard tool exists to measure pain in horses neither in clinical nor in research settings. All method has its advantages and drawbacks mainly because pain is a dynamic process. Evaluation of single behavioural indicators cannot give exact estimation about the level of pain the animal experiencing and physiological parameters are not reliable indicators of pain. Until now, pain scoring systems suited for the assessment of certain types of pain incorporating sensitive and specific behavioural items are the best way to evaluate quickly and easily the level of pain in clinical patients. Quantitative sensory testing methods used mainly in research settings are valuable tool for objective measurement of nociception in horses.

In conclusion, the trigemino-cervical responses to nociceptive electrical stimulation recorded in this study clearly confirmed the reflex interaction between trigeminal afferents and both brainstem motor centres and cervical spinal cord motor neurons in horses. Our data could provide a reference for TCR performed in healthy non-sedated adult horses so that this

reflex can now be used as a new diagnostic tool to assess dysfunction of the trigeminal system in horses.

The present study showed that temporal summation of nociceptive trigeminal afferents evoked by repeated electrical stimulation and recorded by cervical electromyography does not occur in horses. The recovery curves of TCR are significantly faster in humans with migraines and diffuse noxious inhibitory control (DNIC) deficiencies accompany some chronic trigeminal pain syndromes, such as migraines, tension-type headaches and temporomandibular disorders (Proietti et al., 2003; Williams and Rhudy, 2009). Similarly, in horses affected by trigeminal pathology, altered nociceptive modulation and DNIC deficiencies could modify the neurophysiological profile observed in the healthy subjects, representing a novel non-invasive tool for a mechanism-based approach to diagnosis.

## **6. The candidate's publications related to the present dissertation**

### 6.1 Full-text papers published in peer-reviewed journals

**Veres-Nyéki, K.O.,** Spadavecchia, C.: A fájdalom felismerése és elbírálása lovon. Recognition and assessment of pain in horses. Magyar Állatorvosok Lapja (Hungarian Veterinary Journal) 2014 Jan; 136(1): 9-20.

**Veres-Nyéki, K.O.,** Leandri M., Spadavecchia, C.: Assessment of the wind-up phenomenon in the equine nociceptive trigeminal system. Vet J. 2013 Oct; **198**(1): 81-7.

**Veres-Nyéki, K.O.,** Leandri, M., Spadavecchia, C.: Nociceptive trigeminal reflexes in non-sedated horses. Vet J. 2012 Jan; 191(1):101-7.

### 6.2 Papers in conference proceedings

**Veres-Nyéki, K.O.,** Leandri, M., Spadavecchia, C.: Nociceptive trigemino-cervical reflex evoked by repeated transcutaneous electrical stimulation in non-sedated horses: is temporal summation occurring? In: Proceedings of 11th WCVA Congress, Cape Town 2012

**Veres-Nyéki, K.O:** Nociceptive trigeminal reflexes in horses.  
Pain Symposium, Bern, 2011

**Veres, K.O.** and Spadavecchia, C.: The trigemino-cervical reflex in awake horses: preliminary results. In: Proceedings of 10th WCVA Congress, Glasgow 2009

**Veres, K.O.** and Spadavecchia, C.: The trigemino-cervical reflex in horses. Budapest-Wien-Brno ECVIM residents meeting, Üllő