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Learned control over spinal nociception: Transfer and stability of training success in a long-term study

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HIGHLIGHTS

- 4 months after successful nociceptive flexor reflex (RIII reflex) feedback training, the ability for RIII suppression is maintained.
- Transfer (use of the learned strategies for RIII suppression without feedback) is successful.
- This is important for application of RIII feedback training in clinical or day-to-day pain.

ABSTRACT

Objective: Healthy subjects can learn to use cognitive-emotional strategies to suppress their spinal nociception, quantified by the nociceptive flexor reflex (RIII reflex), when given visual RIII feedback. This likely reflects learned activation of descending pain inhibition. Here, we investigated if training success persists 4 and 8 months after the end of RIII feedback training, and if transfer (RIII suppression without feedback) is possible.
Methods: 18 and 8 subjects who had successfully completed feedback training were investigated 4 and 8 months later.
Results: At 4 months, RIII suppression during feedback and transfer was similar to that achieved at the final RIII feedback training session (to 50 ± 22%, 53 ± 21% and 52 ± 21% of baseline, all differences n.s.). At 8 months, RIII suppression was somewhat (not significantly) smaller in the feedback run (to 64 ± 17%) compared to the final training session (56 ± 19%). Feedback and transfer runs were similar (to 64 ± 17% vs. 68 ± 24%, n.s.). Concomitant reductions in pain intensity ratings were stable at 4 and 8 months.
Conclusions: RIII feedback training success was completely maintained after 4 months, and somewhat attenuated 8 months after training. Transfer was successful.
Significance: These results are an important pre-requisite for application of RIII feedback training in the context of clinical pain.

1. Introduction

The descending pain inhibition is a system of endogenous pain control, able to reduce incoming nociceptive signals at the spinal dorsal horn level (Fields and Basbaum, 2006). It can be modulated by cognitive and emotional processes (Tracey and Mantyh, 2007; Bingel and Tracey, 2008; Wiech and Tracey, 2009). Recently, we

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have shown that healthy young adults can learn to use cognitive-emotional strategies to suppress their spinal nociception as quantified by the nociceptive flexor reflex (RIII reflex) when they are given visual feedback on their RIII reflex size, likely by learning to deliberately activate their descending pain inhibition (Ruscheweyh et al., 2015a,b). During three RIII feedback training sessions, subjects had the opportunity to try different cognitive-emotional strategies and perfect the one that worked best for them to suppress their RIII reflex. This training resulted in significant RIII suppression, which improved from session to session. In contrast, subjects who received no feedback or sham RIII feedback had significantly smaller or absent success in RIII suppression (Ruscheweyh et al., 2015a,b). Importantly, the reduction of RIII reflex size achieved during RIII feedback training was significantly correlated with the concomitant reduction in pain intensity ratings (Ruscheweyh et al., 2015a,b).

Chronic pain patients have repeatedly been shown to have a reduced activity of descending pain inhibitory pathways, and it has been speculated that this might be one mechanism underlying pain persistence in these patients (Yarnitsky, 2015). Therefore, learned activation of descending pain control would be a promising approach to pain treatment. Therefore, it is important to investigate (1) if learning success persists after the end of the RIII feedback training and (2) if transfer is possible, i.e. if after completion of the training, suppression of spinal nociception can also be achieved in the absence of feedback on the RIII size.

To address these questions, we tested the RIII suppression and concomitant reduction in pain intensity ratings in 18 young healthy subjects four months after they had successfully learned to suppress their RIII reflex in one of the published RIII feedback training studies (Ruscheweyh et al., 2015a,b). No further RIII feedback training was performed in the interval. Eight of these subjects were also investigated 8 months after feedback training. Suppression of the RIII reflex and pain intensity was tested both under feedback on the RIII size (feedback run) and without feedback (transfer run) and compared to the RIII suppression and pain intensity reduction achieved in the final (third) RIII feedback training session.

2. Methods

2.1. Participants

The study was conducted in accordance with the Declaration of Helsinki and approved by the local ethics committees of the Westfälische Wilhelms-University Münster (No. 2008-475-f-S) and of the Ludwig-Maximilians-University Munich (No. 080-12). Before participation, written informed consent was obtained from subjects. For the present study, healthy subjects who had achieved an RIII reflex suppression to less than 80% of baseline in the final RIII feedback training session of one of the previous RIII feedback training studies (Ruscheweyh et al., 2015a,b) were invited for two follow-up sessions (approximately 4 and 8 months after their final RIII feedback training session). 18 of 39 eligible subjects (5/20 from Ruscheweyh et al., 2015b, 13/19 from Ruscheweyh et al., 2015a) participated in the 4 months, and 8 also participated in the 8 months follow-up session. The remainder chose not to participate or could not be contacted anymore. The difference in recruitment numbers between the two studies is due to the fact that in the earlier study (Ruscheweyh et al., 2015b), subjects were invited to participate in the follow-up session only some time after the end of the feedback training, while a follow-up session was scheduled at the final RIII feedback training session in the later study (Ruscheweyh et al., 2015a).

At the time of the follow-up investigation, all participants continued to fulfil the previously published inclusion criteria: "(1) age between 18 and 40 years, (2) sufficient knowledge of the German language, (3) no neurological, internal or psychiatric conditions, (4) no intake of medication other than oral contraceptives, (5) no history of chronic pain and (6) no nicotine, alcohol or drug abuse" (Ruscheweyh et al., 2015b). On experimental days, participants did not suffer from acute pain and were free of analgesics (no intake within the preceding 48 h). Subjects had not practiced RIII suppression since the end of their RIII feedback training.

2.2. RIII reflex recording and analysis

The RIII reflex was evoked and recorded from the lower extremity as described in detail in our and others' previous reports (Ruscheweyh et al., 2015a,b; Willer, 1977; Arendt-Nielsen et al., 1994; Bouhassira et al., 2003). Briefly, "subjects were tested in a quiet room, with the only other person present being the experimenter. During recording, the subject sat comfortably in a reclining chair with the knee of the recorded leg flexed at ~150°. Stimulation and recording was performed with a Keypoint® Portable EMG System (Natus, Planegg, Germany). Stimulation and recording sites were prepared by degreasing and lightly abrading the overlying skin. Electrical constant current stimulation was delivered to the retromalleolar pathway of the sural nerve with a bipolar bar electrode (distance between electrodes 23 mm, Natus). Each stimulus consisted of five pulses of 1 ms duration, separated by 4 ms, resulting in a total duration of 21 ms. Electromyographic responses were recorded from the ipsilateral biceps femoris (short head) via a pair of Ag/AgCl surface electrodes placed 4–5 cm apart over the muscle belly. Signals were amplified (up to 10,000 times) and band-pass filtered (20–1000 Hz). The segment 90 ms before to 410 ms after stimulation was displayed on the screen, digitized (24 kHz) and stored for offline analysis. The RIII reflex was identified as a polyphasic muscle response appearing with an onset latency between 90 and 130 ms after stimulation (Willer, 1977). For quantification of the RIII reflex response, the reflex area was obtained by integrating the rectified signal between 90 and 150 ms after stimulation, and corrected for the average baseline area of the corresponding run (integrated rectified signal between 85 and 25 ms before stimulation)" (Ruscheweyh et al., 2015a).

Also as described previously, "for assessment of RIII thresholds, stimulus–response curves were recorded by increasing stimulation intensity in 0.5 mA steps starting from 2.0 mA. RIII threshold was defined as the stimulus intensity that first evoked a reflex response exceeding a baseline-corrected area of 100 μV·ms, and the mean of three RIII thresholds was calculated" (Ruscheweyh et al., 2015a). Pain thresholds were determined by letting the participant rate each stimulus on a numerical rating scale (NRS) from 0 to 100 (0 = no pain, 100 = strongest pain imaginable). The pain threshold was defined as the stimulus intensity that first evoked a painful sensation (NRS rating ≥1).

2.3. Experimental design (Fig. 1)

Subjects who had achieved an RIII suppression to <80% of baseline (pre-task block, see below) during the final (last of three) RIII feedback training session in one of our previous RIII feedback training studies (Ruscheweyh et al., 2015a,b) were eligible to participate in the 4 and 8 months follow-up sessions. In both follow-up sessions, after determining RIII reflex thresholds, three 8 min experimental runs (consisting of 4 consecutive 2 min blocks) were performed at ~130% reflex threshold. Each block consisted of 12 stimuli (applied at randomized intervals of 8–12 s in 14 subjects from Ruscheweyh et al., 2015a,b) or of 20 stimuli (applied at fixed intervals of 6 s in 4 subjects from Ruscheweyh et al., 2015b). Subjects rated the average pain intensity of the previous 5 stimuli at