Learned Control Over Spinal Nociception
In Healthy Subjects
And Patients With Chronic Back Pain

Eingereicht von

STEFANIE KRAFFT

Dissertation der

Graduate School of Systemic Neurosciences der

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München, 30. August 2017

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"One good thing about music, when it hits you, you feel no pain."

Bob Marley

Für Heino

und Oma

ABSTRACT

Pain is vital for us. Pain is a warning signal that protects us from injuries or ensures that we treat injured body parts with care to promote healing. On the other hand, also suppression of nociception is essential to reduce pain. As a natural endogenous pain control mechanism, pain-inhibitory nerve tracts descend from the brainstem to the spinal cord where they suppress spinal nociceptive transmission, reducing ascending nociceptive input to the brain and thus diminishing pain sensation. Cognitive and emotional processes modulate this descending pain inhibition. In patients with chronic pain, descending pain inhibition often is impaired, possibly contributing to pain persistence. Therefore, improving descending pain inhibition in patients with chronic pain is a promising target for pain therapy. In this thesis, three studies present the development and implementation of a feedback training method in which subjects learn to apply cognitive-emotional strategies to reduce their spinal nociception, as quantified by the spinal nociceptive flexor reflex (RIII reflex), under visual feedback about their RIII reflex size, likely by activating their descending inhibition. The results showed that, under RIII feedback, healthy subjects as well as patients with chronic back pain could learn to deliberately suppress their RIII reflex, their concomitant experimental pain intensity, and, in parts, somatosensory evoked potentials, a measure of supraspinal nociception. Furthermore, patients significantly improved their descending pain inhibition, as quantified by the conditioned pain modulation effect, and significantly decreased their chronic back pain intensity and anxiety after the feedback training. In conclusion, the RIII feedback training enables subjects to deliberately activate their descending pain inhibition and reduce their spinal nociception. The RIII feedback training could potentially be an innovative drug-saving method to improve impaired descending pain inhibition in patients with chronic back pain and reduce their clinical pain.

OVERVIEW

This thesis is structured in three main chapters. In the first chapter, an introduction reviews about pain pathways, pain processing, pain-inhibitory strategies, and mechanisms underlying chronic pain. Further, the methods and the aim of this thesis are introduced.

The second chapter comprises three research articles that have been published in peer-reviewed journals.

In the first study, the question was whether healthy adults can learn to apply cognitive-emotional strategies in order to activate their descending pain inhibition to control their spinal nociception, as quantified by the RIII reflex, when they receive feedback about the size of their RIII reflex.

Based on the results of the first study, the second study subsequently investigated supraspinal nociception, as quantified by somatosensory evoked potentials, in healthy subjects during RIII feedback training. Further, the efficacy of true versus sham (false) RIII feedback was evaluated, and the excitability of spinal motor neurons during RIII feedback training was examined.

In the third study, the aim was to find out whether also patients with chronic back pain can reduce their RIII reflex and improve their impaired descending pain inhibition during the RIII feedback training. Also, the effect of true versus sham feedback training on chronic back pain intensity and psychological symptoms as clinically relevant measures was evaluated.

The third chapter discusses the results of the three published studies, and puts the findings into the context of current basic and clinical research. Moreover, the limitations of the presented studies are critically discussed, and potential future research is suggested.

CONTENTS

1 INTRODUCTION

In some way or another, the majority of people have encountered pain in their lives. Some people are more susceptible to pain than others. Either way, most people likely would prefer not to be in pain. Already as children, when our parents comforted us with loving hugs or shifted our attention to completing a puzzle after we had hit our head at a table, most of us have probably learned that positive emotions or cognitive distraction reduce pain.

The physiological mechanisms underlying this analgesic (*algesia* = "pain", *analgesia* = "no pain") effect are endogenous pain-inhibiting strategies of the central nervous system. As part of these mechanisms, nerve tracts of the *descending pain inhibition* originate in the brainstem and descend to the spinal cord, where they inhibit the transmission of pain-related information already on the spinal level. Different brain areas, which process cognitive and emotional input, in turn, can activate this descending pain inhibition in the brainstem and thus induce pain reduction. Nonetheless, it is very clever of nature to present us with the sensation of pain: the ability to feel pain is vital for humans to be able to survive. Pain is usually a warning signal.

But first of all: what is *pain*? There is a difference between pain and nociception. According to the definition of the International Association for the Study of Pain (IASP®), *nociception* is "the neural process of encoding noxious [meaning *harmful* or *potentially harmful*] stimuli". *Pain*, on the other hand, is defined as "an unpleasant sensory and emotional experience that is associated with actual or potential tissue damage, or that is described in terms of such damage". This definition clearly emphasizes the close connection between emotions and pain, and points out that pain is a subjective perception. Thus, the genesis and processing of pain is located in the brain, more precisely the cortex,

whereas nociceptive transmission takes place in the peripheral nervous system and in the spinal cord.

There are different kinds of pain. *Acute pain* can occur without or with tissue damage. Acute pain without tissue damage protects us from (potential) tissue damage, e.g. when reflexively withdrawing the hand from the hot stove to prevent burns. Acute pain with tissue damage, on the other hand, tells us that there is something wrong with the body, e.g. an injury or an inflammation. Also acute pain with tissue damage has a protective function – it makes us refrain from performing movements that could potentially worsen the injury, or prevent it from healing. This is a natural way of making sure that injured body parts get the rest that they need for a thorough cure. Inflammatory pain is an example for acute pain with tissue damage and occurs, for instance, after an injury. *Chronic pain* is different from acute pain in several ways. Unlike the protective function of acute pain, chronic pain has lost any physiological function. Chronic pain can occur with or, for poorly understood reasons, without a persisting cause and usually lasts or recurs for more than 3 months. In some people, pain persists even though the cause of the pain, e.g. the injury, has already healed. In these cases, acute pain has evolved into chronic pain. In other patients, chronic pain occurs without any recognizable initial injury, e.g. in some cases of chronic lumbar back pain.

Our understanding of chronic pain is still far from complete. However, one of the characteristics known about patients with chronic pain is impaired descending pain inhibition, which might contribute to the persistence of pain (Yarnitsky, 2010; Kwon et al., 2014). There are many medications (*analgesics*) on the market to treat acute pain, but the therapy of chronic pain is often complex and unsatisfying, since a large percentage of patients report insufficient pain reduction by analgesics on their chronic pain. Further, pain medication intake over a long period is frequently accompanied by, sometimes severe, side effects that likely evolve into independent problems (e.g. opioid dependence). One way to

tackle this problem is the development of non-pharmacologic pain treatments. Accordingly, improving impaired descending pain inhibition in patients with chronic pain is a promising strategy for non-pharmacologic pain therapy (Yarnitsky, 2015).

In this thesis, three studies are presented that show the development and first clinical transfer of a feedback training method that allows healthy subjects and patients with chronic back pain to learn to apply cognitive and emotional strategies to deliberately activate their descending pain inhibition and thus to learn control over their spinal nociception.

The following figure (Figure 1) gives an overview of the pathways and processes described in the following chapters.

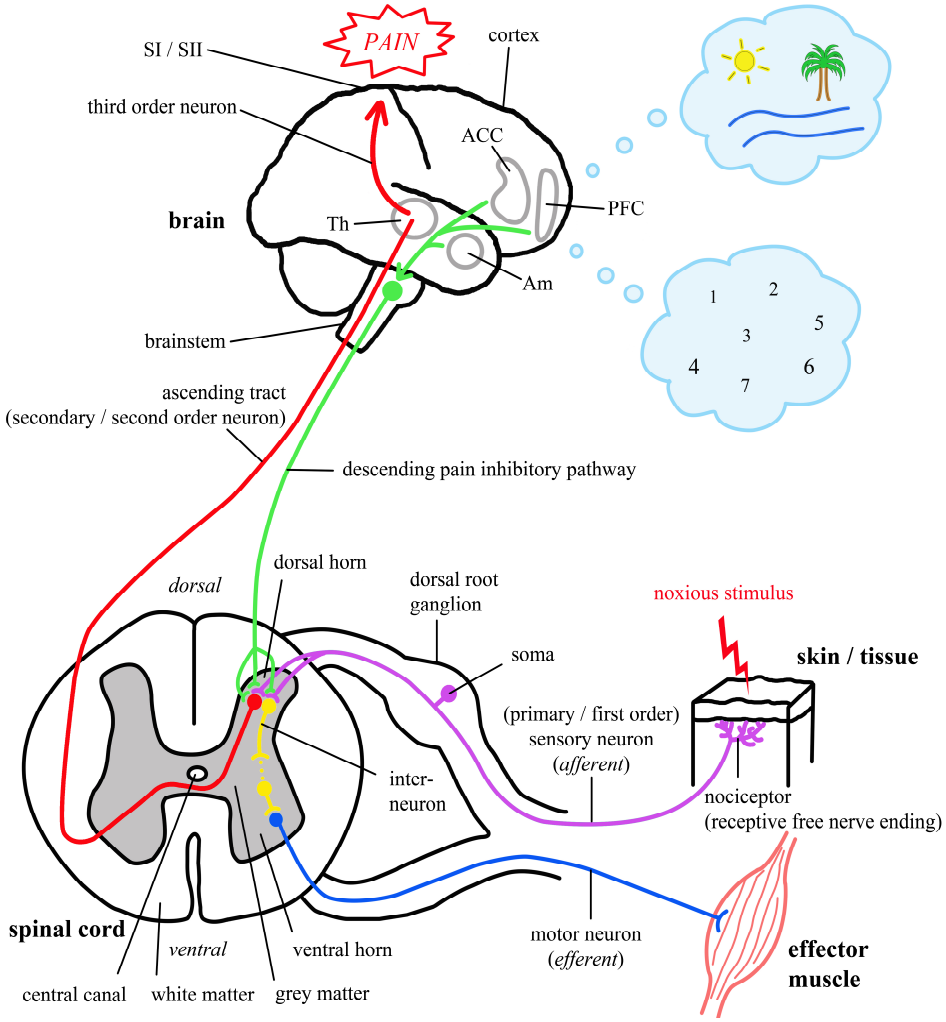

Figure 1: Pathways underlying the hypothesis of this thesis. Nociceptors in the periphery, e.g. in the skin or tissue, sense a noxious stimulus. This nociceptive

information is transferred via afferent sensory neuronal conduction to the spinal cord, entering the grey matter of the spinal cord through the dorsal horn. In the dorsal horn, the information is, on the one hand, transmitted to interneurons that conduct the information to efferent motor neurons that evoke a reflexive movement in the effector muscle. On the other hand, in the dorsal horn, the primary neurons transmit the information to secondary neurons that cross to the contralateral side of the spinal cord, leave the grey matter through the ventral horn, and ascend to the brain through the white matter, eventually terminating in the thalamus. From the thalamus, third order neurons transmit the sensory information to different cortical areas, e.g. to SI and SII. After supraspinal processing, the feeling of pain evolves in the brain. Cognitive and emotional strategies, e.g. recalling pleasant experiences or mental arithmetic, should activate brain areas that are involved in cognitive-emotional processing, e.g. the PFC, the ACC, or the amygdala. These brain areas, in turn, anatomically and functionally target the origin of descending pain inhibitory pathways in the brainstem. These pain inhibitory tracts descend to the dorsal horn of the spinal cord where they inhibit nociceptive transmission by releasing serotonin and noradrenalin. This inhibited spinal nociception, on the one hand, should lead to reduction in reflexive movement of the effector muscle, and, on the other hand, to reduced nociceptive information ascending to the brain, and thus to reduced pain. For clarity, only two interneurons (yellow) are drawn, with the yellow dots indicating more interneurons. The interneurons between the sensory neuron (pink) and the ascending tract (red), as well as the interneurons between the descending pain inhibitory pathway (green) and the ascending tract are omitted. Further, for clarity, all three synapses of the descending inhibitory pathway are emerging from the same neuron, and synapses modulating nociceptive transmission pre- and postsynaptically on interneurons and motor neurons (blue) are omitted. Th: thalamus, Am: amygdala, PFC: prefrontal cortex, ACC: anterior cingulate cortex, SI / SII: primary and secondary somatosensory cortices.

1.1 Ascending pain pathways

In the following paragraphs, the remarkable physiological processes that convey pain-related neural activity from the periphery, via the spinal cord, to the human brain are described (ascending, *bottom-up* information (Bingel and Tracey, 2008)) (see Figure 1).

1.1.1 Peripheral nociception

The process of nociception in mammals starts with the initial detection of noxious stimuli, e.g. in the skin, joints and muscles. Nerve fibers that detect these stimuli are sensory Aδ- and C-fibers (primary afferents). Aδ-fibers report the early, acute pain (“first pain”), and are involved in the

elicitation of protective reflexes (see 1.5 The nociceptive flexor reflex (RIII reflex)). C-fibers, on the other hand, adapt more slowly and signal the delayed, longer lasting pain ("second pain") (Meßlinger, 2010). These distinctive physiological characteristics of the nociceptive neurons are due to different underlying morphologies: Aδ-fibers are thinly myelinated and thus have a faster conduction velocity (about 14 m/s) than C-fibers, which are unmyelinated and consequently have a slower conduction velocity (< 2 m/s) (Bromm and Treede, 1991; Meyer et al., 2006).

The cell bodies (somata) of the primary afferent nociceptive neurons are located in the dorsal root ganglia, with their peripheral axons terminating as branching, unmyelinated receptive "free nerve endings" in the skin and organs, and their central axons terminating in the dorsal horn of the spinal cord (Meßlinger, 2010) (see Figure 1). *Nociceptors* are cutaneous sensory receptors, constituted by the peripheral free endings of nociceptive neurons, that respond preferentially to noxious stimuli (Sherrington, 1906; Meßlinger, 1997; Purves et al., 2004). Different response properties of the nociceptors are determined by the expression of varying transducing ion-channel receptors (see below) (Woolf, 2004) and lead to distinct pain qualities, like burning, aching and pricking. Hence, Aδ-fibers transmit sharp and aching pain (Burgess and Perl, 1967), while C-fibers convey burning or dull pain sensations (Meyer et al., 2006). Multiple forms of noxious stimuli, like thermal, mechanical and chemical stimuli, activate the peripheral receptive terminals of Aδ- and C-fibers, which is why these are *polymodal* nociceptive neurons (Davis et al., 1993).

The peripheral receptive free endings of the nociceptive neurons are where the transduction of noxious stimuli into receptor potentials takes place (Meßlinger, 2010). Noxious stimuli activate thermo-, mechano-, or chemosensitive receptors on the free nerve endings, leading to the opening of ionotropic and metabotropic non-selective cation or sodium (Na^+) channels (Woolf, 2004). Thermal stimuli are detected by some of

the transient receptor potential (TRP) channels, e.g. the transient receptor potential vanilloid-1 (TRPV1) (formerly called capsaicin receptor). The TRPV1 is a non-selective, calcium (Ca^{2+})-permeable, cation channel that is sensitive to noxious heat, capsaicin (the spicy ingredient in chili peppers) and protons, and its activation increases with increasing temperature (Caterina et al., 1997). Activation of TRPV1 by capsaicin leads to local sensitization to activation by heat (Anand and Bley, 2011). The co-activation of this receptor by noxious heat and capsaicin is the reason why spicy food can evoke a burning hot sensation in the mouth. Mechanosensory nociceptors are activated by strong mechanical stimuli like pressure or tissue deformation, likely detected by stretch-activated channels (Meßlinger, 2010). However, sufficient knowledge of the underlying mammalian biophysical, biochemical or pharmacological mechanosensory detection and transduction mechanisms is still lacking (Julius and McCleskey, 2006). Chemical nociceptive activation occurs mainly in injured tissue due to the release of inflammatory factors. These inflammatory factors (e.g. protons, ATP and serotonin) mediate their effects by either binding directly to ionotropic receptors on the sensory nociceptor terminals, or by activating metabotropic G protein-coupled receptors or tyrosine kinase receptors (e.g. bradykinin, histamine, prostaglandins and nerve growth factor) (Julius and McCleskey, 2006). Simultaneously, the inflammatory factor release leads to increased sensitivity of thermal and mechanical nociceptors (Dray, 1995; Julius and Basbaum, 2001).

The stimulus-dependent receptor activation causes opening of the described ionotropic and metabotropic ion channels, and consequently increasing cation influx, e.g. of Ca^{2+} and Na^{+}, resulting in the generation of a receptor potential (Meßlinger, 2010). This receptor potential spreads electrotonically and activates voltage-gated Na^{+} (mainly $Na_v1.7$, $Na_v1.8$, and $Na_v1.9$ (Meßlinger, 2010)), Ca^{2+} and potassium (K^{+}) channels. The ion flux through the voltage-gated ion channels further depolarizes the nociceptor membrane and, when above threshold, elicits action

potentials, which reflect the intensity and duration of the noxious stimulus in their discharge frequency and duration (Woolf, 2004). The action potentials travel from the periphery along the sensory axons, via faster, saltatory and slower, continuous conduction in myelinated (Aδ-) and unmyelinated (C-)fibers, respectively, though the dorsal root ganglion. Finally, the action potentials induce neurotransmitter release at spinal synapses in the dorsal horn, conveying information about the location and intensity of the noxious stimuli from the peripheral to the central nervous system (Julius and McCleskey, 2006; Meyer et al., 2006) (see Figure 1).

1.1.2 Spinal nociceptive transmission and relay from the spinal cord to the brain

After having reached the spinal cord, nociceptive information is conveyed to the brain via different tracts that ascend from the dorsal horn and terminate in the brainstem or in diencephalic structures, such as the thalamus (see Figure 1). Briefly, Aδ- and C-fibers, transmitting noxious peripheral information from the skin, muscles, joints and viscera, enter the spinal cord through the dorsal horn. There, they either directly synapse with secondary neurons that ascend and relay the information to the brain, or synapse with interneurons, which transmit the information to the ascending projecting neurons.

More specifically, the nociceptive afferents mainly terminate in the superficial laminae I and II of the dorsal horn, but also in the deeper laminae III-VI (Rexed, 1952; Light and Perl, 1979; Sugiura et al., 1986; Todd and Koerber, 2006). There, they use the neurotransmitter glutamate to excite postsynaptic projection neurons, whose somata are also located in the dorsal horn superficial and deeper laminae (Todd and Koerber, 2006). The axons of these second order neurons cross to the contralateral

side of the spinal cord, exit the spinal cord grey matter through the ventral horn, and ascend to the brain through the white matter (see Figure 1). These ascending tracts transfer the received noxious information from the spinal dorsal horn to the thalamus, from where it is relayed to cortical and subcortical areas (Dostrovsky and Craig, 2006).

The spinothalamic tract is the main tract of the ascending nociceptive system. This tract originates in the superficial dorsal horn, receiving input from primary afferent Aδ- and C-fibers (Dostrovsky and Craig, 2006), and targets the thalamus directly. The spinomesencephalic and spinoreticular tracts, however, project to different brainstem areas (e.g. the periaqueductal grey matter in the mesencephalon (midbrain)), and, after relays in the brainstem, partly continue to the thalamus and hypothalamus (Willis and Coggeshall, 1991; Craig, 1995; Villanueva and Bernard, 1999; Meßlinger, 2010). In contrast, the spinohypothalamic tract directly projects to the hypothalamus (Dostrovsky and Craig, 2006). Further, the spinomedullary and spinobulbar tracts directly project to homeostatic control regions in the brainstem, including the periaqueductal grey matter (Craig, 2003; Dostrovsky and Craig, 2006). However, the complexity of the spinal and cerebral interconnections involved in the human pain experience still remains to be revealed (Dostrovsky and Craig, 2006).

Besides directly exciting projection neurons, nociceptive afferents terminating in the spinal dorsal horn also release glutamate to excite postsynaptic interneurons (Todd and Koerber, 2006). These interneurons form the majority of the dorsal horn neurons (Rexed, 1952; Todd and Koerber, 2006), and, in turn, synapse with ascending second order neurons. Inhibitory interneurons, using GABA and/or glycine as a transmitter (Todd and Spike, 1993), control the sensory input before it is transmitted via ascending tracts to the brain (gate control theory of pain by Melzack and Wall (1965)), spinal nociceptive transmission (Yaksh, 1989), and spinal withdrawal reflex circuits (Sivilotti and Woolf, 1994). Excitatory interneurons form the majority of the neurons in the

superficial laminae (Todd and Koerber, 2006). These interneurons use the transmitter glutamate, are very heterogeneous according to their sensory neuronal inputs and firing pattern but can be classified based on their cellular gene expression (Benarroch, 2016). Altogether, the organization of the dorsal horn interneurons is complex and the knowledge of their involvement in sensory processes is still incomplete.

Furthermore, nociceptive primary afferents release substance P (Lawson et al., 1997), while its receptor neurokinin 1 (NK1) is expressed on neurons of the dorsal horn as well as of the spinothalamic tract (Yu et al., 1999), implying that substance P and NK1 both play an important role in spinal nociception (Liu et al., 1997; Cao et al., 1998; Hunt and Mantyh, 2001). Some nociceptive neurons contain substance P and calcitonin gene-related peptide (CGRP) (Zhang et al., 1993; Lawson et al., 1997; 2002), both neuropeptides serving as transmitters in neurogenic inflammatory processes (Julius and McCleskey, 2006). The neurons in the dorsal horn express various ionotropic and metabotropic receptors, like the ionotropic glutamate AMPA and NMDA receptors, GABA and glycine receptors, and opioid receptors (Todd and Koerber, 2006). Of these, the NMDA receptors are prominently involved in the development and persistence of chronic pain (Todd and Koerber, 2006). Moreover, some of the dorsal horn neurons express the neurotrophin receptor tyrosine receptor kinase A (trkA), often correlating with CGRP expression (Bennett et al., 1996), and are thus sensitive to the neurotrophin nerve growth factor (NGF) (Averill et al., 1995; Molliver et al., 1995; Todd and Koerber, 2006). However, the exact role of the transmitters and receptors involved in nociceptive transmission in the spinal cord is not yet known.

1.1.3 Supraspinal pain processes

The nociceptive input from the spinal cord to the brain activates a network of various regions of the forebrain, integrating past and present experiences at cortical level, and forming a multidimensional conscious experience of pain that is polymorphous in every individual. This complex nature of pain involves sensory, emotional and motivational components (Melzack and Casey, 1968; Price, 1988). Since the 1990s, when the first human brain imaging studies began to explore the role of different supraspinal (*supraspinal* = "above the spinal cord", i.e. brain) areas in pain processing (Bushnell and Apkarian, 2006), various imaging studies have revealed a subcortical and cortical network that is involved in human acute pain processing. This pain processing network includes sensory, limbic, associative, and motor areas like the primary and secondary somatosensory cortices (SI and SII), anterior cingulate cortex (ACC), thalamus, insular cortex (IC), prefrontal cortex (PFC), and cerebellum (Bushnell et al., 1999; Casey et al., 2001; Bushnell and Apkarian, 2006), each brain area of which is preferentially involved in different aspects of the processing (Bushnell and Apkarian, 2006), as described in more detail below.

Brain areas activated during pain receive indirect nociceptive input via subcortical regions, e.g. the thalamus. The thalamus, constituting the 'sensory gate' to the brain, receives sensory, including nociceptive, input from the periphery via the dorsal horn (Dostrovsky and Craig, 2006), and subsequently distributes this information to cortical regions (see Figure 1). The hypothalamus is another subcortical region activated by pain, likely mediated by spinohypothalamic input and forwarding nociceptive information to the thalamus (Giesler et al., 1994). As part of the limbic system and majorly responsible for homeostatic and vegetative regulation (Persson, 2010), the hypothalamus regulates emotions, attention, as well as autonomic and endocrine reactions, and closely connects the nociceptive input with these specific processes in the brain (Meßlinger,

2010). Further, there is evidence of subcortical pain-related activity in the reward circuitry, namely the amygdala (Becerra et al., 2001). Also the cerebellum, predominantly involved in motor control and visual functions, is active during pain, exhibiting reciprocal spinal connectivity and regulating afferent nociception (Saab and Willis, 2003; Hofbauer et al., 2004). Moreover, ascending tracts terminate in the periaqueductal grey (PAG) matter, which is formed by an accumulation of nuclei and constitutes a homeostatic control region located in the brainstem (Craig, 2003; Dostrovsky and Craig, 2006). This projection leads to modulation of homeostasis and behavioral processes activated by nociceptive input. Furthermore, spinal input to the brainstem modulates spinal and forebrain activity, which affects the pain experience (Dostrovsky and Craig, 2006). Importantly, the PAG has further been shown to be active in human pain-related brain imaging studies, with prominent involvement in pain-inhibiting processes (Tracey and Mantyh, 2007; Bingel and Tracey, 2008).

In primates and humans, the thalamus projects nociceptive input to cortical structures, e.g. to SI and SII (Friedman and Murray, 1986; Rausell and Jones, 1991; Shi and Apkarian, 1995), which, in turn, reciprocally control the thalamic activity itself (Head and Holmes, 1911), and to the ACC (Lenz et al., 1998; Hutchison et al., 1999). The neurons in SI and SII are involved in the perception and discrimination of sensory information (e.g. pain location and duration) (Bushnell and Apkarian, 2006), coding spatial, temporal and intensity information of noxious and innoxious somatosensory stimuli (Kenshalo and Isensee, 1983; Kenshalo et al., 1988; Chudler et al., 1990; Greenspan et al., 1999; Ploner et al., 1999). The ACC and IC, on the other hand, are part of the limbic system (Papez, 1937; MacLean, 1949) and active during emotional, motivational and affective pain processing, as well as cognitive processes like attention (Davis et al., 1997; Rainville et al., 1997; Ostrowsky et al., 2002; Bushnell and Apkarian, 2006). The PFC, another cortical region, receives input from the ACC (Bushnell and Apkarian, 2006), and is

rather involved in cognitive pain processing (Bushnell and Apkarian, 2006).

There are several possibilities to investigate supraspinal nociception in humans, some of which are given below. The most straightforward method to quantify pain is via subjective pain intensity rating, e.g. on a numerical rating scale (NRS [0-10] or [0-100]; 0 = no pain, and 10 or 100 = strongest imaginable pain). More objectively, supraspinal nociception can be measured electroencephalographically by evoked potentials, e.g. somatosensory evoked potentials (SEPs) or pain-evoked potentials (EPs), measuring cortical potential changes. Furthermore, functional magnetic resonance imaging (fMRI) allows the visualization of activity in pain-related brain regions by their changes in blood oxygen levels.

1.2 Descending pain pathways

Pain is vital. We need pain to survive (Baxter and Olszewski, 1960). However, as a counterpart to pain, the human body has powerful endogenous pain control systems (Melzack and Wall, 1965) to modulate the ascending nociceptive information, diminishing acute pain in situations when we need to attend to other vital issues and protecting us from ongoing pain.

Descending, pain-inhibiting nerve tracts originate in the mammalian brainstem and modulate the nociceptive transmission on the level of the spinal cord (Wall, 1967) (*top-down* modulation (Bingel and Tracey, 2008)) (see Figure 1). Briefly, neurons of the midbrain PAG matter project to the locus coeruleus (Bajic and Proudfit, 1999), the adjacent dorsolateral pontine tegmentum (DLPT) and, through excitatory amino acids and opioids, to the rostral ventromedial medulla (RVM), from where neurons descend ipsilaterally to the spinal cord (Le Bars, 2002)

and modulate nociceptive neurons in the dorsal horn (Fields et al., 1991; Fields et al., 2006). The PAG, one of the key regions of the descending pain-modulatory system, in turn, receives projections from the limbic system, like the ACC, IC, amygdala and hypothalamus, and integrates emotional information with ascending spinal nociceptive input (Aggleton, 1992; Bandler and Keay, 1996; Fields et al., 2006).

Neurons that descend from the locus coeruleus and the DLPT to the spinal cord release noradrenalin in the dorsal horn (Fields et al., 1991; Proudfit and Clark, 1991), which exerts postsynaptic excitation and inhibition via α_1- and α_2-adrenoceptors, respectively (Millan, 2002). Neurons descending from the raphe nuclei of the RVM release serotonin to exert nociceptive inhibition in the spinal dorsal horn. The serotonin (5-HT) then binds to 5-HT_3 and 5-HT_1 receptors for postsynaptic excitation and inhibition, respectively (Fields et al., 1991; Millan, 2002). Furthermore, the descending pain-modulatory system releases dopamine in the spinal dorsal horn that presynaptically excites and inhibits neurons via D_1 and D_2 receptors, respectively (Millan, 2002; Yaksh, 2006). To a minor extent, this modulatory system also releases opioids like endorphins and enkephalins that bind to μ-, δ-, and κ-opioid receptors (Millan, 2002; Yaksh, 2006). Noradrenalin, serotonin, dopamine and opioids inhibit spinal nociceptive transmission either by excitation of inhibitory interneurons that release γ-aminobutyric acid (GABA), glycine or opioids and thus inhibit projection neurons, or by inhibition of excitatory interneurons, primary nociceptive afferents or projection neurons (Millan, 2002). The inhibition of the nociceptive information transmission from the primary nociceptive neurons to the secondary spinothalamic tract projection neurons leads to a reduction of nociceptive ascending input to the brain and thus to reduced pain sensation (Millan, 2002; Ossipov et al., 2010). However, noradrenalin and serotonin can also facilitate nociceptive transmission in the dorsal horn and thus enhance ascending nociception and pain sensation. Noradrenalin and serotonin induce this facilitation either by inhibiting inhibitory

interneurons via α_2- and 5-HT_1 receptors, respectively, or by exciting excitatory interneurons, primary afferents or projection neurons via α_1- and 5-$HT_{2,3,4}$ receptors, respectively (Millan, 2002).

1.2.1 Modulation of descending pain pathways

Human pain sensation is regulated by various cognitive and emotional processes, e.g. down-regulated by distraction, positive emotions, and expectations like the placebo effect, and up-regulated by negative emotions like catastrophizing (Tracey and Mantyh, 2007; Bingel and Tracey, 2008; Wiech and Tracey, 2009; Villemure and Schweinhardt, 2010). Brain areas that are involved in these cognitive and emotional processes include the PFC, the ACC, the insula, the amygdala, and the hypothalamus (see Figure 1). These higher brain areas anatomically and functionally target the descending pain inhibition in the brainstem (Tracey and Mantyh, 2007; Bingel and Tracey, 2008; Bushnell et al., 2013). Accordingly, brain imaging studies showed that the supraspinal cognitive and emotional processes mentioned above activate brain areas that are involved in descending pain inhibition, e.g. the PAG in the brainstem (Bantick et al., 2002; Tracey et al., 2002; Valet et al., 2004; Fairhurst et al., 2007; Villemure and Bushnell, 2009). Based on these anatomical and functional supraspinal connections, humans should potentially be able to deliberately reduce pain by using cognitive and emotional strategies, which activate the respective cortical and subcortical brain areas, and hence stimulate their descending pain inhibition in the brainstem (see Figure 1).

Moreover, descending pain-inhibitory pathways can be activated by the ‘pain inhibits pain’ mechanism. In this anti-nociceptive mechanism, a noxious stimulus in the periphery activates descending pain-inhibitory pathways originating in the brainstem. This activation likely takes place

via relays in the subnucleus reticularis dorsalis (SRD) in the caudal medulla of the brainstem (Le Bars et al., 1992; Villanueva and Le Bars, 1995), resulting in inhibition of spinal dorsal horn multireceptive (receiving nociceptive and non-nociceptive input; also referred to as 'wide-dynamic-range' [WDR]) neurons and thus reduction of pain perception (Le Bars et al., 1979; Le Bars, 2002). In animals, this phenomenon is called *diffuse noxious inhibitory controls* (DNIC) (Le Bars et al., 1979), but it exists also in humans. We can experience this, for instance, when we suffer from back pain, and then hit our leg on the edge of a table – in this moment, the second pain, i.e. the bruise on the leg, makes us perceive the first pain, i.e. the back pain, as less painful. Experimentally, the 'pain inhibits pain' effect can be examined by using the *conditioned pain modulation* (CPM) paradigm (Pud et al., 2009; Yarnitsky, 2010). In this paradigm, a noxious test stimulus is applied to any body region, while an additional noxious conditioning stimulus is simultaneously applied to a heterotopic body region, resulting in reduced perceived test stimulus pain intensity compared to the pain intensity of the test stimulus when applied alone. The conditioning stimulus often consists of an immersion into a noxious cold water bath (the so-called 'cold pressure test'), the test stimulus of a noxious thermal or electrical stimulus (Pud et al., 2009).

1.3 Chronic pain

Chronic pain is described as pain that persists past the normal healing time (Bonica, 1953), usually lasting or recurring for more than 3 to 6 months (Merskey and Bogduk, 1994), and thus not exerting any warning function (Treede, 2011). Chronic pain is one of the most frequent, disabling and costly diseases in society (Andersson, 1999; Phillips, 2006). Common chronic pain disorders can be divided into three categories: 1) neuropathic pain resulting from nerve damage or

dysfunction (e.g. diabetic neuropathic pain, postherpetic neuralgia), 2) inflammatory pain (e.g. rheumatoid arthritis), and 3) non-inflammatory/non-neuropathic pain (e.g. fibromyalgia, tension-type headache, irritable bowel syndrome) (Kwon et al., 2014). Chronic low back pain is caused by various etiologies, often representing a mixture of the three categories within the same patient (Kwon et al., 2014). Notably, low back pain causes the most global disability, compared to any other condition (Hoy et al., 2014), because it is the main cause of limited activity and absence from work in large parts of the world (Lidgren, 2003; Steenstra et al., 2005), and causes a vast economic burden on patients and their families, industry and government (Kent and Keating, 2005; Hoy et al., 2014). Patients with chronic back pain have been shown to exhibit increased activity in the PFC (Baliki et al., 2006), potentially reflecting the elaborate emotional and cognitive states that are involved in chronic pain (Bushnell and Apkarian, 2006). Although chronic pain is of such enormous importance to the state of health in society, also affecting the well-being, functioning, and quality of life of the patients (Kwon et al., 2014), it often remains inadequately diagnosed and treated since knowledge of its pathophysiology is still far from complete.

Acute pain usually is of sudden onset, determined cause and limited duration due to treatment (Kwon et al., 2014) or its natural healing course. Since pain has a warning and protective function, pain should vanish as soon as the cause is healed. However, chronic pain persists for a longer period of time, continuously or recurrently, even after the cause has healed, i.e. without persisting cause, or often even without a known cause (*idiopathic* pain) (Kwon et al., 2014). Additionally, chronic pain can be related to a persisting underlying cause, e.g. in rheumatism, arthrosis, or tumor diseases. Also, chronic pain is often based on a combination of a persisting peripheral cause and sensitization processes in the central, or peripheral, nervous system (see 1.3.1 Sensitization). Chronic pain results from – and/or may lead to – a combination of physical injury and psychological, social, and physical problems, e.g.

depression, anxiety, pain catastrophizing, family problems, loss of employment, social isolation, neuromuscular dysfunction, fatigue or decreased activity (Stucky et al., 2001; Keefe et al., 2004; Kent and Keating, 2005; Steenstra et al., 2005). Furthermore, persistent pain involves anatomical, neurochemical, and physiological alterations, which makes the diagnosis difficult (Kuner, 2010; Kwon et al., 2014). Two of these alterations typically involved in chronic pain are sensitization and alteration of descending pain pathways, as described in the following two chapters.

1.3.1 Sensitization

Chronic pain can involve *peripheral sensitization*, the development of hypersensitivity to pain in the peripheral nervous system, and *central sensitization*, hypersensitivity in the central nervous system (Kwon et al., 2014).

In the course of peripheral sensitization, injury and inflammation lead to an increased response of nociceptive primary neurons to noxious and innoxious stimuli (*primary hyperalgesia*) (Lewis, 1935). This hyperexcitability results in even innoxious stimuli provoking pain (*allodynia*) (Merskey and Bogduk, 1994; Woolf, 2004; Kwon et al., 2014), e.g. the painful perception of warm water on sunburned skin. The underlying mechanism of peripheral sensitization is based on neurochemical plastic changes that lower the nociceptor threshold (Davis et al., 1993), increasing the nociceptor sensitivity to stimuli and eliciting spontaneous activity (Andrew and Greenspan, 1999; Kwon et al., 2014). In this plasticity process, sustained strong peripheral noxious stimuli during nerve injury or inflammation cause changes in expression and distribution of ion channels (e.g. voltage-gated Na^+ channels) and synaptic modulators, sensitizing peripheral nociceptors and increasing

their excitability (Woolf, 2004; Kwon et al., 2014). These changes are triggered by inflammatory mediators like bradykinin, prostaglandin E_2, nerve growth factor, tumor necrosis factor α, and interleukins that are released from inflammatory cells in inflamed or damaged tissue (Woolf, 2004; Kwon et al., 2014). If the noxious stimuli persist for a long time, peripheral sensitization can result in central sensitization (Kwon et al., 2014).

Central sensitization describes increased responsiveness of higher order neurons in the nociceptive system. This is best studied in the spinal cord and constitutes an important mechanism for the development of chronic pain (Meyer et al., 2006). Also, central sensitization is clinically important since it can result in allodynia and the spreading of sensitivity to uninjured areas (*secondary hyperalgesia*), caused by hyperexcitability of dorsal horn neurons and concomitant increased nociceptive transmission (Lewis, 1935; Simone et al., 1991; Treede et al., 1992; Woolf, 2004). During the process of central sensitization, the nociceptive transmission from the peripheral nociceptive primary neurons to the spinal dorsal horn neurons is amplified and facilitated by increased induction of receptors and ion channels in the pre- and postsynaptic spinal dorsal horn neuron membranes (Woolf, 2004), enhancing spinal processing. This molecular change includes increased expression of glutamate-receptors of the NMDA type, resulting in increased neuronal responsiveness to glutamate and thus increased excitability of the cell, even to usually subthreshold stimuli (Woolf, 2004). Furthermore, the NMDA receptor is involved in memory processes (Ji et al., 2003). This relation between nociceptive transmission, expression of the NMDA receptor, and memory makes the NMDA receptor constitute an imprint of pain on the cellular structural level, namely the manifestation of pain memory (Ji et al., 2003; Woolf, 2004). Moreover, during the course of central sensitization, Ca^{2+} influx through NMDA receptor channels is one mechanism that leads to activation of intracellular kinases, phosphorylation of ion channels and receptors, and finally changes in

gene expression (Woolf, 2004). This modified gene expression induces new proteins (e.g. interleukins, prostaglandin E_2 and cyclooxygenase-2) and thus alters the molecular structure of the cell (Woolf, 2004) and its response to nociceptive input. Finally, the neuroplastic changes involved in central sensitization, combined with persisting abnormal somatosensory processing, promote the development of chronic pain (Kwon et al., 2014).

1.3.2 Alteration of descending pain pathways

Another mechanism underlying chronic pain is altered descending pain modulation that can consist of either increased facilitation or decreased inhibition in the spinal dorsal horn, involving alterations of serotonergic, noradrenergic, or dopaminergic pathways (Kwon et al., 2014; Ossipov et al., 2014). This change in descending pathways causes altered presynaptic modulation of primary sensory afferents in the dorsal horn, also involving central sensitization, and thus decreases activity of the postsynaptic inhibitory interneurons. This decrease in interneuronal inhibition leads to decreased synthesis of inhibitory transmitters, like GABA and glycine, or loss of inhibitory interneurons. These changes result in an imbalance in excitatory and inhibitory inputs that causes increased nociceptive input to the brain and thus increased pain intensity (Scholz and Woolf, 2002; Woolf, 2004; Baron, 2006; Kwon et al., 2014).

Impaired descending pain inhibition has repeatedly been shown in patients with chronic pain, as quantified by impaired CPM, and might be one reason for prolonged pain persistence (Yarnitsky, 2010; Lewis et al., 2012; Kwon et al., 2014). It is not completely clear whether impaired descending pain inhibition is preexisting and leads to chronic pain, due to less capable inhibition, or if impaired inhibition is a consequence of chronic pain, possibly because the inhibitory capacity is exhausted over

time due to constant effort (Yarnitsky, 2015). However, one study has found that impaired CPM, i.e. impaired descending pain inhibition, is a risk factor for development of chronic pain after a pain-generating event, e.g. after surgery (Yarnitsky et al., 2008). Therefore, improving descending pain inhibition in patients with chronic pain is of clinical relevance, and is a promising approach in pain treatment (Yarnitsky et al., 2012; Niesters et al., 2014; Ossipov et al., 2014; Yarnitsky, 2015).

1.4 Biofeedback

Endogenous physiological processes (e.g. skin temperature, heart rate, regional brain activity) are difficult to access consciously, and it is easier to learn deliberate control over such processes when receiving continuous feedback about the respective physiological parameters ("biofeedback") (Birbaumer et al., 1999; Weiskopf et al., 2004; Nestoriuc and Martin, 2007). In pain therapy, biofeedback training is routinely applied to treat migraine, using, for instance, muscle tension (measured by electromyography [EMG]) or skin temperature as feedback parameters. This biofeedback treatment has been shown to exert analgesic effects, also reducing concomitant psychological symptoms like depression and anxiety (Nestoriuc and Martin, 2007). Previous studies showed that subjects can also learn to influence the activity of their pain associated brain areas, and thus modulate their pain sensation, when they receive real-time fMRI (rt-fMRI) feedback about the activity of these brain areas (deCharms et al., 2005; Chapin et al., 2012; Guan et al., 2015). In clinical settings, cognitive and emotional strategies are regularly used for pain modulation in behavioral therapy of patients with chronic pain (McCracken and Turk, 2002; Turk et al., 2008). As described above (see 1.2.1 Modulation of descending pain pathways), cognitive and emotional processes modulate the descending pain inhibition in the brainstem. Based on the previous studies, it is therefore likely that subjects can also

learn to use cognitive and emotional strategies to deliberately and specifically activate their descending pain inhibition, if they receive feedback about the activity of their descending pain inhibition.

1.5 The nociceptive flexor reflex (RIII reflex)

Nociceptive neurons can detect (potentially) tissue-damaging stimuli and transfer this information from the periphery to the spinal cord or brainstem, and, via higher order neurons, to the brain, where pain perception occurs and protective reflexes are initiated (Fields, 1987; Julius and Basbaum, 2001). These protective reflexes involve reflexive muscle movements that make us withdraw and thus protect us from potentially harmful stimuli. Spinal reflexes are elicited even faster, before the nociceptive information even reaches the brain (see Figure 1). Imagine the following. You are walking along a beach, by the water, in the sand – until you abruptly pull back your leg, and feel pain on the bottom of your foot, because you accidentally stepped on one of the sharp calciferous barnacles on a shell. The leg movement you have experienced here was your nociceptive flexor (or *flexion* or *withdrawal*) reflex, also called RIII reflex (Sherrington, 1910; Skljarevski and Ramadan, 2002).

The RIII reflex, a nociceptive, late, large, and consistent component of the flexor reflex, is a polysynaptic, spinal reflex that is evoked by primary afferent neurons, mainly small-diameter, myelinated, high-threshold nociceptive Aδ-fibers, with unmyelinated C-fibers also contributing (Wiesenfeld-Hallin et al., 1984; Schomburg et al., 2000; Sandrini et al., 2005). After nociceptors in the periphery sense a noxious stimulus, the nociceptive afferents transmit the nociceptive information from the periphery to the dorsal horn grey matter of the spinal cord (see 1.1.1 Peripheral nociception, 1.1.2 Spinal nociceptive transmission and

relay from the spinal cord to the brain; and Figure 1). Via relays in spinal dorsal horn interneurons, the information is transmitted to efferent motor neurons that leave the spinal cord through the ventral root and excite the respective effector muscle leading to the reflex movement (Luhmann, 2010) (see Figure 1). The somatosensory information is furthermore transmitted from the spinal dorsal horn to the brain via ascending neurons in white matter dorsolateral tracts (Luhmann, 2010) (see Figure 1). However, the reflex of this spinal reflex arch is elicited before the nociceptive information even reaches the brain, minimizing the time delay from the noxious stimulation to the protective response. Besides the nociceptive RIII reflex, the flexor reflex consists of a non-nociceptive component, the RII reflex (Sandrini et al., 2005). The RII reflex appears less consistently and, due to its elicitation by large-diameter, fast-conducting low-threshold non-nociceptive Aβ-fibers, with a shorter latency than the RIII reflex (Hugon, 1973; Sandrini et al., 2005). During the elicitation of the flexor reflex, flexor muscles of the stimulated limb contract, while extensor muscles of the limb are inhibited; and the stimulated limb flexes, while the contralateral limb extends, resulting in the withdrawing movement from the source of injury (Sherrington, 1910; Kugelberg et al., 1960; Sandrini et al., 2005). However, widespread multisensorial nociceptive as well as non-nociceptive afferents converge onto the same spinal dorsal horn interneurons, which integrate descending and primary afferent information and thus make the flexor reflex the result of activity of a complex interneuronal network (Lundberg, 1979; Schomburg, 1990; Sandrini et al., 2005). These multireceptive WDR neurons, located in the deep dorsal horn lamina V, a key site of facilitation and inhibition, play an important role in flexor reflex elicitation (Craig, 2003; Sandrini et al., 2005). Besides its protective function, and with its input from various afferents, the flexor reflex is also involved in other complex motor processes, like locomotion and posture (Spaich et al., 2004; Sandrini et al., 2005).

In humans, the activity of descending pain inhibition cannot be measured directly by electrophysiological methods. However, the effects of descending pain inhibition, namely the changes in spinal nociceptive transmission, can be quantified by measurement of the RIII reflex. Active descending pain inhibition reduces the spinal nociception by serotonin and noradrenalin release in the dorsal horn (see 1.2 Descending pain pathways) – which correspondingly also reduces the nociceptive transmission in the spinal dorsal horn that evokes the RIII reflex in the respective effector muscle (Willer et al., 1979; Sandrini et al., 1993). The RIII reflex correlates with pain, by threshold and magnitude (Willer, 1977; Sandrini et al., 2005). Thus, the RIII reflex is commonly used as an objective measure of the spinal nociceptive transmission and pain, its changes in size during a reflex course likely reflecting the activity of descending pain modulation (Willer, 1977; Willer et al., 1979; Sandrini et al., 1993; Skljarevski and Ramadan, 2002; Sandrini et al., 2005).

Experimentally, the RIII reflex is evoked by transcutaneous painful electrical stimulation of the sural nerve at the ankle, and electromyographically recorded by surface electrodes from the biceps femoris muscle in the ipsilateral thigh (Willer, 1977; Skljarevski and Ramadan, 2002; Bouhassira et al., 2003; Sandrini et al., 2005). Previous studies revealed that spinal nociceptive transmission, as quantified by the RIII reflex, is modulated by cognitive and emotional processes that activate descending pain inhibition, such as distraction or catastrophizing (Rhudy et al., 2005; Roy et al., 2009; Ruscheweyh et al., 2011a; Ruscheweyh et al., 2013). These findings provide evidence that the RIII reflex indicates the activity of descending pain inhibition.

Furthermore, the excitability of motor neurons potentially involved in the reflex arch can be quantified by recording late motor responses (*following waves*, F-waves) as follows (see Figure 2). After stimulation of a peripheral motor neuron, the neuronal excitation travels, on the one hand, (orthodromically) towards the effector muscle, and, on the other hand, (antidromically) towards the spinal cord. If the motor neuron is

excitable when the impulse reaches its soma, the excitation is "reflected" at the axon hillock, located in the ventral horn, and transmitted back in a distal direction via the same axon. The F-waves can then be recorded from the effector muscle, as a late response following the orthodromically transmitted muscle response of short latency (Bischoff et al., 2008).

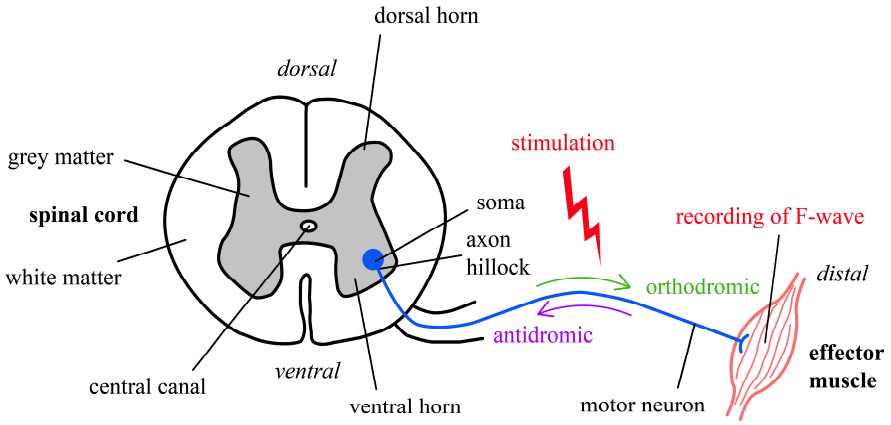

Figure 2: Excitatory conduction evoking F-waves. Stimulation of the motor neuron (blue) evokes neuronal excitation that travels, on the one hand, orthodromically towards the effector muscle, and, on the other hand, antidromically towards the spinal cord. The antidromically transmitted impulse reaches the soma of the motor neuron in the ventral horn, and, if the motor neuron is excitable, is "reflected" at the axon hillock. The impulse is then transmitted back in a distal direction towards the effector muscle, reaching there with a time-delay after the orthodromically transmitted impulse. F-waves, i.e. late responses following the orthodromically transmitted muscle response, can then be recorded from the effector muscle.

1.6 Aim of this thesis

Descending pain inhibition modulates spinal nociception (Wall, 1967). The descending pain-inhibiting pathways in the brainstem are anatomically and functionally targeted by brain areas that are involved in cognitive and emotional processing (Bingel and Tracey, 2008). Further, the RIII reflex constitutes a measure of spinal nociception (Skljarevski and Ramadan, 2002; Sandrini et al., 2005) and is considered to be affected by the activity of descending pain inhibition, as pain sensation and RIII reflex change concordantly (Willer et al., 1979; Willer et al.,

1989; Rhudy et al., 2005; Ruscheweyh et al., 2011a). These findings lead to the hypothesis that it should be possible to learn to apply cognitive and emotional strategies to deliberately activate the respective brain regions that target the brainstem and thus activate descending pain inhibition, and concomitantly reduce the RIII reflex, resulting in pain reduction (see Figure 1). Descending pain inhibition often is impaired in patients with chronic pain, likely contributing to pain persistence (Yarnitsky, 2010; Kwon et al., 2014). Therefore, specific training to improve descending pain inhibition in patients with chronic pain is a promising approach in pain therapy (Yarnitsky, 2015).

This thesis describes the development and first clinical transfer of a visual feedback method that trains healthy subjects and patients with chronic back pain to use cognitive-emotional strategies to deliberately activate their descending pain inhibition and thus reduce their spinal nociception, as quantified by reduction in the RIII reflex. Since it is easier to learn control over mechanisms in the body when feedback about that respective mechanism is given, the RIII reflex size was used as a feedback parameter, with a reduction in RIII size likely reflecting the effect of descending pain inhibition on spinal nociception (see Figure 3).

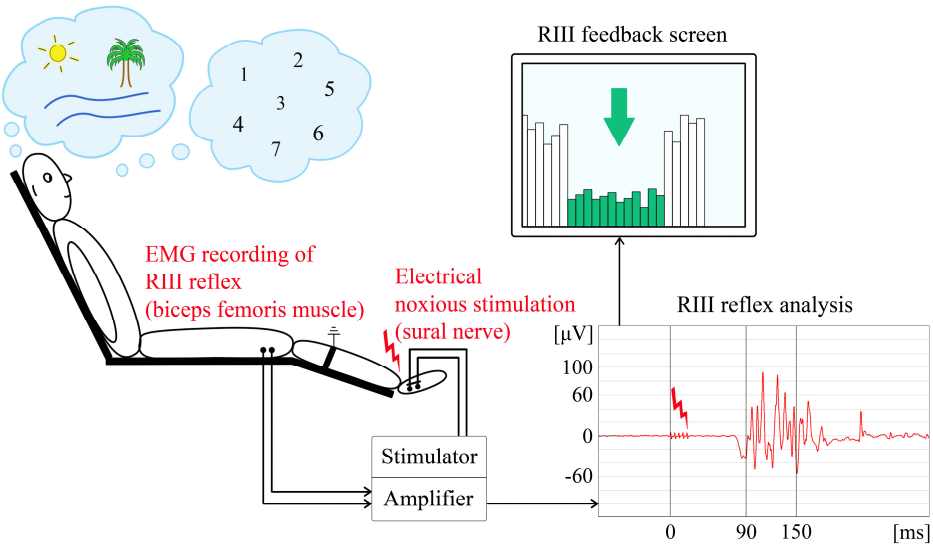

Figure 3: Experimental setup of the RIII feedback training. Subjects were comfortably sitting on a reclining chair, with a grounding electrode around their shin. The electrical noxious stimulation was administered on the sural nerve at the ankle to evoke the RIII reflex in the ipsilateral thigh. EMG surface electrodes recorded the RIII

reflex from the biceps femoris muscle. The reflex size (i.e. area under the curve) was analyzed online 90-150 ms after stimulation. The size of the RIII reflex served as a feedback parameter that was immediately visually presented to the subject in the form of bars on a separate screen. A green arrow and green bars indicated that the subject should reduce his/her RIII reflex size by applying emotional or cognitive strategies.

The aim of the first study was to investigate if young healthy adults, over the course of three RIII feedback training sessions, can learn to apply cognitive-emotional strategies in order to activate their descending pain inhibition and suppress the size of their RIII reflex as well as their subjective pain sensation. Based on the results of this research, the second RIII feedback training study in young healthy adults examined if learned suppression of the RIII reflex also affects supraspinal nociception, quantified by late somatosensory evoked potentials (SEPs) in parallel with the RIII reflex. Furthermore, this study aimed to exclude the possibility that RIII reduction is due to changes in lower motor neuron excitability instead of activation of descending pain inhibition. Since RIII feedback might be associated with expectancy to control the RIII reflex, and pain sensation and expectancy itself (like the placebo effect) can activate descending pain inhibition, the second study moreover added a group of subjects that received sham (false) RIII feedback. Finally, as a first clinical transfer, the aim of the third study was to analyze if also patients with chronic back pain are able to activate their impaired descending pain inhibition and reduce their spinal nociception during RIII feedback training. Also, it was investigated whether the RIII feedback training influences the patients' impaired descending pain inhibition, quantified by an alternative measure of descending pain inhibition, the conditioned pain modulation (CPM) effect. Moreover, regarding possible clinical use of the RIII feedback training, the third study investigated the effect of the feedback training on the patients' clinical pain intensity, anxiety and depression, compared to patients with chronic back pain that received sham RIII feedback training or that did not participate in the feedback training.

2 CUMULATIVE THESIS

2.1 Control over spinal nociception as quantified by the nociceptive flexor reflex (RIII reflex) can be achieved under feedback of the RIII reflex

Summary

This study demonstrated that healthy subjects can learn to apply cognitive and emotional strategies to successfully reduce their RIII reflex and experimental pain under feedback about their RIII reflex size.

Reference:

Control over spinal nociception as quantified by the nociceptive flexor reflex (RIII reflex) can be achieved under feedback of the RIII reflex. Ruscheweyh, R., Weinges, F., Schiffer, M., Bäumler, M., Feller, M., **Krafft, S.**, Straube, A., Sommer, J., Marziniak, M. *European Journal of Pain* 19(4):480-489. Copyright © 2014, European Pain Federation – EFIC®, Wiley. doi: 10.1002/ejp.570.

Author contributions:

RR, MM, AS, JS:	Conception and design.
JS:	Programming and implementation of the experimental software.
FW, MS, MB, MF, SK:	Data acquisition.
RR, FW, MS, MB, MF, SK:	Data analysis and interpretation.
RR:	Manuscript writing.

All authors critically revised the manuscript.

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ORIGINAL ARTICLE

Control over spinal nociception as quantified by the nociceptive flexor reflex (RIII reflex) can be achieved under feedback of the RIII reflex

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Conflicts of interest
None declared.

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Abstract

Background: Descending pain modulatory systems control transmission of nociceptive information at the spinal level, and their activity can be modified by cognitive and emotional processes. Thus, it may be possible to learn using cognitive–emotional strategies to specifically target descending pathways in order to achieve pain reduction.
Methods: The present study used visual feedback of the nociceptive flexor reflex (RIII reflex) to train healthy subjects over three sessions to reduce their spinal nociception (RIII reflex size) by self-selected cognitive–emotional strategies. The study included two feedback groups (fixed vs. random stimulation intervals) and a control group without feedback (15 subjects each).
Results: While all three groups successfully reduced their RIII reflexes ($p < 0.01$), reductions were larger in the feedback groups ($p < 0.05$). Success increased over training sessions in the feedback groups ($p < 0.05$). In the third session, RIII was reduced to $90 \pm 15\%$ of baseline in the control group, and to 72 ± 24 and $66 \pm 22\%$ in the feedback groups. Most subjects used mental imagery or relaxation to achieve RIII reduction. Pain reduction correlated with RIII reduction in the feedback groups, but was not significantly different between feedback and control groups.
Conclusions: The present results suggest that healthy subjects are able to learn using cognitive and emotional strategies to reduce their spinal nociception under feedback of their RIII reflex size. However, future studies will have to include a sham feedback group to differentiate true learning effects from expectancy effects induced by the feedback procedure.

1. Introduction

Descending pain modulatory systems originate in the brainstem and terminate in the spinal dorsal horn, where they inhibit or facilitate nociceptive transmission, co-determining how much nociceptive information from peripheral tissues is relayed to the cortex, and significantly modulating the pain experience following a noxious stimulus (Fields and Basbaum, 2006). Evidence has accumulated that descending pain modulatory systems can be activated by cognitive–emotional processes (Tracey and Mantyh, 2007; Bingel and Tracey, 2008; Wiech and Tracey, 2009). For example, human brain imaging studies have shown that distraction from pain activates several structures such as parts of the prefrontal

What's already known about this topic?
- Descending pain modulation is under cognitive control.
- It might thus be possible to learn using cognitive strategies to suppress spinal nociception.
- The RIII reflex is used as measure of spinal nociception.
- One previous study using a single-session RIII reflex feedback training did not show significant learned suppression of the RIII size.

What does this study add?
- This study shows that learned control over the RIII size is achieved after RIII feedback training over 3 days, significantly different from a control group and increasing with sessions.
- We propose that this may be an interesting, novel approach to target spinal nociception in humans.

cortex, the rostral anterior cingulate cortex (rACC) and the periaqueductal grey, which are known to target descending pain inhibitory systems (Tracey et al., 2002; Valet et al., 2004). Similarly, emotions modify activity in the anterior cingulate cortex and the periaqueductal grey (Fairhurst et al., 2007; Villemure and Bushnell, 2009). Accordingly, human spinal nociceptive transmission is affected by attention and distraction (Willer et al., 1979; Ruscheweyh et al., 2011), the placebo effect (Matre et al., 2006; Eippert et al., 2009) and emotional picture viewing (Rhudy et al., 2005; Roy et al., 2009).

Therefore, it should principally be possible to learn using cognitive and emotional processes to specifically target descending pathways with the goal of achieving pain reduction. Cognitive–behavioural pain therapy successfully uses cognitive and/or emotional strategies, which likely act on both supraspinal and descending pain modulatory systems (McCracken and Turk, 2002; Turk et al., 2008). The effect on descending pain modulation might be further enhanced by providing subjects with a direct feedback ('biofeedback') on the effect their strategies have on their spinal nociceptive transmission. Biofeedback has repeatedly been shown to allow subjects to gain control over physiologic processes that normally are not under direct conscious control, e.g., heart rate, muscle tension, electroencephalographic activity and even regional functional magnetic resonance imaging (fMRI) activity (Birbaumer et al., 1999; deCharms et al., 2005; Nestoriuc and Martin, 2007).

The nociceptive flexor reflex (RIII reflex) is considered a measure of spinal nociceptive transmission (Skljarevski and Ramadan, 2002; Sandrini et al., 2005) and is therefore a potentially suitable feedback parameter for training subjects to regulate their descending pain modulatory subjects. A recent study using RIII size feedback together with instructions for up- or down-regulation of the reflex size did not find significant differences between true feedback, sham feedback and no feedback (Arsenault et al., 2013). However, in this study, subjects participated only in a single session. In the present study, subjects were trained over three sessions, and over three to five runs per session, to reduce their RIII size using cognitive or emotional strategies of their choice. Descending pain modulation by emotions may be more pronounced when unpredictable (vs. predictable) noxious stimuli are used (Rhudy et al., 2006). Therefore, the present study included two feedback groups (fixed vs. random stimuli) and compared results with those of a control group that underwent the same experimental procedures but did not receive feedback on their RIII size.

2. Methods

2.1 Participants

The study was conducted in accordance with the Declaration of Helsinki and was approved by the local ethics committees of the Universities of Münster and Munich. Prior to participation, subjects gave written informed consent. Healthy volunteers were recruited by advertisements on the university campus. Participants had to meet the following 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. In addition, a preparatory session was conducted to familiarize subjects with recording of the RIII reflex, and subjects were excluded if a stable reflex could not be recorded over 8 min (interstimulus interval: 6 s) or if subjects found stimulation too painful. In total, 25% of the subjects were excluded after the preparatory session for one of the two reasons given above. A total of 47 subjects were randomized to the three groups (feedback with fixed stimulation intervals, feedback with random stimulation intervals, control).

The randomization was conducted in two phases. First, 31 subjects were randomly assigned to one of the two feedback groups. The control group was added later at the reviewers' request and was recruited together with the subjects of a follow-up study on RIII feedback using a virtually identical study design. From a total of 64 subjects recruited, 16 were randomized to participate in the control group of the present study. Therefore, randomization was maintained also for the

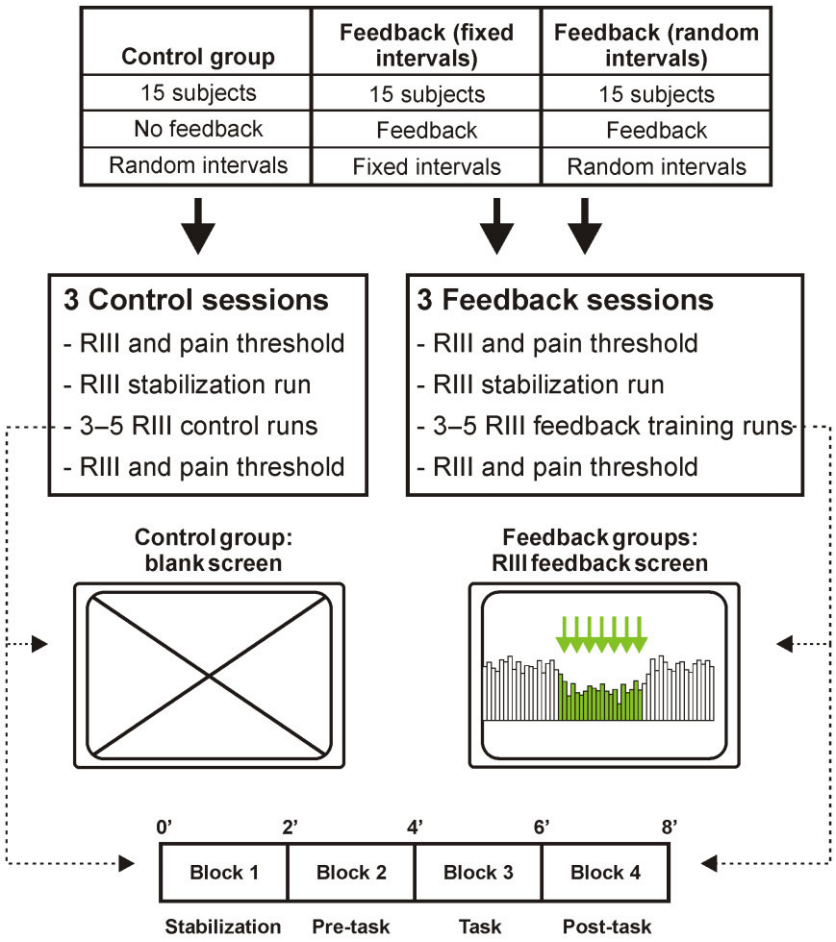

Figure 1 Outline of experimental procedures. A total of 45 subjects, randomized into three groups, attended three feedback training sessions or control sessions. RIII reflexes were evoked every 6 s (fixed intervals) or every 8–12 s (random intervals). RIII stabilization runs consisted of RIII recording for 8 min without feedback or task. During feedback runs, subjects in the feedback groups received feedback on their RIII reflex areas on a separate screen immediately (<2 s) after each stimulus. Each feedback training run consisted of four blocks as displayed in the lower part of the figure. Block 1 was a run-in phase again used for reflex stabilization (stabilization block). Blocks 2 and 4 were the pre- and post-task blocks. During the task block (block 3) subjects tried to reduce RIII reflex size using cognitive or emotional strategies of their choice. In the control group, procedures were identical, but no feedback on the RIII reflex was given. During the task block, control subjects tried to reduce pain (instead of RIII reflex size) by cognitive or emotional strategies. Each subject performed three to five feedback training runs or control runs per session.

control group. In both the feedback group with fixed intervals and in the control group, one subject dropped out after the first experimental session because stimulation was too painful. Thus, a total of 15 subjects were left in every group. Age and sex distribution were similar among the three final groups (control group: age 24 ± 3 years, 9 females; feedback group with fixed stimulation intervals: age 24 ± 3 years, 8 females; feedback group with random stimulation intervals: age 24 ± 3 years, 10 females).

2.2 Study design (see Fig. 1)

Each subject included in the final analysis attended three experimental sessions, which consisted of one 8-min stabilization run and three to five feedback training runs (feedback groups) or control runs (control group) each, as outlined in Fig. 1. On days of assessment, participants were free of acute pain and had not taken analgesics within the preceding 24 h. Stimulus intensity was set at ~130% of RIII reflex threshold. The RIII reflex was evoked every 6 s in the feedback group with fixed stimulation intervals, and every 8–12 s (randomized stimulation intervals) in the feedback group with random stimulation intervals and the control group.

Each feedback or control run consisted of four consecutive 2-min blocks (Fig. 1; 20 stimuli per block for the fixed intervals group, 12 stimuli per block for the random intervals group and the control group). Block 1 was a run-in phase again used for reflex stabilization (stabilization block). Blocks 2 and 4 were the pre- and post-task blocks. Block 3 was the task block. Pain intensity of the electrical stimuli used to evoke the RIII reflex was rated on an 11-point numerical rating scale (NRS) from 0 (no pain) to 10 (strongest possible pain) at the end of each block (as an average rating of the preceding five stimuli). Heart rate was recorded at the end of each block (see Supporting Information Methods S1).

The feedback groups received feedback on their RIII reflex size during the feedback training runs. During the task blocks, they had the task to use cognitive and/or emotional strategies with the aim to reduce their *RIII reflex size*. For the other three blocks, they had the instruction to merely observe their RIII size without trying to change it. The control group did not receive feedback on their RIII reflex size. During the task block of the control runs, they had the task to use cognitive and/or emotional strategies with the aim to reduce the *pain* induced by the electrical stimulus

used to evoke the RIII reflex. For the other three blocks, they had the instruction to merely observe their pain perception without trying to change it.

All subjects received identical instructions regarding strategies that might be useful for reduction of RIII size (feedback groups) or pain perception (control group). The proposed strategies were (1) distraction from pain by recalling pleasant experiences; (2) distraction from pain by making plans for work or leisure; (3) distraction from pain by doing mental arithmetic; and (4) ignoring pain. However, subjects were encouraged to modify these strategies as needed or to use different strategies depending on the success they achieved in RIII reduction (feedback groups) or pain reduction (control group). At the end of each feedback or control run, subjects reported on the strategy they had used.

A minimum of three feedback training runs or control runs was performed per session, but subjects were allowed to complete up to five feedback or control runs per session if they believed that this might increase their success in RIII reflex reduction (feedback groups) or pain reduction (control group). The three feedback/control sessions took place on three separate days within a maximum of 3 weeks.

2.3 Recording and quantification of the RIII reflex

The RIII reflex was evoked and recorded from the lower limb as described previously (Ruscheweyh et al., 2011) according to established techniques (Willer, 1977; Arendt-Nielsen et al., 1994; Bouhassira et al., 2003). 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 (Medtronic, Natus, Langenfeld, 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 within a 50-ms analysis window starting between 90 and 120 ms after stimulation [mean ± standard deviation (SD): 105.4 ± 8.3 ms]. The analysis window was positioned to include the RIII reflex while avoiding contamination by the non-nociceptive RII reflex and was kept constant throughout all recordings taken from a given subject on the same day. More information on the rationale for using a flexible analysis window can be found in Supporting Information Methods S1.

To estimate baseline noise, the baseline area was calculated by integrating the rectified signal within a 50-ms baseline window (85–35 ms before stimulation). The baseline-corrected final RIII area was obtained by subtracting the average baseline area (average of all baseline areas obtained from the respective subject during the respective control or feedback run) from the raw RIII area (Rhudy et al., 2011).

2.4 RIII and pain thresholds

Stimulus–response curves were recorded by increasing stimulation intensity in 0.5 mA steps starting from 0.5 mA. Participants rated the pain intensity of each stimulus on the NRS. The pain threshold was determined as the stimulus intensity that first evoked a painful sensation (defined as an NRS rating ≥1). According to the procedure described in more detail previously (Ruscheweyh et al., 2011), the RIII threshold was defined as the stimulus intensity that first evoked a reflex response exceeding a raw area of 100 μV × ms (see Supporting Information Methods S1 for details). Three consecutive RIII and pain thresholds were determined at the beginning and at the end of each experimental session and averaged.

For the feedback and control runs, a stimulus intensity near 130% of the reflex threshold was chosen that reliably evoked reflexes of sufficient magnitude and was well tolerated by the subject for the duration of the experiment.

2.5 RIII feedback set-up

For RIII feedback, the EMG signal was conveyed to an external computer, where the RIII reflex area was quantified and visual feedback on the RIII size was given to the subject in the form of a bar on a separate screen. As the recording proceeded, the subject was able to follow the course of his RIII size as a new bar was added following each stimulus. During the task block, bars appeared in green and a blinking green downward arrow indicated that subjects should try to reduce their reflex size (see Fig. 1). As a summary, a chart illustrating mean reflex areas ± standard errors within each block was displayed at the end of each feedback run. More details on the feedback setup are found in Supporting Information Methods S1.

2.6 Statistics

Statistical analyses were performed using the Statistical Package of Social Sciences, version 21 for Windows (IBM, Armonk, NY, USA). Values are mean ± SD unless indicated otherwise. $p < 0.05$ was considered statistically significant.

For evaluating pain thresholds and RIII thresholds, a repeated measures analysis of variance (ANOVA) was used,

with session and type of threshold (pain vs. RIII) as within-subject factors and group as between-subject factor.

To test for group differences, task effects and session effects in RIII areas, pain ratings, baseline areas and heart rates, a repeated measures ANOVA was used, with block (pre-task, task and post-task) and session as within-subject factors and group as between-subject factor. Within each session, between three and five feedback training runs were performed. To determine if the task effect increased over runs, within sessions, the first and the last run in each session were compared using repeated measures ANOVA on task block RIII areas (in percentage of combined pre- and post-task values) with session and run as within-subject factors and group as between-subject factor.

Pearson's correlation coefficient was used to test for correlations. Details on the statistical analysis can be found in Supporting Information Methods S1.

3. Results

A total of 45 subjects (15 per group) participated in three feedback training sessions (feedback group with fixed intervals and feedback group with random intervals) or three control sessions (control group).

RIII and pain thresholds were acquired in all three sessions. Average RIII thresholds were 9.5 ± 2.6 mA and average pain thresholds were 7.0 ± 2.8 mA. RIII thresholds were significantly higher than pain thresholds [$F(1,38) = 53.8$, $p < 0.001$]. There were no main effects of group or interactions with group (see Supporting Information Results S1 for details).

3.1 Task effect on RIII areas

Results are shown in Table 1 and Fig. 2. Percent values (compared with the pre-task block) are shown in Supporting Information Table S1. A detailed account of all results of the statistical analysis can be found in the Supporting Information Results S1.

Repeated measures ANOVA on RIII areas with block, session and group as factors revealed a main effect of block [pre-task, task, post-task; $F(1.23,51.73) = 73.9$, $p < 0.001$] as well as interactions between group and block [$F(2.46,51.73) = 4.6$, $p < 0.01$] and between group and block and session [$F(8,168) = 2.0$, $p < 0.05$].

Post-hoc analysis revealed that subjects in all three groups achieved a significant reduction of RIII areas during the task with complete recovery after the end of the task. However, the RIII suppression during the task block was significantly larger in both feedback groups than in the control group [main effect of group: $F(2) = 5.2$, $p < 0.01$; post-hoc tests: feedback with fixed intervals vs. control: $F(1) = 6.0$, $p < 0.05$, feedback with random intervals vs. control $F(1) = 10.7$, $p < 0.01$; comparison between the two feedback groups: n.s.].

In addition, there was a significant effect of session in the feedback groups [$F(2,58) = 11.9$, $p < 0.001$] but not in the control group. Post-hoc tests in the feedback groups revealed significant differences between session 1 and session 2 [$F(1,29) = 10.4$, $p < 0.01$], between session 2 and 3 [$F(2,29) = 14.1$, $p < 0.001$], and between session 1 and session 3 [$F(1,29) = 19.9$, $p < 0.001$].

We next determined if RIII suppression during the task block increased over successive training/control runs within feedback or control sessions. Subjects were allowed to participate in three to five feedback or control runs during each session. As the number of runs per session was therefore individually different, we compared the first and the last training/control run within each session (Supporting Information Fig. S1).

Table 1 Raw values of RIII areas and pain ratings during pre-task, task and post-task blocks.

	Control (n = 15)			Feedback with fixed intervals (n = 15)			Feedback with random intervals (n = 15)		
	Pre-task	Task	Post-task	Pre-task	Task	Post-task	Pre-task	Task	Post-task
RIII areas ± SD (μV × ms)									
Session 1	567 ± 226	510 ± 234	565 ± 230	750 ± 334	611 ± 309	752 ± 340	929 ± 745	736 ± 623	961 ± 802
Session 2	584 ± 364	547 ± 368	625 ± 410	740 ± 256	552 ± 222	770 ± 266	1011 ± 917	663 ± 698	1016 ± 868
Session 3	658 ± 291	580 ± 237	675 ± 319	801 ± 393	529 ± 297	798 ± 337	890 ± 667	548 ± 380	909 ± 751
Pain intensity ratings ± SD (0–10)									
Session 1	3.0 ± 1.0	2.6 ± 1.0	3.0 ± 1.0	3.4 ± 1.0	2.8 ± 0.9	3.2 ± 1.1	2.9 ± 0.7	2.6 ± 0.6	2.9 ± 0.6
Session 2	3.1 ± 1.4	2.8 ± 1.3	3.1 ± 1.4	3.4 ± 1.1	2.8 ± 1.1	3.3 ± 1.1	2.8 ± 0.7	2.5 ± 0.7	2.8 ± 0.7
Session 3	3.0 ± 1.2	2.5 ± 1.0	2.9 ± 1.2	3.4 ± 1.4	2.8 ± 1.4	3.2 ± 0.5	3.0 ± 0.7	2.6 ± 0.7	3.0 ± 0.7

Please note that raw values are averages of individual averages across three to five runs per session. Therefore, percentages of pre-task values given in Supporting Information Table S1 are not identical to percentages of pre-task values calculated from the session average raw values. SD, standard deviation.

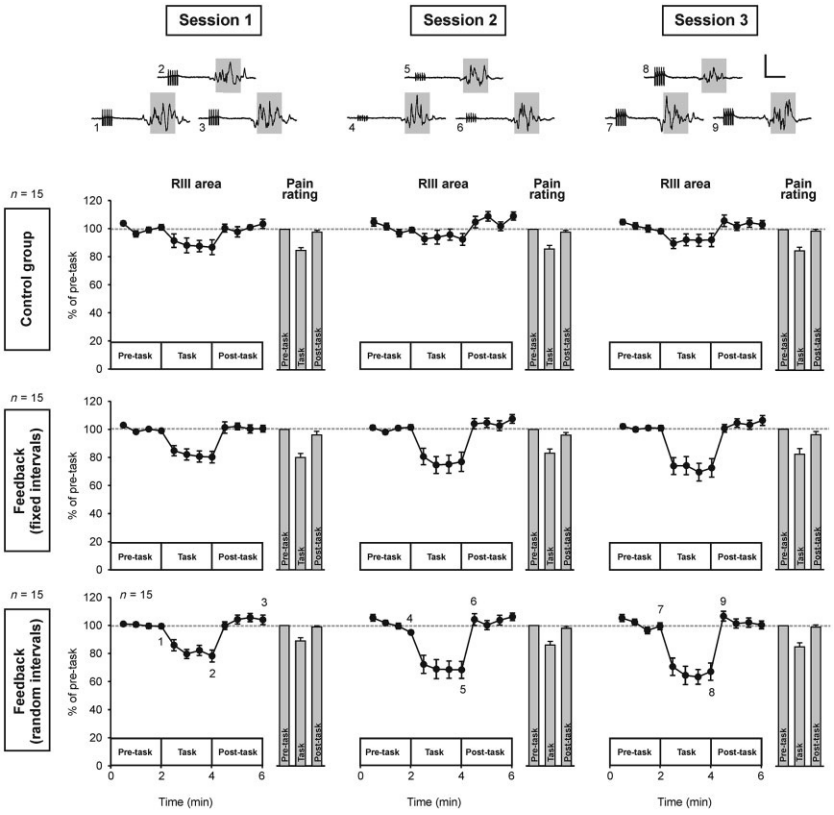

Figure 2 Task effects on RIII areas and pain intensity ratings. Illustration of task effects over the three feedback or control sessions. RIII areas and pain intensity ratings are illustrated as % of the pre-task block and averaged first within subjects over all feedback training or control runs available for the respective session and then between subjects. For RIII areas, each data point illustrates a ~30-s epoch, consisting of five reflexes (in the feedback group with fixed stimulation intervals where stimuli were administered at 6-s intervals) or three reflexes (in feedback group with random stimulation intervals where stimuli were administered at 8- to12-s intervals). Pain intensity ratings were obtained once at the end of each block, as an average rating of the preceding five stimuli. Values are mean ± standard error of the mean. Above the graph, representative examples of original traces from a subject of the feedback group with random stimulation intervals before, during and after the task are shown. All traces are from the same subject. The shaded region corresponds to the analysis window. Bars: 50 μV, 50 ms.

Repeated measures ANOVA on task block RIII areas with session, run and group as factors revealed no significant main effect of run, and no significant interactions with run.

3.2 Task effect on baseline areas

Because changes in baseline electromyographic activity might be a sign of change in motor excitability, we investigated if there were task effects on baseline areas. Raw values and percentages are given in Supporting Information Table S2. There was no effect of task on baseline areas (see Supporting Information Results S1 for details).

3.3 Task effect on pain ratings

Pain ratings decreased during task blocks and largely recovered during post-task blocks (Fig. 2, Table 1 and Supporting Information Table S1). There was a main effect of block [$F(1.3,\ 55.1) = 112.2,\ p < 0.001$], but there were no effects of session or group and no interactions with group (see Supporting Information Results S1 for details).

3.4 Task effect on heart rates

Heart rates were slightly but significantly reduced during task blocks [average pre-task: 70.6 ± 7.7 beats per minute (bpm); average task: 69.0 ± 7.3 bpm; average post-task: 70.4 ± 7.0 bpm; main effect of block: $F(2,72) = 6.4,\ p < 0.01$], without significant group differences or session effects (see Supporting Information Table S3 and Results S1 for details).

3.5 Correlations

In the feedback groups, there were significant correlations between RIII suppression during the task block and pain reduction during the task block for sessions 1 and 2, but not for session 3 (Supporting Information Fig. S2; feedback with fixed intervals, session 1: $r = 0.52,\ p < 0.05$; session 2: $r = 0.77,\ p < 0.001$, session 3: $r = 0.37$, n.s.; feedback with random intervals, session 1: $r = 0.65,\ p < 0.01$; session 2: $r = 0.62$, $p < 0.05$, session 3: $r = –0.10$, n.s.). In contrast, there were no such correlations in the control group.

There were no correlations between task effects on RIII areas and task effects on heart rate in either of the groups.

3.6 Strategies used for RIII reflex reduction

Subjects usually tested different strategies before finding the one that worked best for them. None of the participants reported using more than one strategy per run. Supporting Information Table S4 lists the different strategies used by the subjects and the reflex reduction achieved by them in session 3. The most frequently used and (in the feedback groups) most successful strategies in session 3 were (1) mental imagery (subjects vividly recalled a pleasant experience with visual, auditory and somatosensory details) and (2) relaxation techniques (subjects that had learned a relaxation technique in the past often found they could reduce their RIII reflex using elements of these relaxation techniques that included autogenic training, yoga and meditation). Subjects in the feedback groups also achieved RIII reduction by mentally focusing on reduction of bar size (bars indicating reflex size on the subjects' screen). Mental arithmetic and ignoring pain were less effective, but a direct comparison between strategies is not possible in the present study, as subjects were allowed to freely choose and change their strategies.

4. Discussion

The main result of the present study is that healthy young subjects seem to be able to learn using cognitive–emotional strategies to decrease their nociceptive flexor reflex (RIII reflex), when given feedback over their RIII size. Although the control group without feedback also achieved a certain degree of RIII reduction, the effect was significantly larger under feedback, and increased with training sessions.

4.1 Interpretation of learned RIII reduction

We conducted this study under the hypothesis that under feedback of the RIII reflex size, subjects will learn to use cognitive–emotional processes to control their descending pain modulation, with consequent reduction in pain perception. While it is clear from the present results that subjects in the feedback groups achieved reduction of their motor responses to painful stimuli, the relation to pain perception remained somewhat inconclusive. Therefore, there are some arguments in favour of the above hypothesis but also some drawbacks.

Certainly, the strategies successfully used by the subjects for RIII reduction are known to affect descending pain modulatory systems. For example, mental imagery involves distraction from pain and positive emotions, both of which activate cortical and brainstem structures at the origin of descending pain inhibition (Bantick et al., 2002; Tracey et al., 2002; Valet et al., 2004) and reduce human spinal nociception (Willer et al., 1979; Rhudy et al., 2005; Ruscheweyh et al., 2011). Similarly, relaxation techniques reduce human spinal nociception (Emery et al., 2006). In addition, a parallel reduction of RIII size and pain perception is usually considered a strong indication of the activation of descending pain modulatory systems (Willer et al., 1979; Rhudy et al., 2005; Sandrini et al., 2005; Ruscheweyh et al., 2011). In the present study, there was a correlation between reduction in RIII areas and pain ratings within sessions 1 and 2 in the feedback groups. However, while reduction of RIII areas increased from session to session in the feedback groups, reduction of pain ratings remained stable and was not significantly different from that achieved in the control group. This may be an indication that subjects learned to control their motor response to painful stimuli, without effect on their pain perception (see limitations). Alternatively, this partial dissociation between RIII size and pain perception might in part be due to the use of an 11-point NRS for pain rating, which allows for little gradation. In addition, it can also not be excluded that the RIII reduction during feedback training does not reflect a learning effect but rather an expectancy effect associated with the feedback procedure (see limitations).

4.2 Comparison with other approaches to use feedback of neural activity to achieve pain control

Late components of somatosensory-evoked potentials (SEPs) have been used as feedback parameter with the intention to modulate pain perception. In spite of substantial habituation of SEP amplitudes with repetitive stimulation, some training effects have been documented. However, effects on pain perception have been inconsistent (Rosenfeld et al., 1985; Miltner et al., 1988; Dowman, 1996) maybe because SEPs in part reflect non-nociceptive influences.

More recently, real-time fMRI (rt-fMRI) feedback has been used to train subjects to control activity in pain-related brain regions. Using this technique, subjects are able to learn control over pain-related activity of the rACC, with concomitant changes in experimental and clinical pain (deCharms et al., 2005). rt-fMRI feedback represents a highly innovative approach to learned pain modulation, but may be somewhat

limited by the need of special equipment. In addition, rACC activation is not pain specific, but also occurs during attention, emotion and executive tasks (Allman et al., 2001).

Different from cortical-evoked potentials, habituation is not a major problem with RIII reflexes. In comparison with rt-fMRI feedback training, RIII feedback training is relatively easy to implement. In addition, the RIII feedback training has the potential to protect spinal cord and higher centres from nociceptive input.

A very recent study used the same approach as the present study, providing subjects with feedback on their RIII size and asking them to modulate RIII size. Although subjects achieved significant up- and down-regulation of their RIII reflexes, the feedback group was not significantly different from a control group or a sham feedback group (Arsenault et al., 2013). This might be due to the fact that subjects in the previous study (Arsenault et al., 2013) underwent only two feedback runs on 1 day, while in the present study subjects participated in three to five feedback runs per session and three sessions conducted on three different days. Indeed, in the present study, the difference between feedback and control groups emerged only in sessions 2 and 3, suggesting that feedback training over several days may be crucial for learning RIII suppression.

4.3 Possible approaches to improve feedback training

The goal would be to achieve a maximum of RIII reduction using a minimum of painful stimuli, especially in view of possible application of the feedback training to chronic pain patients. The present data show that feedback training over several days is necessary. However, it might be possible to reduce the number of feedback runs per session without reducing the training effect. Our data indicate that on average there was no increase in RIII reduction from the first to the last run of a session. It was the experimenters' impression that subjects tended to be fatigued by repeated feedback runs, but this remains speculative because fatigue was not measured. In addition, using fewer stimuli per block may be possible. In the present study, the use of 20 stimuli per block, delivered at 6-s intervals, was not significantly different from the use of 12 stimuli per block, delivered at 8–12-s intervals. However, predictable stimuli are usually less unpleasant than unpredictable stimuli. Future studies might therefore test if the use of 12 or fewer stimuli per block at fixed 10-s intervals will be equally effective and less unpleasant than the presently used protocols.

5. Limitations

The present study has a number of limitations. First, it has to be kept in mind that reduction of the RIII reflex does not necessarily imply reduction of ascending nociception, but may also indicate modulation of other reflex components, such as deep dorsal horn interneurons (Schouenborg et al., 1995) or motor neurons. Indeed, several studies have reported a lack of correlation between the extent of pain modulation and RIII modulation (Terkelsen et al., 2004; Piché et al., 2009). In the present study, the correlation between modulation of pain intensity and modulation of RIII area, at least in feedback sessions 1 and 2, suggests that ascending nociception was affected. However, there were no group differences in the extent of pain modulation, and no increase in pain modulation from session to session, suggesting that subjects may have learned to control their motor response to pain, but not necessarily their pain perception. Clearly, further investigation of the RIII feedback paradigm will have to involve control for motor excitability and quantification of supraspinal nociception by a method different from subjective pain ratings.

Second, the RIII feedback procedure itself may induce expectancy to be able to control the RIII reflex size, and thereby achieve pain reduction. This expectancy is conceptionally similar to the expectancy involved in placebo analgesia, which is partially mediated by activation of descending pain inhibitory pathways (Bingel and Tracey, 2008). Therefore, expectancy effects during RIII feedback might lead to both pain reduction and reduction of the RIII size. This effect can only partially be controlled by the use of a control group without feedback, even when the instructions for pain reduction that were given in this group might also induce a certain degree of expectancy. Previous studies on pain reduction by biofeedback have therefore included a control group with sham feedback (deCharms et al., 2005; Arsenault et al., 2013). For these reasons, from the present data it cannot be decided if the RIII and pain reduction during RIII feedback training was due to true learned control of spinal nociception or due to activation of descending pain inhibition by non-specific expectancy effects. This is an important methodological point that will be addressed in subsequent studies.

Third, reductions in pain intensity ratings during the task block were small (by about 15%). Only reduc-

tions above 30% are regarded as clinically significant (Dworkin et al., 2008). However, these were ratings of electrical stimuli, which are very different from clinical pain, and notoriously difficult to rate for many subjects. Further studies will have to show if a clinically significant reduction of acute or chronic clinical pain can be achieved by RIII feedback training.

Fourth, pain ratings were obtained retrospectively at the end of each block. This approach was necessary to allow subjects to concentrate on reflex reduction during the task block.

6. Conclusion

The present results suggest that healthy young subjects are able to learn using cognitive and emotional strategies to reduce their motor responses to painful stimuli when they receive feedback on their RIII reflex size. However, results remained inconclusive on whether and how this learned reduction of spinal nociception translates to reduction of pain perception. In addition, it remains to be shown that the effects are not due to a non-specific expectancy effect related to the feedback procedure. Nonetheless, we believe that the idea of training subjects to activate their descending pain inhibitory systems using feedback of spinal nociception is tempting and merits further study. Subsequent studies will have to control for the motor effect of RIII-reducing strategies, more thoroughly investigate the relation between RIII reduction and supraspinal measures of nociception and pain, and include a control group receiving sham RIII feedback.

Author contributions

R.R., M.M., J.S. and A.S. were responsible for conception and design. Data acquisition was carried out by F.W., M.S., M.B., M.F. and S.K. Data analysis and interpretation were performed by R.R., F.W., M.S., M.B., M.F. and S.K. All authors contributed to the article draft and revision for important intellectual content. In addition, all authors have agreed on the final approval of the version to be published.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

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Results S1. Detailed results of the statistical analysis.
Figure S1. Comparison of RIII areas during the task block, in the first and the last run within each feedback or control session.
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Methods S1

RIII analysis: analysis window

Previous studies have mostly used 40 to 100 ms wide analysis windows with a fixed position (i.e. the same for all subjects), starting at 80-100 ms after stimulation and ending at 130-200 ms after stimulation (Arendt-Nielsen et al., 1994; Bouhassira et al., 2003; Serrao et al., 2004; Neziri et al., 2009; Rhudy et al., 2009). However, RIII onset latencies vary between 90 and 130 ms after stimulation (Willer, 1977) and RII onset latencies vary between 40 and 80 ms (Willer, 1977; Willer et al., 1979; Danziger et al., 1998). In our experience, an RIII reflex recorded at 120-140% threshold intensity is usually not much wider than 50 ms, but may be preceded by an RII reflex extending beyond 100 ms after stimulation. A flexible analysis window thus allows to center analysis over the RIII reflex while avoiding contamination by the RII reflex (see Fig. 2A in Ruscheweyh et al., 2011 for an example). RII reflexes were identified by onset latencies < 80 ms and low stimulation thresholds with respect to pain and RIII thresholds. In addition, the RII reflex often (but not always) exhibited an oligophasic, monomorphic aspect albeit with large variations in size, including failures, while the typical RIII reflex was polyphasic, less constant in shape but more constant in size (see Fig. 2A in Ruscheweyh et al., 2011 for an example). As compared to previous studies not reporting the need of adapting analysis windows (e.g. Arendt-Nielsen et al., 1994; Bouhassira et al., 2003; Serrao et al., 2004; Neziri et al., 2009; Rhudy et al., 2009), the incidence of RII reflexes seems to have been high in the present study (around 20%), possibly because we used a preparatory session and the experimental design required long recording sessions. The RII reflex has been reported to be present more regularly when subjects get used to the experimental procedures (Willer, 1977).

RIII threshold analysis

Previous studies have determined RIII thresholds either using absolute reflex size thresholds (Arendt-Nielsen et al., 1995; Neziri et al., 2010) or requiring reflex activity to exceed a confidence interval around the respective pre-stimulus baseline activity (Campbell et al., 2008; Rhudy et al., 2009). In the present study, baseline areas (obtained by integrating the rectified signal between 55 and 5 ms before stimulation) were 35 ± 13 μV·ms in session 1, 36 ± 15 μV·ms in session 2 and 37 ± 14 μV·ms in session 3 (see also Table S2). Because the RIII threshold was not an outcome parameter in the present study, and because the RIII threshold is usually very clear when assessed at 0.5 mA increments of stimulus intensity, with no reflex below the threshold and a relatively large reflex occurring above the threshold (see Fig. 2 of Ruscheweyh et al., 2011), we opted for a simplified analysis, using an absolute RIII threshold of 100 μV·ms.

Heart rate measurement

Heart rate was assessed using a standard heart rate monitor that analyzes ECG signals obtained via chest belt electrodes (Topline, Sigma Elektro, Neustadt/Weinstraße, Germany) and has been shown to deliver exact and robust measurements of heart rate. Heart rate readings were taken at the end of each block.

Feedback setup

Using the analogue output port of the EMG amplifier, the EMG signal was conveyed to an external computer via an A/D-converter board (PCI-DAS6013, 16 bit, 200000 samples/s, Measurement Computing, Norton, MA, USA). A customized software written by one of the authors (JS) in C++ delivered a trigger to the stimulator unit of the EMG amplifier and acquired the EMG signal between 100 ms before stimulation and 400 ms after stimulation. The RIII reflex area was quantified as described above and immediately displayed to the

subject on a separate screen in form of a bar, with the bar's height representing RIII area. The delay between stimulation and display of the reflex size was <2s. As the recording proceeded, the subject was able to follow the course of his RIII size as a new bar was added following each stimulus. During blocks 1, 2 and 4 of the feedback training run, bars appeared in white, indicating that subjects should observe their reflex size without trying to modify it. During the task block (block 3), bars appeared in green and a blinking green downward arrow indicated that subjects should try to reduce their reflex size. At the end of each feedback training run, a bar chart illustrating mean reflex areas ± standard errors within each block was displayed on the screen to give subjects a summary of the reduction in RIII size achieved during the experiment.

Details of statistical analysis

Statistical analyses were performed using the Statistical Package of Social Sciences, Version 21 for Windows. Values are mean ± standard deviation unless indicated otherwise. $P < 0.05$ was considered statistically significant.

For evaluating pain thresholds and RIII thresholds, a repeated measures analysis of variance (ANOVA) was used, with session and type of threshold (pain vs. RIII) as within subject factors and group as between subject factor.

RIII areas and baseline areas were averaged individually for each run and session within each block (pre-task, task, post-task). As the number of completed feedback or control runs per session varied between 3 and 5, individual *session averages* of raw or percent values (see below) of RIII areas, baseline areas, pain ratings and heart rates for every block (pre-task, task, post-task) were then calculated by averaging data from the 3-5 available feedback or control runs within the respective session and block. For evaluating the task effects on RIII areas, baseline areas, pain ratings or heart rates, some kind of normalization was mandatory, because of large individual differences in pre-task values, especially in the RIII areas (mean

pre-task RIII areas ranged from 152 to 3436 μV·ms). For tables and illustrations, we used percent of pre-task block values, which are easy to interpret. However, these values are not suitable for ANOVA because of zero variance in the pre-task block. For statistical purposes, we therefore used values given as percent of (pre-task block + post-task block)/2. Normality was confirmed using the Kolmogoroff-Smirnov-test for all variables. A repeated-measures ANOVA was used, with block (pre-task, task and post-task) and session as within-subject factors and group as between-subject factor. RIII areas, baseline areas, pain ratings and heart rates were entered into this analysis as individual session averages (see above). Subordinate ANOVAs and planned contrasts were used to decompose significant main effects and interactions. In case of violation of sphericity, the Greenhouse-Geisser correction was used and corrected degrees of freedom are reported. Group differences between the feedback groups and the control group were corrected using Dunnett's adjustment. All other comparisons were corrected using the Bonferroni-Holm adjustment. η^2 was used as a measure of effect size.

Within each session, between 3 and 5 feedback training runs were performed. To determine if the task effect increased over runs, within sessions, the first and the last run in each session were compared using repeated measures ANOVA on task block RIII areas (in percent of combined pre- and post-task values) with session and run as within subject factors and group as between subject factor.

Correlations were tested using Pearson's correlation coefficient.

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Results S1: Detailed results of the statistical analysis

Significant results are marked in bold face.

Details on: RIII and pain thresholds

Average pain thresholds and RIII thresholds per session:

- Session 1: 6.5 ± 2.3 mA; 9.1 ± 2.6 mA
- Session 2: 7.0 ± 2.9 mA; 9.3 ± 3.2 mA
- Session 3: 7.5 ± 3.4 mA; 10.0 ± 3.2 mA

ANOVA on thresholds with type of threshold (pain/RIII), session and group as factors:

- Main effect of type of threshold: $F[1,38] = 53.8$, $\mathbf{p < 0.001}$, $\eta^2 = 0.59$
- Main effect of session: $F[2,37] = 3.4$, $\mathbf{p < 0.05}$, $\eta^2 = 0.16$
- Main effect of group: $F[2] = 1.0$, $p = 0.37$, $\eta^2 = 0.05$
- Interaction between group and session: $F[4,76] = 0.6$, $p = 0.65$, $\eta^2 = 0.03$
- Interaction between group and type of threshold: $F[2,38] < 0.1$, $p = 1.0$, $\eta^2 < 0.01$

Details on: Task effect on RIII areas

Task effects on RIII areas:

ANOVA on RIII areas with block, session and group as factors:

- Main effect of block (pre-task, task, post-task): $F[1.23,51.73] = 73.9$, $\mathbf{p < 0.001}$, $\eta^2 = 0.64$
- Main effect of group: $F[2] = 5.2$, $\mathbf{p < 0.05}$, $\eta^2 = 0.20$
- Interaction between group and block: $F[2.46,51.73] = 4.6$, $\mathbf{p < 0.01}$, $\eta^2 = 0.18$
- Interaction between group and block and session: $F[8,168] = 2.0$, $\mathbf{p < 0.05}$, $\eta^2 = 0.09$

Posthoc analysis:

ANOVA on RIII area with block and session as factors (separately for each group)

Main effects of block:

- Control group: $F[2,28] = 10.3$, $\mathbf{p < 0.001}$, $\eta^2 = 0.42$
- Feedback group with fixed intervals: $F[1.16,16.27] = 26.7$, $\mathbf{p < 0.001}$, $\eta^2 = 0.65$
- Feedback group with random intervals: $F[1.14,15.92] = 38.6$, $\mathbf{p < 0.001}$, $\eta^2 = 0.73$

Contrasts on RIII area between blocks in single groups:

	Pre-task vs. task	Task vs. post-task	Pre-task vs. post-task
Control group	$F[1,14] = 7.9$, $\mathbf{p < 0.05}$, $\eta^2 = 0.36$	$F[1,14] = 16.3$, $\mathbf{p < 0.01}$, $\eta^2 = 0.54$	$F[1,14] = 2.1$, $p = 0.17$, $\eta^2 = 0.13$
Feedback group with fixed intervals	$F[1,14] = 23.4$, $\mathbf{p < 0.001}$, $\eta^2 = 0.63$	$F[1,14] = 38.6$, $\mathbf{p < 0.001}$, $\eta^2 = 0.73$	$F[1,14] = 1.9$, $p = 0.19$, $\eta^2 = 0.1$
Feedback group with random intervals	$F[1,14] = 35.5$, $\mathbf{p < 0.001}$, $\eta^2 = 0.72$	$F[1,14] = 47.7$, $\mathbf{p < 0.001}$, $\eta^2 = 0.77$	$F[1,14] = 3.0$, $p = 0.10$, $\eta^2 = 0.18$

Comparison of RIII suppression during task block between groups:

ANOVA on task block RIII areas with session and group as factors:

- Main effect of group: $F[2] = 5.2$, $\mathbf{p < 0.01}$, $\eta^2 = 0.20$
- Main effect of session: $F[2,84] = 7.4$, $\mathbf{p < 0.01}$, $\eta^2 = 0.15$
- Interaction between group and session: $F[4,84] = 2.8$, $\mathbf{p < 0.05}$, $\eta^2 = 0.17$

Posthoc analysis:

Contrasts between groups:

- Control group vs. feedback group with fixed intervals: $F[1] = 6.0$, $\mathbf{p < 0.05}$, $\eta^2 = 0.18$
- Control group vs. feedback group with random intervals: $F[1] = 10.7$, $\mathbf{p < 0.01}$, $\eta^2 = 0.28$
- Feedback group with fixed intervals vs. feedback group with random intervals: $F[1] = 0.5$, $p = 0.50$, $\eta^2 = 0.02$

Comparison of RIII suppression during task block between groups in single sessions:

ANOVA on task block RIII areas with group as factor (in single sessions):

- Session 1: $F[2] = 1.4$, $p = 0.26$, $\eta^2 = 0.06$
- Session 2: $F[2] = 5.1$, $\mathbf{p < 0.05}$, $\eta^2 = 0.20$
- Session 3: $F[2] = 5.8$, $\mathbf{p < 0.01}$, $\eta^2 = 0.22$

Contrasts between groups in single sessions:

- Session 2: Control group vs. feedback group with fixed intervals: $F[1] = 5.8$, $\mathbf{p < 0.05}$, $\eta^2 = 0.17$
- Session 2: Control group vs. feedback group with random intervals: $F[1] = 11.1$, $\mathbf{p < 0.01}$, $\eta^2 = 0.28$
- Session 2: Feedback group with fixed intervals vs. feedback group with random intervals: $F[1] = 0.7$, $p = 0.42$, $\eta^2 = 0.02$
- Session 3: Control group vs. feedback group with fixed intervals: $F[1] = 7.1$, $\mathbf{p < 0.05}$, $\eta^2 = 0.20$

- Session 3: Control group vs. feedback group with random intervals: F[1] = 12.7, **p < 0.01**, $\eta^2 = 0.31$
- Session 3: Feedback group with fixed intervals vs. feedback group with random intervals: F[1] = 0.4, p = 0.54, $\eta^2 = 0.01$

Comparison the effect of session on RIII suppression during task block between groups:

ANOVA on task block RIII areas with session as factor (separately in groups):

- Main effect of session in feedback group with fixed intervals: F[2,28] = 3.7, **p < 0.5**, $\eta^2 = 0.21$
- Main effect of session in feedback group with random intervals: F[2,28] = 8.9, **p < 0.01**, $\eta^2 = 0.39$
- Main effect of session in control group: F[2,28] = 0.1, p = 0.89, $\eta^2 = 0.01$

ANOVA on task block RIII areas with session as factor (both feedback groups pooled):

- Main effect of session: F[2,58] = 11.9, **p < 0.001**, $\eta^2 = 0.29$

Post-hoc tests (in pooled feedback groups):

- Session 1 vs. session 2: F[1,29] = 10.4, **p < 0.01**, $\eta^2 = 0.26$
- Session 2 vs. session 3: F[2,29] = 14.1, **p < 0.001**, $\eta^2 = 0.33$
- Session 1 vs. session 3: F[1,29] = 19.9, **p < 0.001**, $\eta^2 = 0.37$

Comparison of the effect of run on RIII suppression during task blocks

ANOVA on task block RIII areas with session, run (first vs. last) and group as factors:

- Main effect of run: F[1,42] = 1.2, p = 0.29, $\eta^2 = 0.03$
- Interaction between run and session: F[2,84] = 1.3, p = 0.28, $\eta^2 = 0.03$
- Interaction between run and group: F[2,42] = 0.7, p = 0.50, $\eta^2 = 0.03$

Details on: Task effect on baseline areas

ANOVA on baseline areas with block, session and group as factors:

- Main effect of block: F[1.4,60.1] = 1.0, p = 0.36, $\eta^2 = 0.02$
- Main effect of session: F[2,84] = 0.8, p = 0.44, $\eta^2 = 0.02$
- Main effect of group: (F[2] = 0.01, p = 0.99, $\eta^2 < 0.01$
- Interaction between block and group: F[2.8,60.1] = 0.2, p = 0.90, $\eta^2 = 0.01$
- Interaction between block and session and group: F[6.3, 132.3] = 1.0, p = 0.46, $\eta^2 = 0.04$

Details on: Task effect on heart rates

ANOVA on heart rates with block, session and group as factors:

- Main effect of block: $F[2,72] = 6.4$, $\mathbf{p < 0.01}$, $\eta^2 = 0.15$
- Main effect of session: $F[2,72] = 0.3$, $p = 0.78$, $\eta^2 = 0.01$
- Main effect of group: $F[2] = 1.3$, $p = 0.28$, $\eta^2 = 0.07$
- Interaction between block and group: $F[4,72] = 0.8$, $p = 0.51$, $\eta^2 = 0.04$
- Interaction between block and session and group: $F[8,144] = 1.3$, $p = 0.20$, $\eta^2 = 0.07$

Posthoc tests: Contrasts between blocks:

- Pre-task block vs. task block: $F[1,36] = 10.9$, $\mathbf{p < 0.01}$, $\eta^2 = 0.23$
- Task block vs. post-task block: $F[1,36] = 6.9$, $\mathbf{p < 0.05}$, $\eta^2 = 0.16$
- Pre-task block vs. post-task block: $F[1,36] = 0.9$, $p = 0.34$, $\eta^2 = 0.03$.

Details on: Task effects on pain ratings

ANOVA on pain ratings with block, session and group as factors:

- Main effect of block: $F[1.3, 55.1] = 112.2$, $\mathbf{p < 0.001}$, $\eta^2 = 0.73$
- Main effect of session: $F[2,84] = 3.2$, $p = 0.73$, $\eta^2 = 0.01$
- Main effect of group: $F[2] = 0.83$, $p = 0.44$, $\eta^2 = 0.04$
- Interaction between block and group: $F[2.6, 55.1] = 1.01$, $p = 0.36$, $\eta^2 = 0.05$
- Interaction between block and session and group: $F[6.1,127.0] = 0.42$, $p = 0.91$, $\eta^2 = 0.02$

Posthoc tests: Contrasts between blocks:

- Pre-task block vs. task block: $F[1,42] = 121.0$, $\mathbf{p < 0.001}$, $\eta^2 = 0.74$
- Task block vs. post-task block: $F[1,42] = 74.7$, $\mathbf{p < 0.001}$, $\eta^2 = 0.64$
- Pre-task block vs. post-task block: $F[1,42] = 15.6$, $\mathbf{p < 0.001}$, $\eta^2 = 0.27$

Details on: correlations

Correlations[$] between suppression of RIII areas during task blocks and suppression of pain ratings during task blocks:

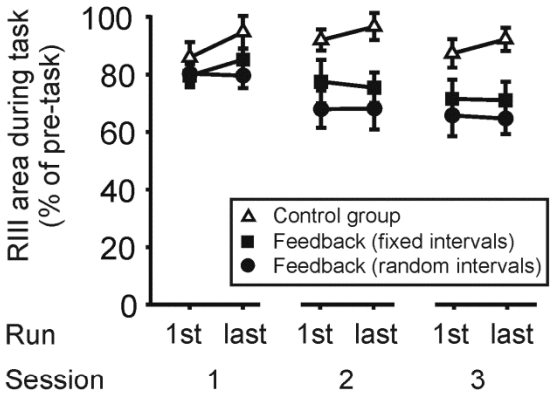
	Control	Feedback with fixed intervals	Feedback with random intervals
Session 1	r = 0.08, p = 0.79	r = 0.52, **p < 0.05**	r = 0.65, **p < 0.01**
Session 2	r = -0.01, p = 0.96	r = 0.77, **p < 0.001**	r = 0.62, **p < 0.05**
Session 3	r = 0.21, p = 0.45	r = 0.37, p = 0.18	r = -0.10, p = 0.74

Correlations[$] between suppression of RIII areas and suppression of heart rates during task blocks:

	Control	Feedback with fixed intervals	Feedback with random intervals
Session 1	r = -0.06, p = 0.83	r = 0.05, p = 0.88	r = 0.03, p = 0.93
Session 2	r = 0.11, p = 0.69	r = 0.44, p = 0.13	r = -0.08, p = 0.79
Session 3	r = 0.12, p = 0.68	r = 0.16, p = 0.61	r = 0.46, p = 0.10

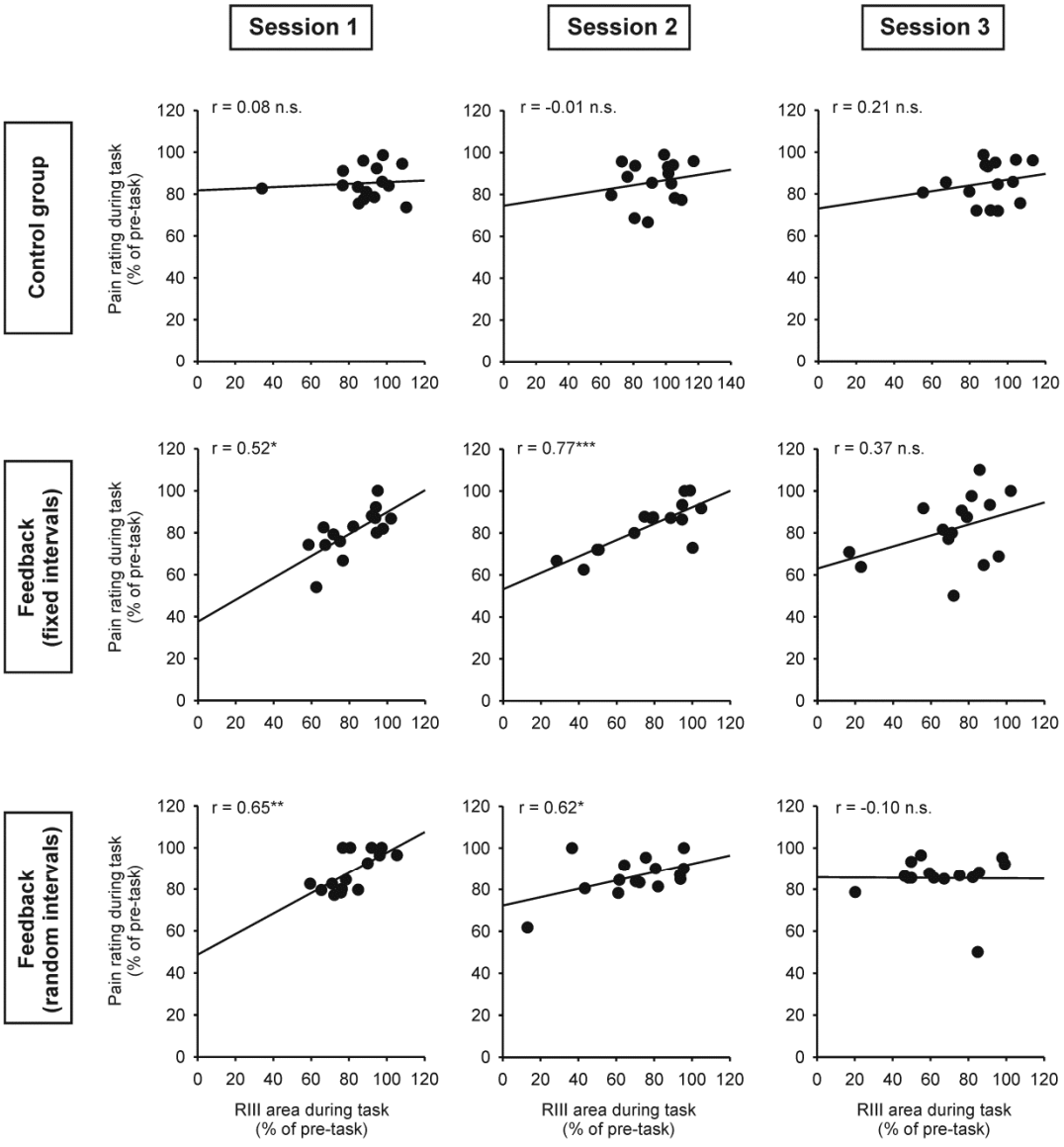
[$]Correlations were performed between RIII areas during the task block, in percent of (RIII areas during pre-task block + RIII areas during post-task block)/2 and pain ratings during the task block, in percent of (pain ratings during pre-task block + pain ratings during post-task block)/2. Correlations with heart rates were performed accordingly.

Fig. S1



Comparison of RIII areas during the task block, in the first and the last run within each feedback or control session. Values are mean ± SEM, expressed in % of the RIII area during the pre-task block.

Fig. S2



Correlations between RIII suppression and reduction of pain ratings during task blocks. Data from all three groups within the three sessions are shown (n = 15 for each group). Regression lines are displayed. Pearson's r is given. *, $p < 0.05$; **, $p < 0.01$, ***, $p < 0.001$; n.s., not significant.

Supplementary Table 1. RIII areas and pain ratings during task and post-task blocks (in percent of the pre-task block)

	Control (n = 15)		Feedback with fixed intervals (n = 15)		Feedback with random intervals (n = 15)	
	Task	Post-task	Task	Post-task	Task	Post-task
	RIII areas (% of pre-task ± SD)					
Session 1	88 ± 18	100 ± 7	82 ± 14	101 ± 10	81 ± 13	103 ± 8
Session 2	93 ± 15	107 ± 14	77 ± 24	105 ± 12	69 ± 24	103 ± 10
Session 3	90 ± 15	102 ± 9	72 ± 24	103 ± 9	66 ± 22	102 ± 8
	Pain intensity ratings (% of pre-task ± SD)					
Session 1	85 ± 8	98 ± 5	80 ± 11	96 ± 10	89 ± 9	99 ± 3
Session 2	86 ± 10	98 ± 5	83 ± 12	96 ± 7	86 ± 10	98 ± 5
Session 3	85 ± 10	99 ± 5	82 ± 16	96 ± 9	85 ± 11	99 ± 6

Supplementary Table 2. Baseline areas during pre-task, task and post-task blocks

	Control (n = 15)			Feedback with fixed intervals (n = 15)			Feedback with random intervals (n = 15)		
	Pre-task	Task	Post-task	Pre-task	Task	Post-task	Pre-task	Task	Post-task
	Baseline areas ± SD [μV×ms] (% of pre-task ± SD)								
Session 1	41.9 ± 14.6	47.0 ± 20.0 (111 ± 20)	45.9 ± 18.0 (108 ± 12)	28.6 ± 6.2	29.6 ± 6.9 (103 ± 11)	29.2 ± 6.7 (103 ± 15)	31.3 ± 7.9	31.4 ± 8.7 (102 ± 16)	32.1 ± 9.3 (106 ± 24)
Session 2	43.1 ± 17.9	44.7 ± 18.6 (104 ± 16)	45.0 ± 19.2 (104 ± 12)	32.8 ± 13.5	31.9 ± 11.2 (99 ± 9)	30.0 ± 6.2 (96 ± 10)	32.1 ± 11.4	32.2 ± 14.1 (101 ± 14)	31.8 ± 12.0 (99 ± 19)
Session 3	49.1 ± 17.5	47.7 ± 16.2 (99 ± 11)	47.8 ± 15.2 (99 ± 7)	28.3 ± 5.5	28.5 ± 6.1 (101 ± 12)	31.0 ± 7.3 (112 ± 28)	33.0 ± 15.2	32.0 ± 11.2 (98 ± 15)	31.6 ± 13.9 (96 ± 14)

Please note that both raw values and percentages are averages of individual averages across the 3-5 runs per session. Therefore, percentages of pre-task values given in the table are not identical to percentages of pre-task values calculated from the session average raw values.

Supplementary Table 3. Heart rates during pre-task, task and post-task blocks

	Control (n = 15)			Feedback with fixed intervals (n = 15)			Feedback with random intervals (n = 15)		
	Pre-task	Task	Post-task	Pre-task	Task	Post-task	Pre-task	Task	Post-task
	Heart rates ± SD [bpm] (% of pre-task ± SD)								
Session 1	71.6 ± 9.2	70.6 ± 8.9 (98 ± 7)	70.2 ± 9.1 (98 ± 5)	69.3 ± 7.6	67.7 ± 7.5 (98 ± 7)	68.1 ± 6.3 (99 ± 8)	70.1 ± 7.4	68.4 ±8.0 (97 ± 4)	70.7 ± 8.5 (101 ± 7)
Session 2	71.5 ± 9.7	71.2 ± 10.5 (100 ± 6)	71.5 ± 8.2 (100 ± 7)	67.8 ± 8.6	66.7 ± 7.2 (99 ± 5)	68.7 ± 7.7 (102 ± 6)	71.7 ± 9.6	69.1 ± 9.4 (97 ± 6)	69.7 ± 9.3 (97 ± 5)
Session 3	72.3 ± 8.9	71.6 ± 9.4 (99 ± 10)	72.1 ± 8.8 (100 ± 3)	71.2 ± 9.1	67.7 ± 7.5 (95 ± 6)	70.6 ± 7.4 (100 ± 9)	69.4 ± 9.2	68.8 ± 9.6 (99 ± 5)	71.0 ± 9.0 (103 ± 4)

Please note that both raw values and percentages are averages of individual averages across the 3-5 runs per session. Therefore, percentages of pre-task values given in the table are not identical to percentages of pre-task values calculated from the session average raw values.

Supplementary Table 4. Strategies used for RIII reflex reduction (feedback groups) or pain reduction (control group) in session 3

	Control group		Feedback (fixed intervals)		Feedback (random intervals)	
	% of subjects	RIII area (% of pre-task ± SD)	% of subjects	RIII area (% of pre-task ± SD)	% of subjects	RIII area (% of pre-task ± SD)
Mental imagery	52%	93 ± 20%	40%	74 ± 27%	26%	60 ± 17%
Relaxation	34%	88 ± 15%	27%	61 ± 26%	28%	61 ± 31%
Focusing on bar reduction	-	-	12%	72 ± 15%	32%	65 ± 21%
Mental arithmetic/work	7%	89 ± 6%	19%	82 ± 12%	9%	79 ± 16%
Ignoring pain	7%	84 ± 8%	3%	98 ± 1%	5%	96 ± 8%

2.2 Learned control over spinal nociception reduces supraspinal nociception as quantified by late somatosensory evoked potentials

Summary

This study with healthy subjects showed that, under true RIII feedback, the use of cognitive-emotional strategies also reduces late, presumably nociceptive SEP amplitudes, in parallel with the RIII reflex. Further, the results showed that true RIII feedback, as compared to sham feedback, is necessary to achieve RIII reflex reduction, and that lower motor neuron excitability is not affected during RIII reflex modulation.

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JS:	Programming and implementation of the experimental software.
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Learned control over spinal nociception reduces supraspinal nociception as quantified by late somatosensory evoked potentials

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We have recently shown that subjects can learn to use cognitive-emotional strategies to suppress their spinal nociceptive flexor reflex (RIII reflex) under visual RIII feedback, and proposed that this reflects learned activation of descending pain inhibition. Here, we investigated if learned RIII suppression also affects supraspinal nociception, and if previous relaxation training increases success. Subjects were trained over three sessions to reduce their RIII size by self-selected cognitive-emotional strategies. Two groups received true RIII feedback (with/without previous relaxation training) and a sham group received false feedback (15 subjects per group). RIII reflexes, late somatosensory evoked potentials (SEPs) and F-waves were recorded and pain intensity ratings collected. Both true feedback groups achieved significant ($p < 0.01$) but similar RIII suppression (to 79 ± 21 and 70 ± 17 % of control). SEP amplitude (100-150 ms after stimulation) was reduced in parallel with the RIII size ($r = 0.57$, $p < 0.01$). In the sham group, neither RIII size nor SEP amplitude were significantly reduced during feedback training. Pain intensity was significantly reduced in all three groups, and also correlated with RIII reduction ($r = 0.44$, $p < 0.01$). F-wave parameters were not affected during RIII suppression. The present results show that learned RIII suppression also affects supraspinal nociception as quantified by SEPs, although effects on pain ratings were less clear. Lower motor neuron excitability as quantified by F-waves was not affected. Previous relaxation training did not significantly improve RIII feedback training success.

Keywords: nociceptive flexor reflex; biofeedback; descending pain inhibition; attentional and emotional pain modulation

1. Introduction

Activation of endogenous descending pain inhibitory systems is a promising approach to pain treatment. It has repeatedly been reported that descending pain inhibition can be activated by cognitive and emotional processes such as distraction and positive emotions [5,34,35]. In a recent study, we showed that healthy young subjects can learn to use cognitive-emotional strategies to suppress their nociceptive flexor reflex (RIII reflex), when given feedback about this parameter [28]. The RIII reflex is considered a measure of spinal nociceptive transmission [30,32]. Our hypothesis therefore is that during RIII feedback training, subjects learn to use cognitive-emotional strategies to activate their descending pain inhibitory systems, which might be an interesting new option for pain treatment [28]. However, it remains to be shown that learned suppression of the RIII reflex indeed affects supraspinal nociception. To address this issue, in the present study we recorded late somatosensory evoked potentials (SEPs) in parallel with the RIII reflex. SEPs evoked by the RIII-inducing nociceptive electrical stimulus to the sural nerve have been extensively investigated [12,14]. They reflect stimulus-related activity in several brain regions known to be involved in pain processing, including primary somatosensory cortex, parietal operculum, insula, and parts of the anterior cingulate and prefrontal cortices [2,14]. Changes in RIII size are not always associated with concordant changes of nociceptive SEP components [9,17], underlining the need to show that learned RIII suppression indeed implies a reduction of supraspinal nociception.

In addition, as the RIII is a motor response, it is important to exclude that subjects learn to reduce their lower motor neuron excitability instead of activating their descending pain inhibition. Therefore, we recorded F-waves as a measure of motor neuron excitability. A further issue is that receiving RIII feedback may be associated with an expectancy to be able to control the RIII reflex and concurrent pain sensation. This expectancy might by itself activate the descending pain inhibition, as happens during placebo analgesia [5]. In the

present study we therefore added a group with sham (false) feedback. Moreover, because our previous study suggested that subjects may successfully use relaxation techniques to achieve RIII suppression, we also investigated if previous relaxation training enhances RIII feedback training success. Finally, because electrical pain stimuli are difficult to rate for many subjects, we also tested the effect of the learned RIII-reducing strategies on heat pain ratings.

In summary, three groups of 15 subjects were investigated. The *true feedback group* received feedback on their RIII reflex during training. The *relaxation+true feedback* group participated in a relaxation training before starting RIII feedback training. The *sham feedback group* received false feedback, corresponding to the RIII time course of a successfully trained subject. SEPs were recorded in parallel to the RIII reflex. F-waves were recorded from successful subjects during an additional session. The effect of learned RIII-reducing strategies on heat pain ratings was tested at the end of each training session.

2. Methods

2.1. Participants

The study was conducted in accordance with the Declaration of Helsinki and was approved by the local ethics committee of the University of Munich. Prior to participation, subjects gave written informed consent. Healthy volunteers were recruited by advertisements on the university campus. Participants had to meet the following criteria: (1) age between 18 and 40 years, (2) not actively practising any relaxation technique, (3) sufficient knowledge of the German language, (4) no neurological, internal or psychiatric conditions, (5) no intake of medication other than oral contraceptives, (6) no history of chronic pain, (7) no nicotine, alcohol or drug abuse and (8) recording of a stable RIII reflex over 8 min at subjectively acceptable pain levels during a preparatory session (criteria for a stable RIII reflex were: RIII area $\geq$ 200 μV·ms throughout the recording, no failures, average area of the last 6 reflexes

within 50 to 150% of the average area of the first 6 reflexes). A total of 45 subjects were randomized to the three groups (sham feedback, true feedback, relaxation+true feedback). Age and sex distribution were similar among groups (sham: 23 ± 3 years [mean ± SD], 8 females; true feedback: 23 ± 4 years, 9 females; relaxation+true feedback: 26 ± 7 years, 9 females).

2.2. Study design (see Fig. 1)

The study design and experimental setup was similar to that used in the previous study [28]. Feedback training was performed in three sessions (8.5 ± 9.2 days apart), which consisted of one 8-min stabilization run (not analyzed), one SEP painless run, two sham or true feedback training runs, and one heat pain rating run (Fig. 1). Each experimental session lasted 1.5 to 2 hours. Subjects in the relaxation+true feedback group participated in a ~4-weeks relaxation training before starting feedback training. On days of assessment, participants were free of acute pain and had not taken analgesics within the preceding 24 hours. Stimulus intensity was set at ~130% of RIII reflex threshold, usually evoking a mild to moderate pain sensation (20-40 on the NRS [0-100]). The RIII reflex was evoked every 8-12 s (randomized stimulation intervals). SEPs evoked by the electrical stimulus were recorded in parallel. In addition, SEPs in response to stimuli slightly below pain threshold were recorded for 8 min (SEP painless run, no RIII reflexes evoked).

Each feedback training run consisted of four consecutive 2-min blocks (Fig. 1, 12 stimuli per block). Block 1 was a run-in phase again used for reflex stabilization (stabilization block, not analyzed). Blocks 2 and 4 were the pre- and post-task blocks. Block 3 was the task block. Pain intensity of the electrical stimuli used to evoke the RIII reflex was rated on a numerical rating scale (NRS) from 0 (no pain) to 100 (strongest pain imaginable) at the end of each block (as an average rating of the preceding five stimuli).

During feedback training runs, subjects in the true feedback groups received visual feedback on their RIII reflex size on a separate screen (Fig. 1). Subjects in the sham feedback group thought they received feedback on their RIII reflex size, but instead received feedback corresponding to the reflex size course of a subject from the previous study [28] who had successfully learned to suppress his reflex to an average of 74% of control. During task blocks, indicated on the feedback screen by green bars and a blinking downward arrow, subjects had the task to use cognitive and/or emotional strategies with the aim to reduce their RIII reflex size. For the other three blocks, they had the instruction to merely observe their RIII size without trying to change it.

All subjects received identical instructions regarding strategies that might be useful for reduction of RIII size: (1) recalling pleasant experiences, (2) making plans for work or leisure, (3) mental arithmetic, (4) ignoring pain. Subjects in the relaxation+true feedback group were invited to also try using the progressive relaxation technique (in the form without muscle contraction). However, subjects were encouraged to modify these strategies as needed or to use different strategies depending on the success they achieved in RIII reduction. At the end of each true or sham feedback run, subjects reported on the strategy they had used (listed in Supplementary Table 1).

Subjects who achieved an average suppression of the RIII reflex during the task block of <80% of the pre-task block were invited to participate in an additional session for F-wave recording. 13 of 16 eligible subjects participated.

2.3. Relaxation training

Subjects randomized to the relaxation group received a 1.5-hour instruction from a psychologist experienced in relaxation training. Progressive muscle relaxation (PMR) has been repeatedly shown to be effective in pain disorders [25] and to be able to increase RIII reflex thresholds [16]. Because muscle contraction will interfere with reflex recording,

subjects were instructed in both the classical form of PMR (with muscle contraction) and the form without muscle contraction as described by Öst (1987) as part of his applied relaxation program [24]. Subjects received written instructions and a training CD and practised at home for about a month, with the instruction to increasingly use the form without muscle contraction. Compliance was monitored with a training diary. Subjects rated their inner tension on a NRS (ranging from 0 = no tension at all to 100 = strongest tension imaginable) before and after every relaxation training session. The AT symptom questionnaire, which has been validated for assessing the effect of relaxation training on six categories of symptoms (fatigue, inner tension, performance difficulties, psychophysiological dysregulation, pain, and lack of self-determination) [22] was administered before and after the relaxation training period.

2.4. Recording and quantification of the RIII reflex

The RIII reflex was evoked and recorded from the lower limb as described previously [27,28] according to established techniques [3,8,36]. Subjects were tested in a quiet room devoid of visual distractors, 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 (Medtronic, Natus, Langenfeld, 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 10000 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 [36]. 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 feedback run (integrated rectified signal between 85 and 25 ms before stimulation). RIII areas were then expressed in % of the average pre-task RIII area because of large individual differences in RIII areas that were due to both, inherent individual differences in RIII size and technical improvement of recording conditions during the study.

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.

2.5. SEP recording and quantification

SEPs evoked by sural nerve stimulation were recorded from the vertex (Cz) with reference to the forehead (Fpz). Bipolar recordings with frontal reference have been used before in recording of nociceptive potentials, e.g. contact-heat or laser evoked potentials [19,20]. In the present study, Fpz was preferred over linked earlobes as reference because (1) recordings were less prone to artefacts and (2) this montage reduces the contribution of brain areas involved in pain modulation (prefrontal cortex, anterior cingulate cortex), because these areas are located between the recording electrodes [14], and therefore increases the relative contribution of afferent nociceptive areas (primary somatosensory cortex, parietal operculum, insula) to the signal. As we were especially interested in determining the effect of RIII feedback training on ascending nociception, this was advantageous.

The signal was sampled 90 ms before to 410 ms after stimulation, amplified up to 10000-fold, band-pass filtered at 0.5-500 Hz and stored for offline analysis using the Keypoint Portable. Trials were rejected when the amplitude exceeded 250 μV [10], visually inspected for artifacts, baseline corrected (with the baseline taken between 5 and 65 ms before stimulation), and averaged within recording blocks (pre-task, task, post-task). For technical reasons (the two channels of the amplifier were used for RIII and SEP recording), an electrooculogram was not recorded. However, in an identical setting, less than 5% of the trials have been contaminated by artifacts from the eyes [18], and it has been shown previously that when short inter-stimulus intervals are used and extensive habituation to the stimulus is allowed (by first recording stimulus-response-curves, responses to non-painful stimuli), no startle response is evoked from the orbicularis oculi muscle [13].

2.6. Heat pain rating

Heat stimuli were applied using a Pathway system (Medoc, Israel) equipped with a 30*30 mm ATS thermode from a baseline temperature of 32°C. The target temperature was individually tailored to evoke a pain intensity of 30-40 on the NRS [0-100] and maintained for 5 s. Ascending and descending ramps were 5°C/s. The heat pain stimulus was applied three times with an interstimulus interval of 90 s, to three different locations on the lateral calf (sural nerve territory). During the second application (task block), subjects used their best RIII-suppressing strategy. After each heat pain stimulus, subjects rated the stimulus pain intensity on the NRS [0-100]. No feedback was provided during heat pain experiments.

2.7. F-wave recording and quantification

F-waves were recorded from 13 selected subjects (see above) in an additional session using standard procedures [6]. F-waves were evoked by stimulating the tibial nerve at the ankle (0.1 ms, intensity supramaximal for evoking the M-response, 0.5 Hz) and recorded from the

abductor hallucis muscle (band-pass filter 0.1-10 kHz, amplification up to 10000-fold, stored for offline analysis using the Keypoint Portable). A standard 4-block RIII feedback training run was performed and 20 consecutive F-waves were recorded at the middle of each block. Signals were baseline corrected and the peak-to-peak amplitude and area of F-waves were quantified within a 25 ms analysis window starting at the onset of the earliest F-wave, and averaged within blocks [23]. F-wave persistence was quantified for every block by counting the number of F-waves reaching a peak-to-peak amplitude of ≥20 μV.

2.8. Statistics

Statistical analyses were performed using the Statistical Package of Social Sciences (SPSS), Version 21 for Windows. Values are mean ± standard deviation unless indicated otherwise. $P < 0.05$ was considered statistically significant.

A repeated measures analysis of variance (ANOVA) followed by the appropriate subordinate ANOVAs and post-hoc Bonferroni tests was performed on RIII areas, SEP amplitudes and electrical and heat pain ratings, with block (pre-task, task and post-task) and session as within-subject factors and group as between-subject factor. Because of large individual differences in RIII areas, RIII areas were expressed in percent of pre-task values in the text and tables. However, these values are not suitable for ANOVA because of zero variance in the pre-task block. For statistical purposes, we therefore used values given as percent of (pre-task block + post-task block)/2. A repeated measures ANOVA with block as within-subject factor was performed on F-wave amplitudes, areas and persistence. Pearson's correlation coefficient was used to test for correlations.

3. Results

3.1. Relaxation training

Subjects randomized to the relaxation+true feedback group participated in a relaxation training. These subjects on average practiced for 726 ± 272 minutes on 32 ± 8 days before starting RIII feedback training. There was a significant reduction of inner tension [0-100] after relaxation training (from 40 ± 15 to 27 ± 11, data from all training units pooled, $T[14] = 7.6$, $p < 0.001$). The AT symptom questionnaire total score (before: 24.8 ± 11.3, after: 19.2 ± 11.0) and the inner tension and dysregulation subscales were significantly reduced after the relaxation training (all $p < 0.05$).

3.2. Baseline areas

Baseline electromyogram areas measured during the RIII feedback training are shown in Table 1. Statistical analysis revealed that there was no main effect of block ($F[41,2] = 0.5$, $p > 0.5$) or group ($F[42,2] = 2.3$, $p > 0.1$) and no interaction between both ($F[84,4] = 1.8$, $p > 0.1$). There were also no main effects of or interactions with session (not shown).

3.3. RIII areas

RIII thresholds were on average 8.4 ± 2.7 mA, without significant group differences: $F[2] = 0.5$, $p = 0.6$). Results of RIII areas during the RIII feedback training are shown in Table 1 and Fig. 2. Statistical analysis revealed that both true feedback groups but not the sham feedback group achieved RIII suppression during the task block that increased over sessions.

More specifically, ANOVA on RIII areas with block (pre-task, task, post-task), session and group as factors revealed a main effect of block ($F[2,41] = 52.4$, $p < 0.001$) and a significant interaction between group and block ($F[4,84] = 7.9$, $p < 0.001$).

Posthoc analysis revealed that both true feedback groups achieved a significant reduction of RIII areas during the task block with complete recovery after the end of the task (pre vs. task

and task vs. post: all $F[1,14] > 14.0$, $p < 0.01$; pre vs. post: all $F[1,14] < 0.3$, $p > 0.6$). In the sham group, there was no RIII reduction during task (pre vs. task: $F[1,14] = 2.2$, $p = 0.16$), but a small increase in RIII areas during the post-task block (task vs. post and pre vs. post: both $F[1,14] > 4.8$, $p < 0.05$).

Consistently, RIII suppression during task block was significantly stronger in both true feedback groups than in the sham feedback group (effect of group: $F[2,42] = 10.3$, $p < 0.001$; sham vs. true feedback: $F[1,28] = 9.2$, $p < 0.01$; sham vs. relaxation+true feedback: $F[1,28] = 28.6$, $p < 0.001$). The relaxation+true feedback group achieved a larger RIII suppression during task than the true feedback group (to 70.3 vs. 79.3 % of pre-task), but the difference did not reach significance ($F[1,28] = 1.7$, $p = 0.2$).

Within the true feedback groups, there was a significant training effect of RIII suppression over sessions (main effect of session: $F[2,27] = 3.3$, $p < 0.05$). The average RIII area during task (in % of pre-task) was 80 ± 23%, 74 ± 21% and 71 ± 21% in sessions 1, 2 and 3. Posthoc testing revealed a significantly larger RIII suppression in session 3 compared to session 1 ($T[29] = 2.6$, $p < 0.05$) but not between sessions 1 and 2 or sessions 2 and 3 ($p > 0.1$). There was no significant interaction between session and group ($F[2,27] = 0.2$, $p = 0.8$).

3.4. SEPs

Results are shown in Table 1 and Fig. 3. Average waveforms evoked by suprathreshold stimulation (see Fig. 3) consistently showed (1) a positive peak around 45 ms, (2) a negative peak around 75 ms, (3) a negative peak around 120 ms and (4) a broad positive peak around 260 ms. Inspection of Fig. 3A revealed that the negative SEP peak around 120 ms behaved similar to RIII areas (reduction during task block in the true feedback groups but not in the sham group). Comparison of the grand average SEP curves evoked by non-noxious (slightly below pain threshold) and noxious stimulation is shown in Fig. 3B. In contrast to earlier SEP components (positive peak around 45 ms and negative peak around 75 ms), the negative peak

around 120 ms was distinctly increased during noxious stimulation compared to non-noxious stimulation, and is therefore likely to reflect nociceptive SEP components. We therefore defined an analysis window to pick up this peak (100-150 ms, the upper limit of 150 ms was chosen because the positive peak around 260 ms made significant contributions to the signal after this time point), called the potential $SEP_{100\text{-}150}$, and measured mean amplitudes within this window.

Statistical analysis revealed a significant effect of block ($F[2,39] = 8.7$, $p < 0.001$) and interaction between block and group ($F[4,80] = 3.0$, $p < 0.05$) for the $SEP_{100\text{-}150}$ mean amplitude. Posthoc analysis revealed that both true feedback groups achieved a significant reduction of $SEP_{100\text{-}150}$ amplitudes during the task block with complete recovery after the end of the task (pre vs. task: all $F[1,14] > 14.5$, $p < 0.01$, task vs. post: all $F[1,14] > 6.3$, $p < 0.05$; pre vs. post: all $F[1,14] < 3.6$, $p > 0.05$). In the sham group, there were no $SEP_{100\text{-}150}$ differences between blocks (all $F[1,14] < 0.3$, $p > 0.6$). $SEP_{100\text{-}150}$ reduction during task was significantly larger in both true feedback groups compared to the sham group (both $F[1,28] > 10.0$, $p < 0.01$) but not different between the two true feedback groups ($F[1,28] = 0.6$, $p = 0.4$). There was no significant effect of session on the task $SEP_{100\text{-}150}$ amplitudes, also if the analysis was limited to the true feedback groups ($F[2,25] = 0.3$, $p = 0.7$).

3.5. Electrical pain rating

Pain ratings decreased during task blocks and largely recovered during post-task blocks, but this was independent of group and session (Table 1, Fig. 2). More specifically, there was a main effect of block ($F[2,41] = 49.3$, $p < 0.001$), due to a significant reduction of pain ratings during task compared to pre-task and post-task (both $F[1,42] > 57.2$, $p < 0.001$) and a small residual reduction of pain ratings during the post-task block compared to the pre-task block ($F[1,42] = 5.0$, $p < 0.05$). There was no interaction between block and group ($F[4,84] = 1.1$, $p = 0.36$). There was also no effect of session or interaction with session (all $F < 1.2$, $p > 0.3$).

3.6. Heat pain rating

Electrical pain stimuli are difficult to rate for many subjects. Therefore, we also tested the effects of the individual strategies used for RIII reduction on heat pain ratings, during a separate experimental run (Fig. 1). Pain ratings decreased during task blocks and recovered during post-task blocks, but this was independent of group and session (Table 1). More specifically, there was a main effect of block ($F[2,41] = 28.4$, $p < 0.001$), due to a significant reduction of pain ratings during task compared to pre- and post-task (both $F[1,42] > 35.1$, $p < 0.001$) and a small but significant increase of pain ratings during the post-task block compared to the pre-task block ($F[1,42] = 10.6$, $p < 0.01$). There was no interaction between block and group ($F[4,84] = 1.9$, $p = 0.1$). There was also no effect of session or interaction with session (all $F < 2.5$, $p > 0.05$).

3.7. F-waves

F-waves were recorded during an additional session in 13 subjects who had a successful suppression of the RIII reflex during sessions 1 to 3 (mean <80% of pre-task). RIII suppression during task block reached 57 ± 20% of the pre-task block, similar to the value reached by the same subjects in session 3 (62 ± 14%). There was no significant effect of block on F-wave amplitude, area or persistence (results and statistics in Table 2).

3.8. Correlations between RIII reduction and other parameters

For analysis of correlations, all variables were expressed in percent of their average values in the pre-task block. There were significant correlations (illustrated in Fig. 4) between RIII suppression during task and reduction of electrical pain ratings during task ($r = 0.44$, $p < 0.01$) and $SEP_{100\text{-}150}$ reduction during task ($r = 0.57$, $p < 0.001$) but only a trend for significance for the correlation with heat pain reduction during task ($r = 0.27$, $p = 0.07$).

3.9. Strategies used for RIII reduction

Strategies used for RIII reflex reduction during the task block are listed in Supplementary Table 1. Subjects usually tested different strategies before finding the one that worked best for them. In the relaxation+true feedback group, a large part of subjects tried using the progressive relaxation technique without muscle contraction as learned during relaxation training. In the other groups, mental imagery (vivid recall of pleasant experiences) was the most frequently used technique.

4. Discussion

Main results of the present study are that (1) subjects receiving true feedback but not sham feedback learned to suppress their RIII reflex using cognitive-emotional strategies, and this was paralleled by a reduction in late SEP amplitude, and partially paralleled by a reduction in pain ratings, (2) motor excitability as estimated by F-waves was not affected during learned RIII suppression and (3) previous relaxation training did not significantly improve the RIII feedback training success.

This corroborates the results of our previous study [28], showing that healthy young volunteers can learn to use cognitive-emotional strategies to suppress their RIII reflex if they receive feedback on their RIII size. It further extends the previous results by showing that if subjects were given false (sham) feedback, they did not learn RIII suppression. This rules out the possibility that RIII suppression is due to expectancy processes related to the feedback procedure itself.

4.1. Strategies used for RIII reduction and effects of previous relaxation training

Previous work has shown that cognitive-emotional strategies such as hypnosis, relaxation techniques and distraction can modulate the RIII reflex in different directions, and interindividual differences seem to be large [7,16,21,27]. The presently used feedback setup

allowed participants to try several strategies and choose the one that worked best for them. Interestingly, mental arithmetic, which was proposed as a possible strategy, but may have little effect on RIII size [33], was used by few subjects in the true feedback groups but by many subjects in the sham feedback group (Supplementary table 1).

Part of the subjects participated in relaxation training before RIII feedback training, and many indeed tried the progressive relaxation technique for RIII suppression. However, although the relaxation+true feedback group achieved a larger average RIII suppression (to 70%) than the true feedback group (79%), the difference was not significant. Possibly, a more intensive relaxation training would have been more effective. Also, AT symptom questionnaire scores were rather low in the present (healthy) sample, likely reflecting a good inherent capacity for relaxation. Therefore, relaxation training might have a larger effect on RIII feedback training success in chronic pain patients.

4.2. Lack of effect on F-waves

We propose that during RIII feedback training, subjects learned to voluntarily activate their descending pain inhibitory systems. However, in addition to nociceptive primary afferents and interneurons, the RIII reflex also relies on spinal motor neurons, so that subjects might have learned to reduce their RIII reflex by reducing their lower motor neuron excitability. The present results show that persistence, amplitude and area of F-waves were not changed during learned RIII suppression. Although F-waves reflect the excitability of only a small portion of the total motor neuron pool, they seem to be sensitive for detection of inhibitory influences on motor neuron excitability [4,23,29]. Therefore, the absence of any changes in F-wave parameters suggests that learned RIII suppression did not work by reducing lower motor neuron excitability.

4.3. Interpretation of SEP recordings

SEPs were recorded in an attempt to determine the effect of learned RIII reduction on ascending nociception. Under the present recording conditions (vertex with frontal reference), average waveforms evoked by suprathreshold stimulation (Fig. 3) consistently showed (1) the P45, likely generated in SI [1], (2) a negative peak around 75 ms, likely corresponding to N100 or central negativity CN70-100, generated by SI and the somatosensory association area [14,15], (3) a negative peak around 120 ms, likely corresponding to centro-temporal negativity (CTN) 100-180, generated by the parietal operculum (SII) and insula [14]) and (4) a broad positive peak around 260 ms (P260), generated by the inferior parietal cortex and the supplementary somatosensory area [14]. The present recording conditions were chosen to increase the relative contribution of predominantly afferent nociceptive areas (primary somatosensory cortex, parietal operculum, insula) and reduce the contribution of areas involved in pain modulation (anterior cingulate cortex, prefrontal cortex). Consistently, the negative peak around 150 ms (N150) which is generated by the anterior cingulate and medial frontal cortex [14] was not seen in the present SEP recordings.

The present results show that the $SEP_{100\text{-}150}$ component was reduced in parallel to the RIII reflex size. The $SEP_{100\text{-}150}$ component likely corresponds to the CTN100-180 described by Dowman, which is evoked by activity in the insula and parietal operculum and has been shown to be pain-related [11,14]. Consistently, $SEP_{100\text{-}150}$ was markedly increased during noxious stimulation as compared to non-noxious stimulation (Fig. 3B). Insula and parietal operculum are brain regions typically showing pain-related activity in human imaging studies, which is reduced during analgesia and activation of descending pain inhibitory systems (e.g. during placebo analgesia) [2,5]. Unfortunately, there is no way to prove if an SEP component reflects the amount of nociceptive information reaching the brain or rather the way the brain processes the nociceptive information arriving from the spinal cord. However, we found clear correlations between changes in RIII areas and $SEP_{100\text{-}150}$ amplitudes, suggesting that the

$SEP_{100-150}$ at least partially reflected ascending nociception. It must also be considered that the $SEP_{100-150}$ component might be contaminated by the negative peak around 75 ms, which is thought to partially reflect non-noxious activity [14,15]. In addition, a previous study has shown an SEP increase at ~150 ms during distraction from pain. This activity, however, has been localized to the anterior cingulate cortex [10], which likely contributes little to the SEP signal in the present study.

In conclusion, the parallel reduction of $SEP_{100-150}$ and RIII size seen in the present study suggests that learned RIII suppression does reduce those components of spinal nociception involved in ascending nociception, decreasing nociceptive input to the brain. However, it must be kept in mind that part of the $SEP_{100-150}$ reduction seen in the present study may also be due to altered processing of nociceptive information reaching the brain.

4.4. Effects on pain ratings

Similar to our previous results [28], effects on pain ratings of electrical and heat pain stimuli were less clear. Although changes in pain ratings correlated with changes in RIII size, pain ratings were reduced not only in the true feedback groups but also in the sham group, which did not achieve a significant RIII reduction during feedback training. This might in part reflect an expectation bias in the sham group due to false feedback pretending a rather successful RIII suppression. Alternatively, the pain rating results may indicate that learned RIII reduction is not related to reduced pain intensity. Several previous studies have also found poor correlations between RIII size and pain ratings [26,33]. It has been proposed that RIII reflex size may preferentially reflect the activity of deep dorsal horn interneurons, not directly related to ascending nociception [31]. In addition, RIII reflex activity is driven mainly by primary afferent Aδ-fibres, not reflecting nociceptive information conveyed by C-fibres [30,32]. Moreover, the RIII feedback training, in addition to its effects on spinal nociception, may also have direct effects on supraspinal nociception. All this might lead to dissociation

between RIII size and pain ratings. A further point of criticism is that reductions of pain ratings during the task block were small (by about 15%). In addition, in order to not disturb concentration during the task phase, we collected pain ratings retrospectively at the end of each block, which may have introduced a bias. In conclusion, further studies in patients will have to show if a significant reduction of acute or chronic clinical pain can be achieved by RIII feedback training.

4.5. Limitations

Major limitations of the study are already discussed above and include (1) the fact that the $SEP_{100-150}$ reduction may reflect either reduction of ascending nociception or altered brain processing of ascending nociception, (2) the open question why pain ratings were also reduced in the sham group that did not show RIII or $SEP_{100-150}$ reduction, (3) the fact that pain ratings were collected retrospectively at the end of each block, (4) the fact that reductions of pain ratings achieved during RIII feedback training were small (by about 15%) and (5) the use of a single supervised relaxation training session, followed by self-training which may have limited the success of relaxation training. Moreover, (6) pain intensity ratings of the single electrical stimuli during RIII recording were relatively low (around 20 [0-100]), partly due to the fact that subjects were required to undergo a large number of these stimuli during an experimental session. It remains to be shown if results can be generalized to conditions with stronger pain, as encountered in chronic pain conditions.

4.6. Conclusion

Results of the present study suggest that during RIII feedback training, subjects learn to use cognitive-emotional strategies to activate their descending pain inhibitory systems, and that this likely affects the amount of nociceptive information reaching the brain, as quantified by

SEPs. Additional studies will have to show if a significant reduction of acute or chronic clinical pain can be achieved by RIII feedback training.

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Fig. 1

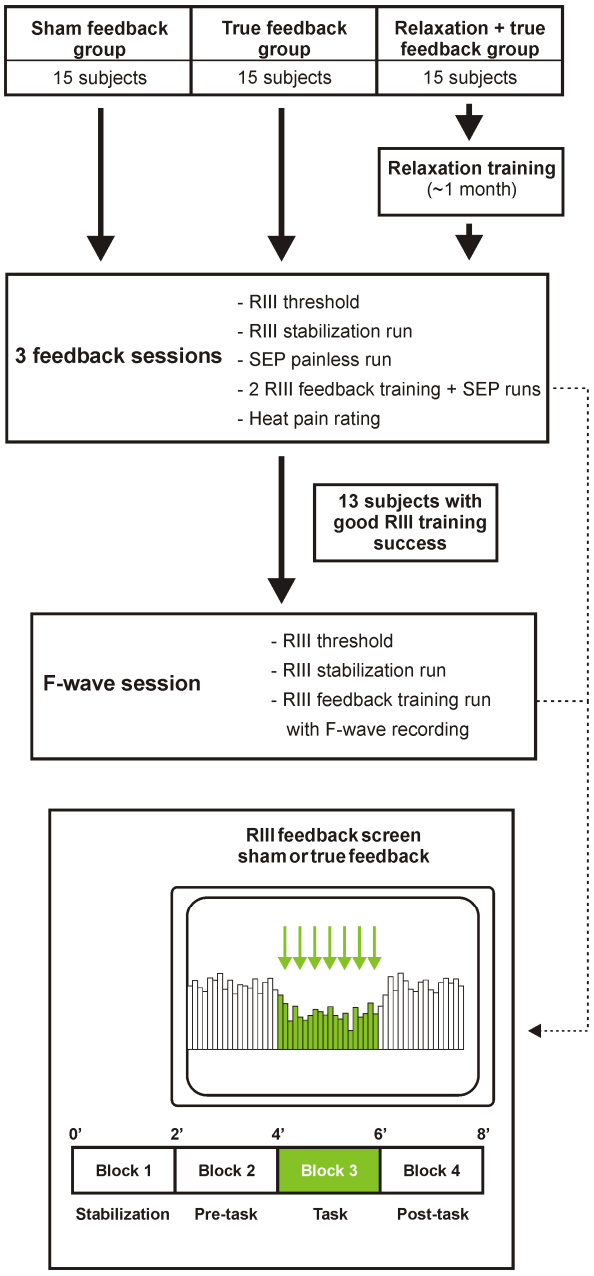

Fig. 1. Outline of experimental procedures. A total of 45 subjects, randomized into three groups, attended three true or sham feedback training sessions. The relaxation+true feedback group participated in a 1-month relaxation training before starting the feedback training. RIII stabilization runs consisted of RIII recording for 8 min without feedback or task. SEP painless runs consisted of SEP (somatosensory evoked potential) recording in response to stimulation slightly below pain threshold for 8 min. No RIII reflexes were evoked by this stimulation

intensity. During feedback runs, stimulation intensity was set to ~130% RIII threshold. Subjects in the true feedback groups received feedback on their RIII reflex areas on a separate screen immediately (<2s) after each stimulus. Each feedback training run consisted of four ~2min blocks as displayed in the lower part of the figure. During the task block (block 3) subjects tried to reduce RIII reflex size by using cognitive or emotional strategies of their choice. Two training runs were performed per session. In the sham feedback group, procedures and instructions were identical, but subjects inadvertently received a false feedback, corresponding to the RIII reflex area course of a subject who had successfully learned to suppress his RIII reflex in the previous study [28]. SEPs were recorded in parallel to the RIII reflex during feedback runs. 13 subjects who had an average RIII reduction during task block of <80% of pre-task participated in an additional session where F-waves were recorded at the middle of each block.

Fig. 2

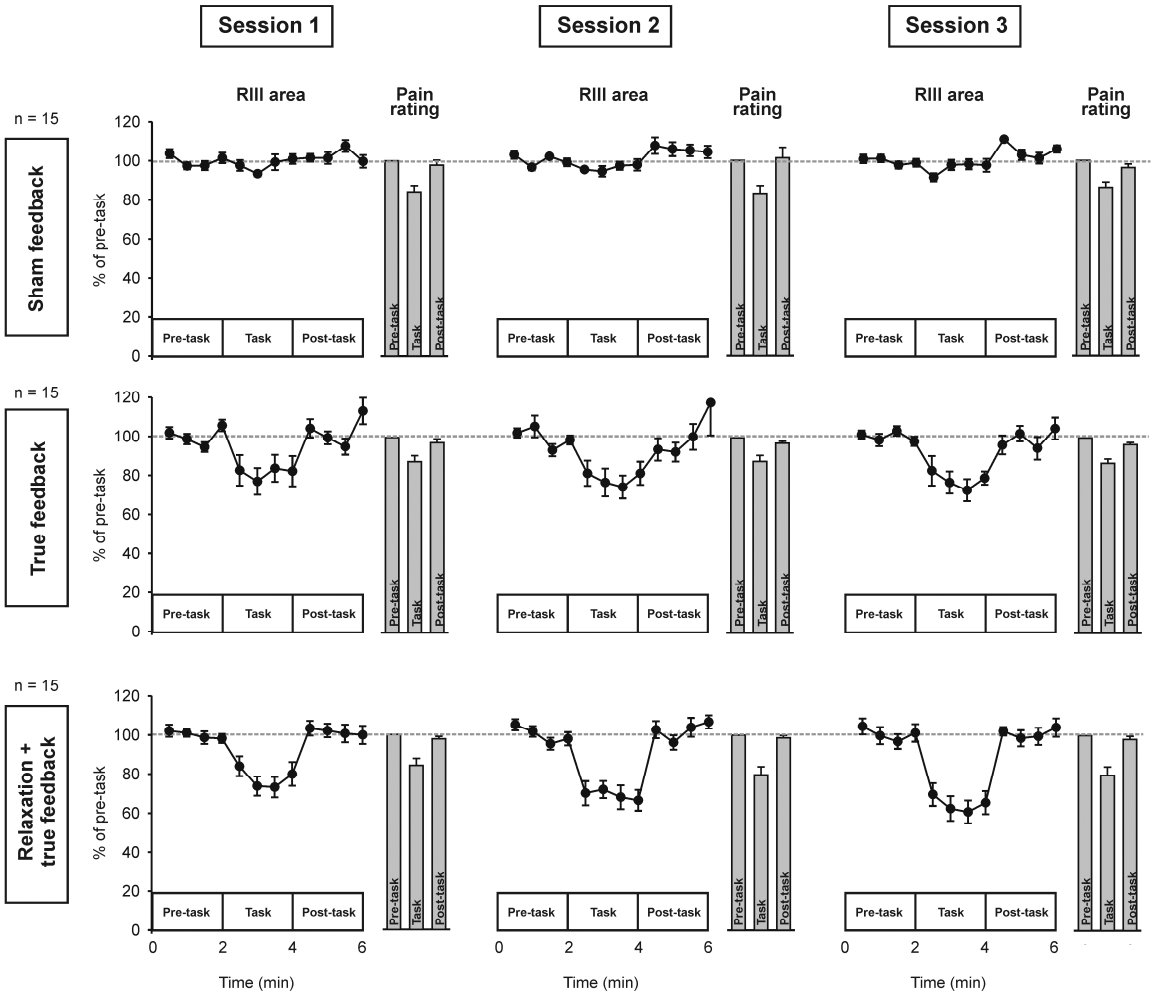

Fig. 2. Effects of feedback training on RIII areas and pain intensity ratings in the three sessions. RIII areas and pain intensity ratings are illustrated as % of the pre-task block, averaged within the respective session and group. For RIII areas, each data point illustrates a ~30s epoch, consisting of 3 reflexes. Pain intensity ratings were obtained once at the end of each block, as an average rating of the preceding five stimuli. Values are mean ± SEM.

Fig. 3

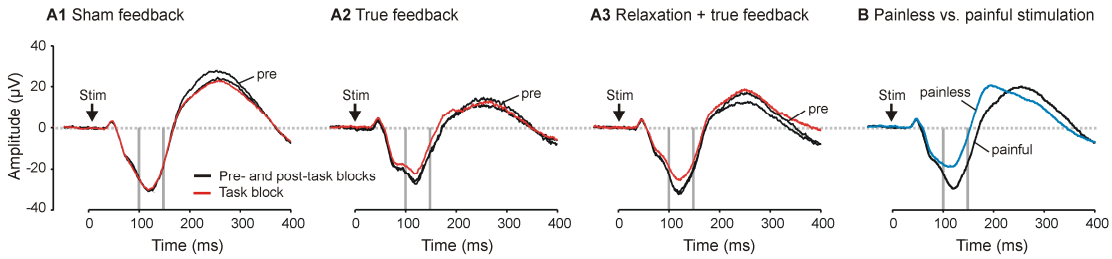

Fig. 3. Effects of feedback training on somatosensory evoked potentials (SEPs). A. SEP traces of pre-task, task and post-task blocks are shown (grand averages over sessions 1 to 3) for every group. Task block traces are marked in red. **B.** SEP traces evoked by stimulation slightly below pain threshold (painless, blue) and at ~130% RIII threshold (during RIII feedback training, painful, black) are shown (averages over all pre-task blocks and all subjects). Grey lines mark the 100-150 ms analysis window used to quantify the $SEP_{100\text{-}150}$ amplitude.

Fig. 4

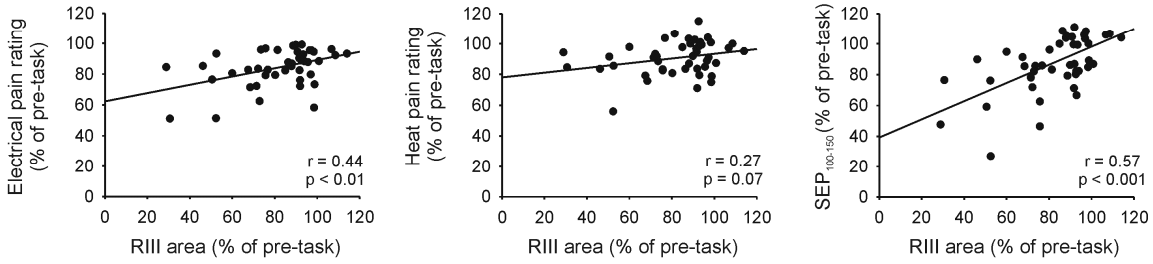

Fig. 4. Correlations between RIII areas, pain ratings and SEP amplitudes. All values are task block values expressed in % of pre-task and represent averages of sessions 1 to 3.

Table 1. Baseline areas, RIII areas, pain ratings and SEP amplitudes during pre-task, task and post-task blocks

	Sham feedback (n = 15)			True feedback (n = 15)			Relaxation + true feedback (n = 15)		
	Pre-task	Task	Post-task	Pre-task	Task	Post-task	Pre-task	Task	Post-task
Baseline areas [μV*ms]	64.0 ± 18.8	65.5 ± 17.0	60.5 ± 14.1	49.1 ± 13.7	52.8 ± 15.8	52.5 ± 16.3	59.9 ± 17.5	59.3 ± 16.0	62.7 ± 19.5
RIII areas [% of pre-task]	100	96.8 ± 8.7	104.6 ± 7.4	100	79.3 ± 20.5	101.0 ± 10.2	100	70.3 ± 17.1	101.4 ± 6.3
$SEP_{100-150}$ amplitude [μV]	26.2 ± 11.2	25.7 ± 9.8	25.9 ± 11.7	21.8 ± 6.7	17.3 ± 7.6	20.7 ± 7.6	28.0 ± 13.0	22.3 ± 10.3	26.9 ± 13.4
Pain intensity ratings (electrical) [0-100]	19.9 ± 8.3	17.4 ± 8.3	19.3 ± 8.5	28.9 ± 15.9	25.7 ± 15.6	28.2 ± 15.9	23.7 ± 7.6	19.5 ± 7.7	23.2 ± 7.4
Pain intensity ratings (heat) [0-100]	33.1 ± 10.9	30.2 ± 11.4	35.4 ± 11.3	38.2 ± 9.4	35.6 ± 8.6	40.1 ± 8.7	34.6 ± 9.0	29.7 ± 6.9	34.9 ± 8.4

Averages over sessions 1 to 3 are shown. Values are mean ± SD. RIII areas are given in % of pre-task values because there were large individual differences in RIII areas, that are partly inherent to the RIII reflex, and partly were due to technical improvement of recording conditions during the study.

Table 2. F-wave results (n = 13).

	Pre-task	Task	Post-task	Statistics
Peak-to-peak amplitude [μV]	267 ± 146	268 ± 155	275 ± 182	$F[2,11] < 0.1$; $p = 0.98$
Area [μV*ms]	776 ± 392	766 ± 420	826 ± 573	$F[2,11] = 0.2$; $p = 0.83$
Persistence [%]	100 ± 0	99 ± 3	100 ± 0	$F[2,11] = 1.9$; $p = 0.17$

F-wave measurements were obtained during an additional session from 13 subjects who during sessions 1 to 3 had achieved a mean RIII suppression to 80% or less (6 from the true feedback group, 7 from the relaxation+true feedback group).Values are mean ± SD. Results of the ANOVA with block (pre-task, task, post-task) are given. There was no significant effect of block.

Supplementary Table 1. Strategies used for RIII reflex reduction.

	Sham feedback	True feedback	Relaxation + true feedback
Mental imagery	44 %	38 %	19 %
Relaxation (progressive relaxation without muscle contraction[$])	0 %	0 %	56 %
Relaxation (other)	9 %	24 %	22 %
Focusing on bar reduction	3 %	18 %	2 %
Mental arithmetic/work	44 %	10 %	1 %
Ignoring pain	0 %	10 %	0 %

Strategies used in sessions 1 to 3 were pooled. [$]as learned during relaxation training preceding RIII feedback training

2.3 Learned control over spinal nociception in patients with chronic back pain

Summary

The results of this study revealed that also patients with chronic back pain can learn to suppress their spinal nociception under RIII feedback training, likely by deliberate activation of descending pain-inhibiting systems. Moreover, patients with chronic back pain exhibited improved descending pain inhibition, and reduced chronic pain and anxiety after the RIII feedback training. However, the efficacy of true versus sham RIII feedback remained inconclusive in the patients.

Reference:

Learned control over spinal nociception in patients with chronic back pain. **Krafft, S.**, Göhmann, H. D., Sommer, J., Straube, A., Ruscheweyh, R. *European Journal of Pain* 21(9):1538-1549. Copyright © 2017, European Pain Federation – EFIC®, Wiley. doi: 10.1002/ejp.1055.

Author contributions:

RR, AS:	Conception and design.
JS:	Programming and implementation of the experimental software.
HDG:	Screening and provision of patients, technical help.
SK:	Assessment of participants, data acquisition.
SK, RR:	Data analysis and interpretation, manuscript writing.

All authors critically revised the manuscript.

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ORIGINAL ARTICLE

Learned control over spinal nociception in patients with chronic back pain

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Conflicts of interest
The authors have no conflicts of interest to declare.

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Abstract

Background: Descending pain inhibition suppresses spinal nociception, reducing nociceptive input to the brain. It is modulated by cognitive and emotional processes. In subjects with chronic pain, it is impaired, possibly contributing to pain persistence. A previously developed feedback method trains subjects to activate their descending inhibition. Participants are trained to use cognitive-emotional strategies to reduce their spinal nociception, as quantified by the nociceptive flexor reflex (RIII reflex), under visual feedback about their RIII reflex size. The aim of the present study was to test whether also subjects with chronic back pain can achieve a modulation of their descending pain inhibition under RIII feedback.
Methods: In total, 33 subjects with chronic back pain received either true (n = 18) or sham RIII feedback (n = 15), 15 healthy control subjects received true RIII feedback.
Results: All three groups achieved significant RIII suppression, largest in controls (to 76 ± 26% of baseline), intermediate in chronic back pain subjects receiving true feedback (to 82 ± 13%) and smallest in chronic back pain subjects receiving sham feedback (to 89 ± 14%, all $p < 0.05$). However, only chronic pain subjects receiving true feedback significantly improved their descending inhibition over the feedback training, quantified by the conditioned pain modulation effect (test pain reduction of baseline before training: to 98 ± 26%, after: to 80 ± 21%, $p < 0.01$).
Conclusion: Our results show that subjects with chronic back pain can achieve a reduction of their spinal nociception and improve their descending pain inhibition under RIII feedback training.
Significance: Subjects with chronic back pain can learn to control their spinal nociception, quantified by the RIII reflex, when they receive feedback about the RIII reflex.

1. Introduction

Descending pain inhibition is a powerful endogenous pain control system that originates in the brainstem and descends to the spinal dorsal horn. There, it inhibits nociceptive transmission by releasing serotonin and noradrenalin and thus reduces nociceptive input to the brain (Millan, 2002; Ossipov et al., 2010). Higher brain regions like the prefrontal or anterior cingulate cortex anatomically and functionally target the origin of the descending pain

inhibition (Bingel and Tracey, 2008). These regions are involved in cognitive and emotional processing, making descending pain inhibition susceptible to cognitive-emotional modulation (Tracey and Mantyh, 2007; Ruscheweyh et al., 2011; Bushnell et al., 2013). For example, distraction or positive emotions lead to a net activation of descending pain inhibition, reducing pain perception, whereas negative emotions or pain catastrophizing deactivate the system (Rhudy and Meagher, 2001; Sullivan et al., 2001; Ruscheweyh et al., 2013). Based on this knowledge, we have developed a feedback method to train subjects to use cognitive-emotional strategies to activate their descending pain inhibition (Ruscheweyh et al., 2015b). The polysynaptic spinal nociceptive flexor reflex (RIII reflex), a measure of spinal nociceptive transmission (Skljarevski and Ramadan, 2002; Sandrini et al., 2005), was used as the feedback parameter. In recent experiments, healthy young adults were able to learn to use cognitive-emotional strategies to reduce their RIII reflex under visual feedback about the reflex size, most likely by activating their descending pain inhibitory system. Subjects receiving sham feedback did not learn RIII reduction. Learned RIII reduction was associated with reduction of experimental pain perception and the amplitude of late somatosensory evoked potentials (SEPs), suggesting reduced transmission of nociceptive input to supraspinal regions (Ruscheweyh et al., 2015a; Ruscheweyh et al., 2015b).

Compared to healthy controls, subjects with chronic pain have repeatedly been shown to exhibit impaired descending pain inhibition, which might be one reason for pain persistence (Yarnitsky, 2010). Thus, improving descending pain inhibition in subjects with chronic pain is a promising target for pain therapy (Yarnitsky, 2015).

The aim of the present study therefore was to test whether also subjects with chronic back pain are able to achieve reduction of their spinal nociception under RIII feedback training, and whether this has effects on the descending pain inhibition as quantified by the conditioned pain modulation (CPM) paradigm. We included three groups of participants: (1) patients with chronic back pain who received true RIII feedback, (2) patients with chronic back pain who received sham (false) RIII feedback and (3) healthy controls who received true RIII feedback. Effects on RIII reflex size, experimental pain perception and SEPs were quantified. CPM was assessed before and after the feedback training. The main focus of our study was to determine whether subjects with chronic back pain can achieve a suppression of their spinal nociception. However, as part of an exploratory analysis regarding possible clinical use of the feedback training, we also assessed back pain intensity, anxiety and depression before, after and 3 months after feedback training in the two chronic back pain groups and, for comparison, in subjects with chronic back pain who did not participate in the feedback training.

2. Methods

2.1 Participants

The study was conducted in accordance with the World Medical Association Declaration of Helsinki and approved by the local ethics committee of the Ludwig-Maximilians-University Munich (No. 080-12). Before participation, subjects gave written informed consent. Recruitment and experiments were performed between February 2014 and November 2015 at the community hospital Traunstein, Germany. Follow-up interviews were held until March 2016.

For participation in the feedback training, the RIII reflex of all participants had to be stable (area $\geq$ 200 μV•ms throughout the recording) for at least 8 min at subjectively acceptable pain levels during a preparatory session. Patients with chronic back pain had to show persistent back pain for $\geq$ 6 months, rated $\geq$ 2 on the numerical rating scale [NRS (0–10; 0 = no pain, 10 = strongest imaginable pain)]. Healthy controls did not show any history of chronic pain. For more detailed inclusion criteria, see Methods S1.

In all, 55 patients with chronic back pain attended the preparatory session (Fig. S1). Patients were excluded when the stimulus was too painful or the RIII reflex not stable. However, some of these patients participated in interviews about back pain intensity and questionnaires about anxiety and depression to assess the natural course of the chronic pain disorder. This group was called the 'no feedback training' patient group (Fig. S1). Patients with a stable RIII reflex were randomly assigned to one of the two feedback groups. All patients were blinded to group assignment, and received identical instructions. Blinding of the experimenter was not possible for technical reasons. In all, 18 patients in the true feedback group and 15 patients in the sham feedback group completed the feedback training (Fig. S1). Before their participation in our study, 9 of the 18 true feedback and 11 of the 15 sham feedback

patients had participated in the 5-week multidisciplinary chronic pain treatment programme of the pain clinic.

As our previous RIII feedback training studies investigated only young healthy controls (23 ± 4 and 26 ± 7 years) (Ruscheweyh et al., 2015a; Ruscheweyh et al., 2015b), we included age-matched older healthy controls in the present study. In all, 18 healthy controls attended the preparatory session. In total, 15 of them showed a stable RIII reflex and were included in the true feedback control group (Fig. S1).

The sample size of 15 subjects per group with complete data was chosen based on our previous studies that found significant group differences at this sample size (Ruscheweyh et al., 2015a; Ruscheweyh et al., 2015b).

For more detailed subject disposition, see Figure S1.

2.2 Study design

The study design (Fig. 1) was similar to that used in our previous work (Ruscheweyh et al., 2015a; Ruscheweyh et al., 2015b). On the assessment days, controls were free of acute pain and had not taken pain medication within the preceding 2 days. Patients had taken their usual medication, including pain medication.

During the preparatory session (baseline), CPM (see 2.5), back pain intensity, anxiety and depression (see Methods S2) were assessed. Only participants with a stable RIII reflex (see 2.1) were selected for the feedback training sessions.

Feedback training started at the earliest 1 day after the preparatory session (Fig. S1). The three feedback training sessions were conducted with intervals of 5 ± 3 days between sessions. At each feedback session, RIII reflex and pain thresholds were determined (Fig. 1). Stimulus intensity was set at ~150% of the reflex threshold, usually evoking a mild pain sensation (average pain intensity of 2.6 ± 1.4 on the NRS [0–10]). The reflex was evoked at randomized stimulation intervals every 8–12 s, and SEPs were recorded in parallel. Three 8-min runs were performed: one RIII stabilization run (not analysed) and two feedback runs. Each feedback run consisted of four consecutive 2-min blocks of 12 stimuli each (Fig. 1). Block 1 was a stabilization block (not analysed). Blocks 2 and 4 were the pre-task (baseline) and post-task blocks. Block 3 was the task block. The pain intensity of the electrical stimuli used to evoke the RIII reflex was rated at the end of each block (as an average rating of the preceding five stimuli) on the NRS [0–10].

During feedback runs, subjects in the true feedback groups received correct visual feedback about their RIII reflex size on a separate screen in the form of bars immediately (< 2 s) after the electrical stimulus (Fig. 1). Subjects in the sham feedback group saw the reflex size course of a subject who had successfully suppressed her reflex to an average of 74% of baseline in a previous study (Ruscheweyh et al., 2015b). Subjects were instructed to use cognitive and/or emotional strategies to reduce their RIII reflex size during task blocks, indicated on the feedback screen by green bars and a blinking downward arrow. For the other three blocks, they were told to merely observe their RIII size, without trying to change it. All subjects received identical instructions regarding potentially useful strategies: (1) recalling pleasant experiences, (2) mental arithmetic, (3) making plans for work or leisure and (4) ignoring pain. However, subjects were encouraged to modify these strategies as needed or to use different strategies depending on their achieved success in RIII reduction. At the end of each feedback run, subjects reported the strategy they had used (see Table S2).

At the end of the third feedback session, CPM, back pain intensity, anxiety and depression were assessed again.

Three months after their last appointment, all patients were contacted again for follow-up interviews about back pain intensity, and questionnaires about anxiety and depression (Fig. S1).

The primary outcome measure was the suppression of the RIII reflex size achieved during RIII feedback training. Secondary outcome measures were RIII feedback training effects on experimental pain ratings, SEP amplitudes and the CPM effect. To obtain hints towards a potential clinical usefulness of RIII feedback training, we performed an explorative analysis on measures of anxiety, depression and clinical pain.

2.3 RIII reflex recording and quantification

The RIII reflex was evoked and recorded from the lower limb as described previously (Ruscheweyh et al., 2011; Ruscheweyh et al., 2015b) according to established techniques (Willer, 1977; Bouhassira et al., 2003) (Methods S3). Stimulation and recording were performed with a Keypoint® Portable EMG System (Natus, Planegg, Germany). Electrical constant current stimulation was delivered to the retromalleolar pathway of the sural nerve with a bipolar

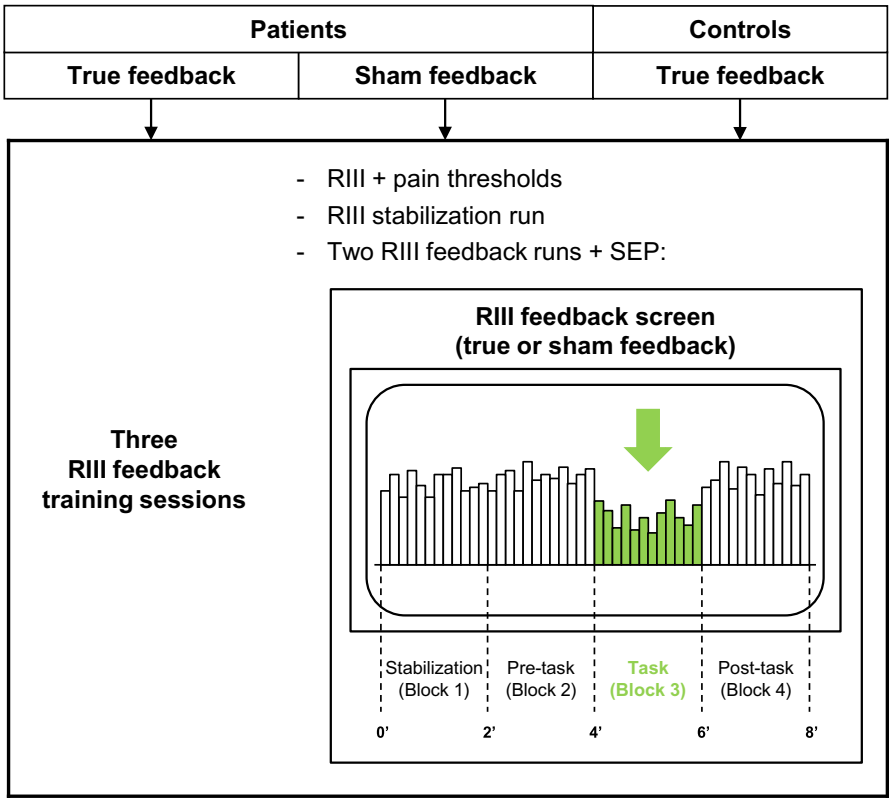

Figure 1 Outline of the study design. Patients were randomly assigned to the true or sham feedback patient group. All controls received true feedback. At the beginning of each of the three feedback training sessions, RIII and pain thresholds were evaluated. For RIII runs, stimulation intensity was set to ~150% of the RIII threshold and the RIII reflex was evoked at randomized intervals (every 8–12 s) for 8 min. An RIII stabilization run was conducted without feedback or task. During the two RIII feedback runs, true feedback subjects received feedback about their RIII reflex areas on a separate screen immediately (< 2 s) after each stimulus. Sham feedback patients received false feedback, corresponding to the RIII reflex area course of a subject who had successfully learned to suppress her RIII reflex in a previous study (Ruscheweyh et al., 2015b). RIII reflexes and SEPs were recorded in parallel during feedback runs. Each RIII feedback run consisted of four consecutive 2-min blocks, with 12 stimuli per block. During the task block (block 3), subjects had the task to reduce the RIII reflex size (displayed on the feedback screen) using the cognitive or emotional strategies of their choice.

bar electrode (23 mm distance between poles; Natus, Langenfeld, Germany). Each stimulus consisted of five pulses of 1 ms duration, separated by 4 ms, resulting in a total duration of 21 ms. Electromyographical responses were recorded from the ipsilateral biceps femoris (short head) by two 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 (20–500 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, with an onset latency between 90 and 120 ms after stimulation (Willer, 1977). For quantification of the RIII reflex response, the reflex area was obtained by integrating the rectified 60 ms signal window between 90 and 150 ms after stimulation and corrected for the average baseline area of the corresponding feedback run (integrated rectified 60 ms signal window between 90 and 30 ms before stimulation). For the assessment of RIII thresholds, stimulus–response curves were recorded by increasing stimulation intensity in 0.5 mA steps starting from 2.0 mA. In accordance with the procedure described in more detail previously (Ruscheweyh et al., 2011), the RIII threshold was defined as the stimulus intensity that first evoked a reflex response exceeding a baseline-corrected area of 100 μV•ms. The mean of three RIII thresholds was calculated. Subjects rated the pain intensity of each stimulus on the NRS [0–10]. The pain threshold was determined as the stimulus intensity that first evoked a painful sensation (defined as an NRS rating > 0).

2.4 Somatosensory evoked potential recording and quantification

SEPs were recorded from the vertex (Cz) with reference to the forehead (Fpz) in response to the electrical sural nerve stimulation used to evoke the RIII reflex (Methods S4). The signal was sampled 90 ms before to 410 ms after stimulation, amplified up to 10,000-fold, band-pass filtered at 0.5 to 500 Hz and stored for offline analysis using the Keypoint® Portable. Trials were rejected when the amplitude exceeded 100 μV (Dowman, 2004), visually inspected for artefacts, baseline-corrected (with the baseline taken between 0 and 60 ms before stimulation) and averaged within recording blocks (pre-task, task, post-task).

In accordance with our previous procedure (Ruscheweyh et al., 2015a), we defined an analysis window to pick up the 100–150 ms peak, which is related to activity in the insula and parietal operculum (Dowman et al., 2007), called the potential $SEP_{100–150}$, and measured mean amplitudes within this window.

2.5 Conditioned pain modulation

The CPM paradigm was performed as described previously (Pud et al., 2009; Yarnitsky, 2010). The test stimulus was a heat pain stimulus, applied to the volar forearm using a TSA II NeuroSensory Analyzer (Medoc, Ramat Yishai, Israel) equipped with a 30 × 30 mm thermode from a baseline temperature of 32 °C. The target temperature was individually tailored to evoke a pain intensity between 5 and 6 on the NRS [0–10]. The average target temperature was 48.2 ± 1.5 °C. Ascending and descending ramps were 8 °C per second and the time at target temperature was 30 s. The conditioning stimulus was a cold pressure test on the contralateral hand for 60 s. The hand was immersed up to the wrist, with fingers separated, in a cold water bath with a temperature individually tailored to evoke a pain intensity of ≥ 3 after 30 s. The average water temperature was 7.0 ± 4.4 °C.

The test stimulus (heat) was first administered alone. After a 5-min break, the conditioning stimulus (cold water) was started. 30 s after the conditioning stimulus onset, the test stimulus was applied again, simultaneously with the conditioning stimulus. The first and second test stimuli were applied to two different locations on the volar forearm, randomized between subjects, and the test stimulus pain intensity was rated on the NRS every 10 s.

2.6 Statistical analysis

Statistical analyses were performed using the Statistical Package of Social Sciences (SPSS Statistics; IBM, Ehningen, Germany), version 23 for Windows. Values are mean ± SD unless otherwise indicated. $p < 0.05$ was considered statistically significant. Analysis of variance (ANOVA) and chi-square tests were used to compare RIII thresholds, pain thresholds, age and sex between groups, as appropriate. Repeated-measures ANOVA followed by the appropriate subordinate ANOVAs and post-hoc Bonferroni tests were performed on RIII areas, SEP amplitudes and electrical pain ratings, with block (pre-task, task and post-task) and session as within-subject factors and group as between-subject factor. Partial η^2 is given as a measure of effect size. Paired t-tests were used to compare CPM effects, back pain ratings and HADS scores at baseline and after feedback training. Differences of means and 95% confidence intervals (95% CI) are given. Pearson's r was used to test for correlations.

3. Results

A total of 36 patients with chronic back pain and 15 healthy controls were initially recruited for the RIII feedback training. Three patients assigned to the true feedback group were excluded during training (see Fig. S1) and therefore not analysed. Thus, a total of 48 subjects (18 true feedback patients, 15 sham feedback patients, 15 true feedback controls) completed three feedback training sessions. Age and sex distributions were similar among groups (true feedback patients: 52 ± 9 years, 12 females; sham feedback patients: 53 ± 9 years, 10 females; controls: 52 ± 11 years, 8 females; age: F[2] = 0.1, $p = 0.95$; sex: $\chi^2[2] = 0.8$, $p = 0.7$). An additional 14 patients excluded from feedback training because of unstable reflexes were used as controls for the natural course of back pain (56 ± 6 years, 11 females).

Strategies used for RIII reflex reduction are stated in Results S1 and Table S2. RIII areas and experimental pain ratings were analysed in all 48 subjects. In part of the subjects, reproducible SEP amplitudes could not be obtained, leaving 14 true feedback and 10 sham feedback patients, and 11 true feedback controls for SEP analysis. Due to technical problems, the CPM test could not be performed in two patients of the true feedback group. Thus, 16 true feedback patients, 15 sham feedback patients and 15 true feedback controls were included in the CPM analysis.

3.1 RIII areas

Effects of the feedback training on RIII areas are shown in Table 1 and Figure 2. RIII suppression during the task block was largest in the true feedback controls (to 76 ± 26% of pre-task), intermediate in the true feedback patients (to 82 ± 13%) and smallest in the sham feedback patients (to 89 ± 14%). Statistical analysis showed that all three groups achieved a significant reduction of RIII areas during the task block with complete recovery in the post-task block (true feedback patients: $F[2,16] = 13.8$, $p < 0.001$; sham feedback patients: $F[2,13] = 4.2$, $p < 0.05$; controls: $F[2,13] = 8.1$, $p < 0.01$; post-hoc tests pre-task vs. task and task vs. post-task: all $p \leq 0.05$; pre-task vs. post-task: all $p > 0.4$). For group comparison, repeated-measures ANOVA was performed with group, block and session as factors. There was a significant interaction between block and session ($F[4,42] = 5.0$, $p = 0.001$), due to an increase in RIII suppression from session to session (session 1: 89 ± 18%, session 2: 81 ± 21%, session 3: 78 ± 24%) that was not dependent on group ($F[8,86] = 1.4$, $p = 0.22$). Moreover, there was a trend for a significant interaction between block and group ($F[4,90] = 2.4$, $p = 0.054$). Subordinate ANOVAs showed significant interactions between block and group when the sham feedback patients and the true feedback controls were compared ($F[2,27] = 3.6$, $p < 0.05$), but not when the true feedback patients were compared with either of the other groups (sham feedback patients: $F[2,30] = 1.7$, $p = 0.18$; controls: $F[2,30] = 1.6$, $p = 0.22$). For more detailed statistical analysis, see Results S2.

3.2 Experimental pain ratings

Pain ratings significantly decreased during the task block to 77 ± 11% ($F[2,13] = 16.8$, $p < 0.001$) of pre-task in the true feedback controls and to 85 ± 13% ($F[2,16] = 22.2$, $p < 0.001$) and 83 ± 10% ($F[2,13] = 20.0$, $p < 0.001$) in the true and sham feedback patients, respectively, with recovery during the post-task block, without group differences (interaction between block and group: $F[4,90] = 0.2$, $p = 0.96$; Table 1, Fig. 2 and Results S3). Similar to the RIII area results, there was a significant interaction between block and session ($F[4,42] = 4.9$, $p = 0.001$), which indicated an increase in pain intensity suppression from session to session (see Results S3 for details).

3.3 Somatosensory evoked potentials

SEP results are displayed in Table 1 and Figure 3. During task blocks, the mean SEP amplitude

Table 1 RIII areas, experimental pain intensity ratings and SEP amplitudes during pre-task, task and post-task blocks.

	Patients						Controls		
	True feedback			Sham feedback			True feedback		
	Pre-task	Task	Post-task	Pre-task	Task	Post-task	Pre-task	Task	Post-task
RIII areas [μV • ms]	916.4 ± 588.4	765.7 ± 551.3	894.5 ± 580.0	684.3 ± 363.0	608.7 ± 336.7	676.2 ± 383.0	1006.8 ± 544.7	756.0 ± 542.8	1008.1 ± 570.7
Pain intensity ratings [0–10]	2.8 ± 1.4	2.4 ± 1.3	2.8 ± 1.3	2.7 ± 1.6	2.3 ± 1.4	2.7 ± 1.6	2.2 ± 1.3	1.7 ± 1.1	2.1 ± 1.4
$SEP_{100-150}$ amplitudes [μV]	15.2 ± 7.2	13.0 ± 7.3	14.7 ± 7.7	16.5 ± 6.2	15.1 ± 4.9	14.3 ± 6.1	15.3 ± 5.1	13.7 ± 7.5	14.8 ± 5.8

Averages over all three sessions are shown, with two runs per session. Values are given as mean ± SD. RIII area and pain intensity rating values include 18 true feedback patients, 15 sham feedback patients and 15 true feedback controls. $SEP_{100–150}$ amplitude values include 14 true feedback patients, 10 sham feedback patients and 11 true feedback controls. SD: standard deviation, SEP: somatosensory evoked potential.

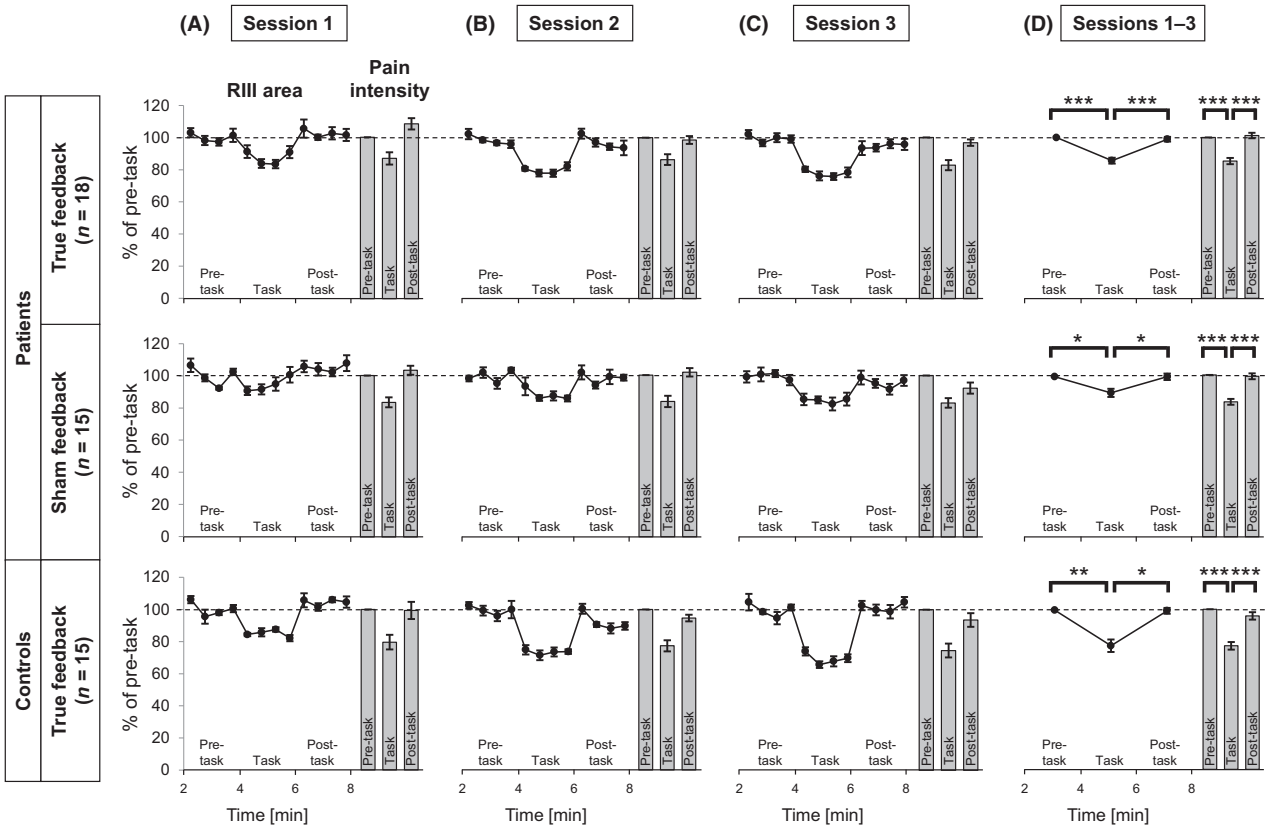

Figure 2 Effects of RIII feedback training on RIII areas and electrical pain intensity ratings. RIII areas and electrical pain intensity ratings are illustrated as % of pre-task block, averaged within the respective group and session and over the two runs within each session (A–C), and over the three sessions (D). For RIII areas, each data point illustrates the mean of 30 s (three reflexes, A–C) or the entire block (2 min, 12 reflexes, D). Pain intensity ratings were obtained once at the end of each block, as an average rating of the preceding five stimuli. Values are mean ± SEM. SEM: standard error of the mean, *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

between 100 and 150 ms ($SEP_{100–150}$) was reduced to 86 ± 23%, 76 ± 36% and 93 ± 14% of pre-task in true feedback controls, true feedback patients and sham feedback patients, respectively. Statistical analysis showed that only the true feedback patients exhibited a significant $SEP_{100–150}$ reduction during the task block that recovered during the post-task block (main effect of block: $F[2,12] = 6.3$, $p < 0.01$; post-hoc tests: task vs. pre-task and vs. post-task: both $p < 0.05$, pre-task vs. post-task: $p = 0.42$). The true feedback controls showed an $SEP_{100–150}$ reduction during the task block that recovered during post-task, however, without reaching significance (main effect of block: $F[2,9] = 1.9$, $p = 0.2$). The sham feedback patients showed a significant reduction from pre-task to post-task, but not during task ($F[2,8] = 4.7$, $p < 0.05$; post-hoc tests: task vs. pre-task and vs. post-task: both $p > 0.1$, pre-task vs. post-task: $p < 0.05$). However, group differences were not significant (interaction between block and group: $F[4,64] = 1.6$, $p = 0.2$) (Results S4). There were no significant correlations between SEP changes and RIII suppression during the task block ($r = 0.17$, $p = 0.34$ across all participants, see Results S4 for results within groups).

3.4 Conditioned pain modulation

Results are shown in Table 2 and in Figure 4. Significant reduction of test stimulus pain intensity [0–10] during conditioning stimulation, compared to test stimulus only application (baseline), was called a significant CPM effect. Before RIII feedback training, only the true feedback controls showed a significant CPM effect (reduction to 81 ± 22% of baseline, $T[14] = 3.2$, $p < 0.01$). The true feedback patients showed no CPM effect (reduction to 98 ± 26% of baseline, $T[15] = 0.4$, $p = 0.7$), while in the sham feedback

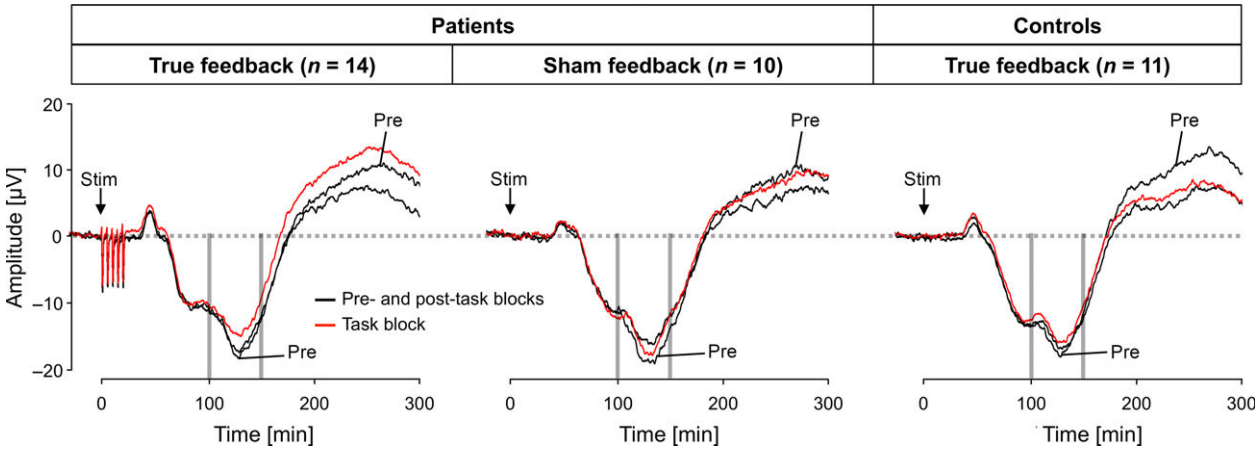

Figure 3 Effects of RIII feedback training on somatosensory evoked potentials. SEP traces obtained in parallel with RIII recording during pre-task, task and post-task blocks were averaged over two runs per session and three sessions within each group. Task block traces are marked in red. Stimulation onset is marked with 'stim' and an arrow. Grey lines show the 100–150 milliseconds analysis window used to quantify $SEP_{100–150}$ amplitudes.

Table 2 Results of conditioned pain modulation testing before and after feedback training.

		Patients				Controls	
		True feedback n = 16		Sham feedback n = 15		True feedback n = 15	
		Before feedback training	After feedback training	Before feedback training	After feedback training	Before feedback training	After feedback training
Test stimulus pain intensity rating [0–10]	Test stimulus only	5.6 ± 0.7	5.4 ± 1.1	5.5 ± 0.6	5.6 ± 1.3	5.7 ± 1.1	5.3 ± 1.1
	Test stimulus + conditioning stimulus	5.5 ± 1.4	4.3 ± 1.5	4.8 ± 1.6	4.6 ± 1.8	4.6 ± 1.4	4.4 ± 1.7

CPM testing was performed during the preparatory session (before feedback training) and at the end of the last feedback training session (after feedback training). The test stimulus was a heat pain stimulus, the conditioning stimulus was a cold water pain stimulus. The test stimulus pain intensity was rated once alone (test stimulus only) and once when it was applied simultaneously with the conditioning stimulus (test stimulus + conditioning stimulus). Values are given as mean ratings on the NRS [0–10] ± SD. CPM: conditioned pain modulation, NRS: numerical rating scale, SD: standard deviation.

patient group, there was a trend towards a significant CPM effect (reduction to 87 ± 25%, T[14] = 1.9, $p = 0.08$). After feedback training, all three groups showed a significant CPM effect. Test stimulus ratings during conditioning stimulus were reduced to 80 ± 21% in true feedback patients (T[15] = 3.7, $p < 0.01$), 81 ± 22% in sham feedback patients (T[14] = 3.1, $p < 0.01$) and 83 ± 31% in controls (T[14] = 2.5, $p < 0.05$). Of the three groups, only the true feedback patients significantly improved their CPM effect through RIII feedback training (CPM effect after vs. before feedback training: F[1,15] = 10.6, $p < 0.01$) (Results S5). However, CPM effect increases and RIII suppression were not significantly correlated (r = -0.03, $p = 0.86$ across all participants, see Results S5 for results within groups).

3.5 Exploratory analysis of clinical pain

Back pain intensity (minimum, average and maximum pain during the previous week) was assessed at baseline and directly after feedback training and again 3 months later (Methods S2 and Table S3). Random assignment of patients to the true and sham feedback groups resulted in a similar age and sex distribution, but sham feedback patients reported significantly lower back pain than true feedback patients (minimum back pain: difference of means: −1.32 on the NRS [0–10]; average back pain: difference of means: −1.18; both $p < 0.05$).

Only the true feedback patients achieved a significant reduction of average (−0.8 ± 1.5, $p < 0.05$) and maximum (−1.4 ± 1.8, $p < 0.01$) back pain from

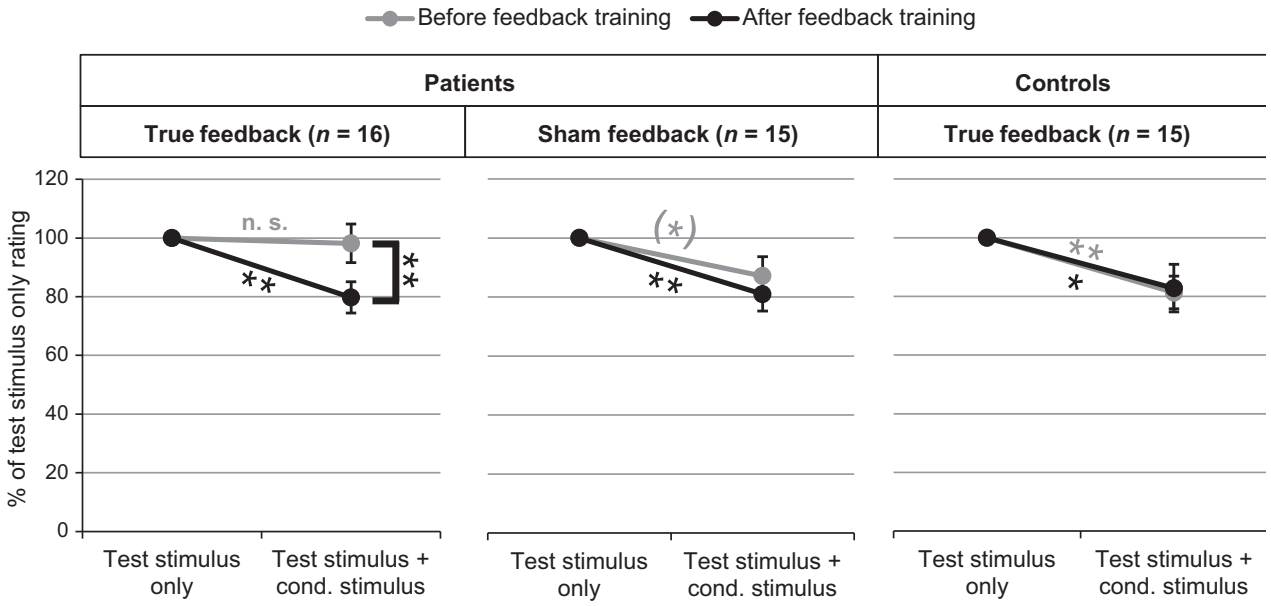

Figure 4 Conditioned pain modulation. The test stimulus was a heat pain stimulus, the conditioning stimulus was a cold water pain stimulus. Test stimulus pain intensity was rated once alone (test stimulus only) and once when it was applied simultaneously with the conditioning stimulus (test stimulus + conditioning stimulus). Test stimulus pain ratings are illustrated as % of test stimulus only ratings, averaged within the respective group before and after RIII feedback training. Patients did not achieve a significant CPM effect before feedback training, but after feedback training it was significant. Only true feedback patients improved their CPM effect significantly after feedback training, compared to before. Values are mean ± SEM. SEM: standard error of the mean, n.s.: not significant, $^{(*)}p < 0.1$, $*p < 0.05$, $**p < 0.01$.

baseline to after feedback training. Three months later, the reductions were somewhat smaller and no longer significant. Sham feedback patients and patients who did not participate in the feedback training did not show any significant pain reduction at any time point (Results S6 and Table S3).

3.6 Exploratory analysis of anxiety and depression

Anxiety and depression (HADS scores) were assessed at baseline and directly after feedback training and after 3 months (Methods S2 and Table S3). After the feedback training, only the true feedback patients showed a significant reduction of anxiety (-0.9 ± 1.6; $p < 0.05$), compared to baseline. Three months later, the reduction was somewhat smaller and no longer significant. Sham feedback patients, true feedback controls and no feedback training patients did not show any significant anxiety reduction at any time point. Depression scores did not significantly change in any of the four groups (Results S7 and Table S3).

4. Discussion

The main result was that during RIII feedback training, subjects with chronic back pain were able to significantly suppress their spinal nociception using cognitive-emotional strategies. Notably, this was associated with improvement of descending pain inhibition, as quantified by the CPM paradigm. An exploratory analysis also suggested a reduction in clinical pain and anxiety ratings after RIII feedback training. We propose that these outcomes are based upon the mechanisms we previously postulated, namely improvement of descending pain inhibition (Ruscheweyh et al., 2015a; Ruscheweyh et al., 2015b).

4.1 Healthy controls receiving true RIII feedback

We found that older healthy controls were also able to learn RIII suppression. The controls' RIII suppression over three feedback sessions in the present study (to 76 ± 26%) was comparable to the published results in young healthy controls (66 ± 22% (Ruscheweyh et al., 2015b) and 79 ± 21% (Ruscheweyh et al., 2015a)). Similar to the results in young subjects (Ruscheweyh et al., 2015a), the $SEP_{100–150}$ amplitude, which is related to activity in the insula and parietal operculum (Dowman et al., 2007), showed a reversible reduction during the task block

although not reaching significance. The non-significant effect might partly be due to the large variability of SEP amplitudes, both intra- and interindividually. In addition, as reported before in somatosensory and contact heat evoked potentials (Kemp et al., 2014; Granovsky et al., 2016), SEP amplitudes in the older adults studied here were considerably smaller (average around 15 μV) than our previous data in young subjects (average around 26 μV). In some subjects, no reproducible SEPs could be recorded.

4.2 Subjects with chronic back pain receiving true RIII feedback

Since subjects with chronic pain exhibit impaired descending pain inhibition (Yarnitsky, 2010), it was not clear whether subjects with chronic back pain could learn to reduce the RIII reflex at all. However, results show that subjects with chronic back pain can also reduce their RIII reflex although nominally a little less than healthy controls (average RIII reduction to 76 ± 26% in controls, to 82 ± 13% in true feedback patients). Concurrently, $SEP_{100–150}$ amplitudes were significantly and reversibly reduced during the task block, as previously shown in healthy subjects (Ruscheweyh et al., 2015a). Consistent with previous studies indicating impaired descending inhibition in chronic pain (Yarnitsky, 2010), the true feedback patients had no CPM effect before the RIII feedback training (reduction of pain perception to 98 ± 26% of baseline). However, after the training, they showed a significant CPM effect (to 80 ± 21% of baseline), being the only group exhibiting significant CPM improvement over training. An exploratory analysis also showed a significant reduction of the true feedback patients' chronic back pain and anxiety after training. Three months later, back pain and anxiety were still reduced but the reduction was no longer significant.

4.3 Subjects with chronic back pain receiving sham RIII feedback

Despite random group assignment, the sham feedback patients exhibited less clinical pain at baseline than the true feedback patients, and an almost significant CPM effect. This may indicate a less severe chronic pain syndrome and a less impaired descending pain inhibition in the sham feedback patients compared to the true feedback patients, making them less than ideal comparison groups.

The sham feedback patients achieved significant RIII suppression although it was the smallest of all three groups and the RIII suppression was significantly smaller than in the true feedback controls. This was different from the previous study in young healthy adults, in which the sham feedback group did not achieve any RIII suppression (Ruscheweyh et al., 2015b). One possible reason for this may be that most sham feedback patients had previously participated in a multidisciplinary chronic pain treatment programme, and had already learned to use cognitive-emotional strategies for pain reduction that they then successfully applied during the training, even without true feedback.

However, in contrast to the true feedback patients, the sham feedback patients did not show significant improvement of the CPM effect after feedback training, and no significant reduction of clinical pain or anxiety in the exploratory analysis. This suggests that the true feedback training is superior to the sham feedback training although the RIII suppression did not differ significantly between the two groups. However, an alternative explanation for the CPM effect improvement in the true but not in the sham feedback patients might be that only the true feedback patients showed a complete lack of a CPM effect at baseline. Therefore, interpretation of the CPM data has to be cautious.

Sham feedback patients showed no significant reduction of $SEP_{100–150}$ amplitudes in the task block, but they did show significant reduction in the post-task block. It is not clear how to interpret these findings.

4.4 Subjects with chronic back pain receiving no RIII feedback training

Subjects with chronic back pain who did not participate in the RIII feedback training should reflect the natural course of chronic back pain and its concomitant psychological symptoms. In these subjects, neither back pain intensity nor anxiety or depression were reduced over time.

4.5 Limitations

The major limitations of the study and the RIII feedback training have been discussed above and in our previous publications (Ruscheweyh et al., 2015a; Ruscheweyh et al., 2015b). They include the limited comparability of the sham and true feedback patient groups because of baseline differences in clinical pain, and the fact that RIII suppression was not significantly different between sham and true feedback patients (possibly because 11 of the 15 sham feedback patients had already learned strategies to activate descending pain inhibition during their multidisciplinary pain

treatment programme). Second, several findings were of marginal significance, raising the possibility that the study was underpowered. The sample size was chosen based on our previous RIII feedback studies (Ruscheweyh et al., 2015a; Ruscheweyh et al., 2015b), but maybe investigation of patients requires larger sample sizes. Third, similar to our previous studies, electrical pain intensity ratings were similarly reduced in all three RIII feedback training groups. Nonetheless, only true feedback patients achieved significant improvement of the CPM effect and, in the exploratory analysis, significant reduction of chronic back pain after feedback training although with a smaller effect 3 months later. Fourth, analysis of SEP amplitudes was limited due to smaller amplitudes and more subjects without reproducible SEPs compared to the previous study, likely because of the older age of the participants. Fifth, sural nerve stimulation does not selectively excite nociceptive fibres, potentially introducing non-nociceptive components into SEP and RIII measurements. Indeed, SEPs exhibit non-nociceptive components also at late time points after stimulation (Dowman, 1994; Dowman et al., 2007). Dowman's extensive work suggests that significant nociceptive SEP components start ~75 ms after stimulation (Dowman, 1994; Dowman and Schell, 1999; Dowman et al., 2007). Consistently, we showed that the $SEP_{100–150}$ component analysed here distinctly increased during noxious, compared to non-noxious, stimulation and therefore likely includes nociceptive components (Ruscheweyh et al., 2015a). The RIII reflex, which is thought to be mediated by (presumably nociceptive) Aδ afferents, can be contaminated by the non-noxious RII reflex and the supraspinally mediated startle response (Dowman, 1992; Sandrini et al., 2005). The use of the 90–150 ms analysis window should minimize RIII contamination by these components (Dowman, 1992; France and Suchowiecki, 2001). However, the RIII reflex arch also includes non-nociceptive neurons, such as deep dorsal horn interneurons (Schouenborg et al., 1995) and motor neurons. Therefore, RIII reflex reduction does not necessarily indicate reduction of ascending nociception and/or activation of descending pain inhibition (Schouenborg et al., 1995; Terkelsen et al., 2004; Piché et al., 2009). In our previous study (Ruscheweyh et al., 2015a), we demonstrated that RIII suppression during feedback training is likely not based on reduction in motor excitability, and has an effect on late, presumably nociceptive SEP amplitudes, as was also the case in the present study. Therefore, despite the presented considerations, we propose that RIII suppression during feedback training reflects activation of descending pain inhibition. Sixth, the proportion of subjects with chronic pain excluded from the study due to unstable RIII reflexes (22 of 55 subjects with chronic back pain; 40%) was considerably higher than the proportion of excluded controls (three of 18 controls; 17%). In our experience, 20%–40% of young healthy subjects have to be excluded because of unstable reflexes if stability over 8 min is mandatory. It remains unclear whether the present group differences are by chance or related to the presence or absence of chronic pain.

4.6 Conclusion

Our results suggest that subjects with chronic back pain can learn to use cognitive-emotional strategies to activate their descending pain inhibition under RIII feedback. This was associated with improvement in an alternative measure of descending pain inhibition, the CPM effect. Exploratory analysis also suggested improvement in back pain intensity and anxiety after feedback training. RIII feedback training could be an innovative drug-saving method in pain therapy, but further work is necessary to simplify the procedure, corroborate superiority of true vs. sham RIII feedback training in pain patients and specifically quantify the effect on clinical outcomes.

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Author contributions

Stefanie Krafft: assessment of participants, data acquisition, data analysis and interpretation, manuscript writing. Heinz-Dieter Göhmann: screening and provision of patients, technical help, manuscript revising. Jens Sommer: programming and implementation of the experimental software, manuscript revising. Andreas Straube: conception and design, manuscript revising. Ruth Ruscheweyh: conception and design, data analysis and interpretation, manuscript writing and revising. All authors discussed the results and commented on the manuscript.

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Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article:

Table S1. Pain and pain-modulatory medication.

Table S2. Strategies used for RIII reflex reduction.

Table S3. Clinical back pain intensity, anxiety and depression at baseline, directly after, and three months after feedback training.

Figure S1. Subject disposition.

Appendix S1. Supplementary Methods and Results.

Supplementary material

Supplementary Methods

Methods S1. Participants

All participants had to meet the following criteria: (1) age between 18 and 70 years, (2) no severe neurological, internal, or psychiatric conditions, (3) sufficient knowledge of the German language, (4) no nicotine, alcohol, or drug abuse, and (5) no pregnancy. Patients with chronic back pain were recruited at the outpatient pain clinic of the community hospital Traunstein, Germany, and additionally had to meet the following criteria: (1) chronic back pain (lumbar, cervical or thoracic) for ≥ 6 months, rated ≥ 2 on the NRS, (2) back pain not the consequence of a tumor or vertebral body fracture, and (3) either before or at least 8 weeks after participation in the 5-week specialized multidisciplinary chronic pain treatment programme at the pain clinic. Patients were allowed to: (1) have additional pain sites besides back pain, (2) exhibit mild-to-moderate depression, and (3) continue their stable usual pain medication (listed in Supplementary Table 1). Healthy controls were recruited by local advertisements and had to meet the following additional criteria: (1) no history of chronic pain (no persistent pain for a period of 6 months), and (2) no intake of any pain or central acting medication within 2 days before each training session. Each experimental session lasted 2 to 4 hours.

Methods S2. Clinical pain, anxiety and depression

In interviews about their clinical pain, patients rated the intensity of their minimum, average, and maximum back pain during the last week on the NRS [0-10].

For evaluation of anxiety and depression, the Hospital Anxiety and Depression Scale (HADS) questionnaire was used (Herrmann-Lingen et al., 1995). One missing item per questionnaire was allowed, and substituted by the average of the remaining items.

Methods S3. RIII reflex recording and quantification

Subjects were tested in a quiet room devoid of visual distractors, with only the experimenter present. During recording, the subject sat comfortably in a reclining chair with the knee of the

recorded leg flexed at ~150°. Stimulation and recording sites were prepared by degreasing and lightly abrading the overlying skin.

Methods S4. Somatosensory evoked potential recording and quantification

As in our previous study (Ruscheweyh et al., 2015a), we preferred Fpz as reference as this montage should reduce the contribution of brain areas involved in pain modulation (prefrontal cortex, anterior cingulate cortex) (Dowman et al., 2007) and increase the contribution of afferent nociceptive areas (primary somatosensory cortex, parietal operculum, insula) to the signal. This was advantageous as we were interested in determining the effect of RIII feedback training on ascending nociception. For technical reasons (the two channels of the amplifier were used for RIII and SEP recording) an electrooculogram was not recorded. However, it has been shown previously that less than 5% of trials show contamination of artifacts from the eyes (Goffaux et al., 2011), and that, after habituation to the stimulus and when short inter-stimulus intervals are used, no startle response is evoked from the orbicularis oculi muscle (Dowman, 1992).

Supplementary Results

Results S1. Strategies used for RIII reflex reduction

The cognitive-emotional strategies subjects used for RIII reflex reduction are listed in Supplementary Table 2. Subjects usually tested different strategies before finding the one that worked best for them. Subjects from all groups most frequently used mental imagery (vivid recall of pleasant experiences). Other frequently used strategies were relaxation (e.g. concentration on breathing) and distraction by mental arithmetic or work (e.g. day planning or recollection of a text).

Results S2. RIII areas

Average RIII thresholds were at 8.1 ± 2.3 mA, without group differences ($F[4,88] = 1.3$, $p = 0.3$, $\eta^2 = 0.06$). Average stimulation intensity during feedback runs was 12.3 ± 3.9 mA, also without group differences ($F[4,90] = 0.6$, $p = 0.7$, $\eta^2 = 0.02$). All three groups achieved a significant reduction of RIII areas during the task block with complete recovery in the post-task block (true feedback patients: $F[2,16] = 13.8$, $p < 0.001$, $\eta^2 = 0.45$; sham feedback

patients: F[2,13] = 4.2, $p < 0.05$, $\eta^2 = 0.23$; controls: F[2,13] = 8.1, $p < 0.01$, $\eta^2 = 0.37$; post-hoc tests pre-task vs. task and task vs. post-task: all $p \leq 0.05$, $\eta^2 > 0.24$; pre-task vs. post-task: all $p > 0.4$, $\eta^2 < 0.04$). Repeated measures ANOVA with group, block and session as factors showed a significant interaction between block and session (F[4,42] = 5.0, $p = 0.001$, $\eta^2 = 0.1$), due to an increase in RIII suppression from session to session (session 1: 89 ± 18%, session 2: 81 ± 21%, session 3: 78 ± 24%) that was not dependent on group (F[8,86] = 1.4, $p = 0.22$, $\eta^2 = 0.06$). There was a trend for a significant interaction between block and group (F[4,90] = 2.4, $p = 0.054$, $\eta^2 = 0.1$). Subordinate ANOVAs showed significant interactions between block and group when the sham feedback patients and the true feedback controls were compared (F[2,27] = 3.6, $p < 0.05$, $\eta^2 = 0.11$), but not when the true feedback patients were compared with either of the other groups (sham feedback patients: F[2,30] = 1.7, $p = 0.18$, $\eta^2 = 0.05$; controls: F[2,30] = 1.6, $p = 0.22$, $\eta^2 = 0.05$).

Results S3. Experimental pain ratings

Average experimental pain thresholds were at 4.9 ± 2.0 mA, without group differences (F[4,88] = 1.0, $p = 0.41$, $\eta^2 = 0.04$). Statistical analysis showed that pain reduction was significant in all groups, but not different between groups. More specifically, all three groups achieved a significant reduction of pain ratings during task blocks, with complete recovery during post-task blocks (true feedback patients: F[2,16] = 22.2, $p < 0.001$, $\eta^2 = 0.57$; sham feedback patients: F[2,13] = 20.0, $p < 0.001$, $\eta^2 = 0.59$; controls: F[2,13] = 16.8, $p < 0.001$, $\eta^2 = 0.55$; post-hoc tests pre-task vs. task and task vs. post-task: all $p < 0.01$, $\eta^2 > 0.5$; pre-task vs. post-task: all $p > 0.4$, $\eta^2 < 0.04$). Repeated measures ANOVA with group, block and session as factors showed that the pain reduction during task blocks was independent of group (interaction between block and group: F[4,90] = 0.2, $p = 0.96$, $\eta^2 = 0.01$). Similar to the RIII area results, there was a significant interaction between block and session (F[4,42] = 4.9, $p = 0.001$, $\eta^2 = 0.1$), which indicated an increase in pain intensity suppression from session to session (session 1: 84 ± 15%, session 2: 83 ± 14%, session 3: 80 ± 14%), not dependent on group (F[8,86] = 0.4; $p = 0.92$, $\eta^2 = 0.02$).

Results S4. Somatosensory evoked potentials

Only the true feedback patients exhibited a significant $SEP_{100\text{-}150}$ reduction during the task block that recovered during the post-task block (main effect of block: F[2,12] = 6.3, $p < 0.01$, $\eta^2 = 0.33$; post-hoc tests: task vs. pre-task and vs. post-task: both $p < 0.05$ and both $\eta^2 > 0.29$,

pre-task vs. post-task: $p = 0.42$, $\eta^2 = 0.05$). The true feedback controls showed an $SEP_{100\text{-}150}$ reduction during the task block that recovered during post-task, however without reaching significance (main effect of block: $F[2,9] = 1.9$, $p = 0.2$, $\eta^2 = 0.16$). The sham feedback patients showed a significant reduction from pre-task to post-task, but not during task ($F[2,8] = 4.7$, $p < 0.05$, $\eta^2 = 0.34$; post-hoc tests: task vs. pre-task and vs. post-task: both $p > 0.1$ and both $\eta^2 < 0.27$, pre-task vs. post-task: $p < 0.05$ and $\eta^2 = 0.51$). The changes in SEP amplitudes during task blocks were independent of group (interaction between block and group: $F[4,64] = 1.6$, $p = 0.2$, $\eta^2 = 0.09$). There were no significant correlations between SEP changes and RIII suppression during the task block in any of the groups (true feedback patients: $r = -0.32$, $p = 0.27$; sham feedback patients: $r = 0.61$, $p = 0.06$; controls: $r = 0.53$, $p = 0.09$).

Results S5. Conditioned pain modulation

Before RIII feedback training, only the true feedback controls showed a significant CPM effect (reduction to 81 ± 22% of baseline, $T[14] = 3.2$, $p < 0.01$, difference of means: -1.11 on the NRS [0-10], 95% CI: -0.37 to -1.86). The true feedback patients showed no CPM effect (reduction to 98 ± 26% of baseline, $T[15] = 0.4$, $p = 0.7$, difference of means: -0.12 on the NRS [0-10], 95% CI: -0.58 to 0.82), while in the sham feedback patient group, there was a trend towards a significant CPM effect (reduction to 87 ± 25%, $T[14] = 1.9$, $p = 0.08$, difference of means: -0.7 on the NRS [0-10], 95% CI: -0.1 to 1.5). After feedback training, all three groups showed a significant CPM effect. Test stimulus ratings during conditioning stimulus were reduced to 80 ± 21% in true feedback patients ($T[15] = 3.7$, $p < 0.01$, difference of means: -1.1 on the NRS [0-10], 95% CI: -0.46 to -1.74), 81 ± 22% in sham feedback patients ($T[14] = 3.1$, $p < 0.01$, difference of means: -1.04 on the NRS [0-10], 95% CI: -0.33 to -1.78), and 83 ± 31% in controls ($T[14] = 2.5$, $p < 0.05$, difference of means: -0.91 on the NRS [0-10], 95% CI: -0.14 to -1.69). Of the three groups, only the true feedback patients significantly improved their CPM effect through RIII feedback training (CPM effect after vs. before feedback training: $F[1,15] = 10.6$, $p < 0.01$, $\eta^2 = 0.42$). CPM effect increases and RIII suppression were not significantly correlated in any of the groups (true feedback patients: $r = 0.24$, $p = 0.36$; sham feedback patients: $r = -0.11$, $p = 0.69$; controls: $r = -0.04$, $p = 0.88$).

Results S6. Exploratory analysis of clinical pain

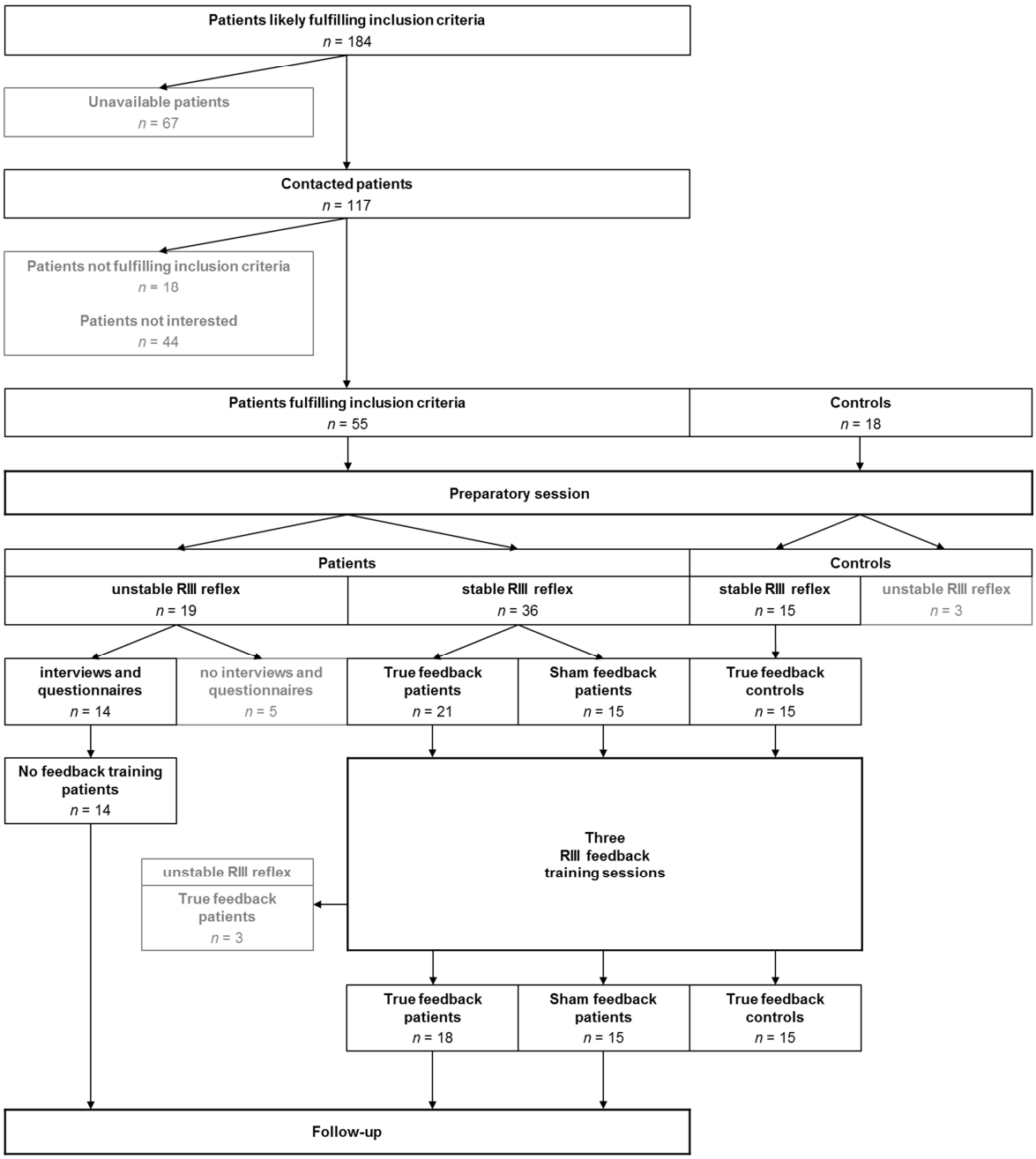
The exploratory clinical pain analysis included 18 true feedback, 15 sham feedback, and 14 no feedback training (baseline and 3 months later) patients. Random assignment of patients to the true and sham feedback groups resulted in a similar age and sex distribution, but sham feedback patients reported significantly lower back pain than true feedback patients (minimum back pain: T[31] = 2.6, difference of means: -1.32 on the NRS [0-10], 95% CI: -0.28 to -2.37; average back pain: T[31] = 2.1, difference of means: -1.18, 95% CI: -0.06 to -2.31; both $p < 0.05$; maximum back pain T[29] = 1.3, $p = 0.2$, difference of means: -0.84, 95% CI: -0.45 to 2.13).

Only the true feedback patients achieved a significant reduction of average (-0.8 ± 1.5, T[17] = 2.2, $p < 0.05$, 95% CI: -0.03 to -1.54) and maximum (-1.4 ± 1.8, T[17] = 3.2, $p < 0.01$, 95% CI: -0.48 to -2.29) back pain from baseline to after feedback training. Minimum pain was not significantly reduced (-0.4 ± 2.1, T[17] = 0.7, $p = 0.5$, 95% CI: -0.67 to 1.41). Three months later, the reduction of average and maximum pain was somewhat smaller and no longer significant in the true feedback patients (average: -0.7 ± 2.0, T[17] = 1.5, $p = 0.2$, 95% CI: -0.31 to 1.73; maximum: -0.8 ± 2.0, T[17] = 1.6, $p = 0.1$, 95% CI: -0.23 to 1.75). None of the pain ratings was significantly reduced from baseline to after feedback training or to 3 months after feedback training in sham feedback patients (baseline to after: minimum: -0.2 ± 1.1, T[14] = 0.7, $p = 0.5$, 95% CI: -0.41 to 0.77; average: -0.5 ± 1.6, T[14] = 1.3, $p = 0.2$, 95% CI: -0.35 to 1.43; maximum: -0.3 ± 1.6, T[14] = 0.7, $p = 0.5$, 95% CI: -0.6 to 1.13; baseline to 3 months after: minimum: +0.9 ± 2.0, T[14] = -1.7, $p = 0.1$, 95% CI: -1.98 to 0.25; average: +0.6 ± 1.5, T[14] = -1.4, $p = 0.2$, 95% CI: -1.42 to 0.29; maximum: +0.7 ± 2.0, T[14] = -1.3, $p = 0.2$, 95% CI: -1.78 to 0.45).

For comparison with the natural course of back pain, we also assessed back pain intensity at the preparatory session and 3 months later in 14 patients with chronic back pain that were excluded from feedback training after the preparatory session because a stable reflex could not be recorded (Supplementary Table 3). These patients showed no difference in pain ratings between the two time points (minimum: +0.4 ± 2.2, T[13] = -0.6, $p = 0.6$, 95% CI: -1.64 to 0.93; average: -0.2 ± 2.1, T[13] = 0.4, $p = 0.7$, 95% CI: -1.02 to 1.45; maximum: +0.1 ± 2.7, T[13] = -0.2, $p = 0.9$, 95% CI: -1.65 to 1.44).

Results S7. Exploratory analysis of anxiety and depression

One sham feedback and one no feedback training patient did not return the HADS questionnaires after 3 months. Thus, analysis of anxiety and depression included 18 true feedback patients; 15 (at baseline and directly after training) and 14 (after 3 months) sham feedback patients; and 14 (baseline) and 13 (3 months later) no feedback training patients.
After the feedback training, only the true feedback patients showed a significant reduction of anxiety (-0.9 ± 1.6; T[17] = 2.5, $p < 0.05$, 95% CI: -0.15 to -1.73), compared to baseline. Three months later, the reduction was somewhat smaller and was no longer significant (-0.6 ± 2.8; T[17] = 0.9, $p = 0.4$, 95% CI: -0.8 to 2.02). Sham feedback patients and true feedback controls did not show a significant anxiety reduction after feedback training (sham feedback patients: T[14] = 0.7, $p = 0.5$, difference of means: -0.38 [HADS-A score], 95% CI: -0.77 to 1.52; controls: T[14] = -0.2, $p = 0.9$, difference of means: +0.07, 95% CI: -0.89 to 0.76) or 3 months after feedback training (sham feedback patients: T[13] = 0.5, $p = 0.6$, difference of means: -0.3, 95% CI: -1.08 to 1.68; controls: no data collected). Depression scores did not significantly change in any of the groups after the feedback training (true feedback patients: T[17] = 1.0, $p = 0.3$, difference of means: -0.44 [HADS-D score], 95% CI: -0.46 to 1.35; sham feedback patients: T[14] = 0.8, $p = 0.4$, difference of means: -0.53, 95% CI: -0.88 to 1.95; controls: T[14] = -0.4, $p = 0.7$, difference of means: +0.07, 95% CI: -0.46 to 0.32) or 3 months after feedback training (true feedback patients: T[17] = 1.0, $p = 0.4$, difference of means: -0.61, 95% CI: -0.73 to 2.0; sham feedback patients: T[13] = 0.3, $p = 0.8$, difference of means: -0.21, 95% CI: -1.36 to 1.79; controls: no data collected). In the patients that were excluded from feedback training but completed the questionnaires, there was no significant reduction of anxiety or depression after 3 months (anxiety: T[12] = 0.2, $p = 0.8$, difference of means: +0.15, 95% CI: -1.53 to 1.84; depression: T[12] = -1.8, $p = 0.1$, difference of means: +1.88, 95% CI: -4.18 to 0.41).



Supplementary Figure 1. Subject disposition. 184 patients with chronic back pain were initially identified from the outpatient pain clinic patient records as likely fulfilling the inclusion criteria. 67 of these patients could not be contacted (mainly due to unavailability), the other 117 were informed about the study. 18 of them were excluded because they did not fulfill the inclusion criteria (e.g. back pain was < 2 on the NRS [0-10] or exclusion criteria had occurred since their last appointment in the pain clinic). 44 were not interested in participation. 55 patients attended the preparatory session, 19 of them were excluded from the feedback training because the reflex was unstable or the stimulus too painful. Five of these patients were not interested in further participation, but 14 participated in follow-up interviews and questionnaires (no feedback training patients) to assess the natural course of the chronic pain disorder. 36 patients were recruited for feedback training, of which 21 were randomized to the true, and 15 to the sham feedback patient group. Three patients of the true feedback group dropped out at the first or second training session because the RIII reflex became unstable or the stimulus too painful. 18 healthy controls attended the preparatory session. Three of them were excluded because the reflex was unstable or the stimulus too painful, 15 participated in the feedback training. Thus, 18 patients of the true feedback group, 15 patients of the sham feedback group, and 15 controls completed the feedback training. Feedback and no feedback training patients participated in follow-up interviews about back pain intensity and questionnaires about anxiety and depression 3 months later. (Format modified from original publication.)

Supplementary Table 1. Pain and pain-modulatory medication.

	Patients			Controls
	True feedback *n* = 18	**Sham feedback** *n* = 15	**No feedback training** *n* = 14	**True feedback** *n* = 15
Opioids	3	3	4	-
Non-opioid analgesics	13	11	10	1
Pain-modulatory anti-depressants	6	4	5	-
Pain-modulatory anti-epileptics	2	1	4	-
Muscle relaxants	2	1	1	-

Medication was classified into the categories opioids, non-opioid analgesics, pain modulatory anti-depressants, pain modulatory anti-epileptics and muscle relaxants. Numbers of subjects that took medication of the respective category are given in the table. Patients took the medication daily during the course of the study or on demand (≥ 1x/month). One control took pain medication on demand but not within 2 days before the feedback training sessions.

Supplementary Table 2. Strategies used for RIII reflex reduction.

	Patients		Controls
	True feedback ***n*** **= 18**	**Sham feedback** ***n*** **= 15**	**True feedback** ***n*** **= 15**
Mental imagery	62%	61%	47%
Relaxation	30%	18%	13%
Mental arithmetic / work	9%	34%	32%
Acceptance of / ignoring pain	10%	4%	17%
Other	7%	2%	10%

RIII reflex reduction strategies used by the subjects of the present study were categorized into mental imagery (e.g. vivid recall of pleasant experiences), relaxation (e.g. concentration on breathing or body scan), mental arithmetic / work (e.g. day or duty planning, recalling or making up a text), acceptance of / ignoring pain, and the use of other strategies (e.g. praying, imagination of something cold). Strategies were pooled across all three sessions. Some subjects used more than one strategy during a feedback training run. Therefore, the total percentage in one group can be > 100%.

Supplementary Table 3. Clinical back pain intensity, anxiety and depression at baseline, directly after, and three months after feedback training.

		Patients								Controls	
		True feedback *n* = 18			Sham feedback *n* = 15			No feedback training *n* = 14		True feedback *n* = 15	
		Baseline	After feedback training	Three months after feedback training	Baseline	After feedback training	Three months after feedback training	Baseline	Three months later	Baseline	After feedback training
Back pain [0-10]	Minimum	3.1 ± 1.6	2.8 ± 1.5	2.9 ± 2.0	1.8 ± 1.3	1.6 ± 1.4	2.7 ± 2.1	3.1 ± 1.6	3.5 ± 2.2	-	-
	Average	4.9 ± 1.7	4.1 ± 1.4	4.2 ± 2.0	3.7 ± 1.5	3.2 ± 1.5	4.3 ± 1.8	5.0 ± 1.6	4.8 ± 2.1	-	-
	Maximum	7.1 ± 1.7	5.7 ± 2.0	6.3 ± 2.2	6.2 ± 1.9	6.0 ± 2.4	6.9 ± 1.8	6.8 ± 1.6	6.9 ± 2.6	-	-
Anxiety [HADS-A score]		11.2 ± 3.8	10.2 ± 3.6	10.6 ± 4.4	8.8 ± 4.4	8.5 ± 3.9	8.6 ± 4.7 (14)	10.3 ± 3.7	10.5 ± 4.6 (13)	3.7 ± 1.9	3.8 ± 2.4
Depression [HADS-D score]		10.2 ± 4.7	9.7 ± 4.6	9.6 ± 4.6	7.6 ± 5.3	7.1 ± 4.6	7.4 ± 5.2 (14)	8.2 ± 3.4	10.0 ± 4.0 (13)	1.4 ± 2.0	1.5 ± 2.0

Minimum, average, and maximum back pain intensity ratings on the NRS [0-10] during the previous week are shown. Anxiety and depression were measured by the HADS-A and HADS-D questionnaires respectively. Baseline pain and HADS values were assessed at the preparatory session. Values after feedback training were assessed at the end of the last feedback training session (feedback groups). Values after three months were assessed three months after the last feedback training session (feedback patient groups) or three months after the preparatory session (no feedback training group). Controls did not participate in the three months assessment. Values are given as mean ± SD. Numbers of subjects are given in parentheses where different from the total number. A: anxiety, D: depression, HADS: Hospital Anxiety and Depression Scale, NRS: numerical rating scale, SD: standard deviation. (Format modified from original publication.)

3 DISCUSSION

In the three presented studies, this thesis introduced a new feedback training method that helps healthy subjects and patients with chronic back pain to deliberately activate their descending pain inhibition and thus reduce their nociceptive transmission on the level of the spinal cord, as well as the concomitant pain perception. During this feedback training consisting of three sessions, subjects applied cognitive and emotional strategies of their choosing (e.g. vivid recall of pleasant experiences or mental arithmetic) to deliberately activate brain areas that anatomically and functionally target the origin of descending pain inhibition in the brainstem (see Figure 1). Active descending pain inhibition subsequently reduces nociceptive transmission in the spinal cord. In the feedback training, spinal nociception was quantified by measurement of the RIII reflex, a commonly used measure of spinal nociception. To this end, the RIII reflex was evoked by painful electrical stimulation of the sural nerve at the ankle and recorded by EMG surface electrodes from the ipsilateral biceps muscle in the thigh. The size of the RIII reflex served as a feedback parameter that was visually presented to the subject in the form of bars on a separate screen (see Figure 3). On the feedback screen, reduction of the bar size indicated successful reduction of the RIII reflex, i.e. of spinal nociception, to the subject. In this way, subjects could immediately follow the effect of their strategies on the RIII reflex, and adjust their strategies to optimize RIII reflex suppression.

In the first two studies (Chapters 2.1 and 2.2), the RIII feedback training was implemented in healthy subjects. Briefly, these studies revealed that subjects can learn to use cognitive-emotional strategies to reduce their RIII reflex and pain perception. Moreover, it was shown that subjects suppressed their RIII reflex to a larger extent under true than under sham (false) or no RIII feedback. Further, the studies demonstrated that cognitive-emotional strategies also result in suppression of supraspinal

nociception, as quantified by late cortical SEPs, and do not affect the motor components of the RIII reflex, as quantified by motor neuron excitability, during RIII feedback training. After implementation in healthy subjects, the feedback training was applied to patients with chronic back pain (Chapter 2.3). The RIII feedback training in patients resulted in RIII reflex and experimental pain reduction during the training, and improved descending pain inhibition as well as reduced clinical pain and anxiety after the training.

3.1 Rationale and modalities of using the RIII reflex as a feedback parameter

The study of pain requires objective measurements of nociceptive processes to improve our comprehension of pain in its complexity. The RIII reflex, a measure of spinal nociception (Skljarevski and Ramadan, 2002; Sandrini et al., 2005), is therefore an appropriate tool to use as a feedback parameter.

The first study of this thesis (Chapter 2.1) revealed that healthy subjects can indeed learn control over spinal nociception, as quantified by the RIII reflex. Furthermore, the results showed that feedback about the RIII reflex, as compared to no feedback, is necessary for learning successful suppression of the RIII reflex. This finding is consistent with previous results demonstrating that biofeedback about physiological parameters helps subjects to learn to deliberately control these physiological processes (Birbaumer et al., 1999; Nestoriuc and Martin, 2007). Notably, the RIII feedback training likely needs to be performed over several sessions to achieve significant differences in RIII reflex reduction between feedback and control groups, as the comparison to a similar study of another research group reveals (Arsenault et al., 2013). Arsenault and colleagues (2013) had used a comparable RIII feedback

training paradigm, though applied in one training session only, and did not find significant group differences. These results demonstrate the importance of allowing subjects and patients an adequate amount of time, over several training sessions, to find out the cognitive-emotional strategies that work best for them individually to suppress their RIII reflex.

Moreover, the first presented study with healthy subjects showed that the learned RIII suppression success during RIII feedback training was independent of random or fixed stimulation intervals. This finding is different from previous research reporting increased descending modulation on the spinal level when applied noxious stimuli are unpredictable, as compared to predictable stimuli (Rhudy et al., 2006).

3.2 Cognitive-emotional strategies reduce the RIII reflex

The hypothesis that led to the development of the RIII feedback training was that subjects should be able to learn to apply cognitive and emotional strategies to deliberately activate descending pain inhibition and thereby reduce their RIII reflex, a measure of spinal nociception, and pain perception (see Figure 1), while receiving feedback about the size of their RIII reflex (see Figure 3).

The results of all three studies (Chapters 2.1, 2.2, 2.3) showed that subjects indeed were able to learn to significantly reduce their RIII reflex when applying cognitive-emotional strategies under RIII feedback. In the present RIII feedback training, the RIII feedback allowed subjects to immediately view the effect of their applied strategies on their RIII reflex, i.e. their spinal nociception (see Figure 3). During three RIII feedback training sessions, subjects could try different strategies, select the strategy that worked best for them individually, and optimize its use for the largest possible RIII suppression. Thus, subjects could learn to

deliberately modulate their RIII reflex. Previous research indicated that positive emotions and distraction from pain, both of which are part of the strategies proposed to the subjects in the present studies, activate regions in the cortex and in the brainstem, the location where the descending pain inhibition originates (Bantick et al., 2002; Tracey et al., 2002; Valet et al., 2004), and suppress nociceptive transmission in the spinal cord (Willer et al., 1979; Rhudy et al., 2005; Ruscheweyh et al., 2011a). Also cognitive activity has been demonstrated to interfere with descending pathways controlling the RIII reflex (Bjerre et al., 2011). Furthermore, deCharms and colleagues (2005) showed that subjects under rt-fMRI feedback can learn to control the activity of the rostral ACC (rACC), a pain- and emotion-related region, and simultaneously modulate pain perception. In view of these previous results, subjects in the studies of this thesis likely did learn to activate their descending pain inhibition and hence reduce their RIII reflex by applying cognitive-emotional strategies. The following chapters of this discussion will further substantiate this claim.

The second study with healthy subjects (Chapter 2.2) showed that acquisition of relaxation techniques prior to the feedback training improved the RIII suppression success to some extent, but not significantly. This finding was different than anticipated, as the results of the initial study with healthy subjects (Chapter 2.1) suggested a superior RIII suppression by the use of relaxation techniques. Also a study by another research group (Emery et al., 2006) reported reductions in human spinal nociception following the application of relaxation techniques. In the initial study with healthy subjects (Chapter 2.1), subjects voluntarily chose relaxation techniques for RIII suppression, whereas the healthy subjects in the second study (Chapter 2.2) were randomly assigned to the relaxation group, but were still allowed to choose their strategy for RIII suppression. Possibly, some subjects in the relaxation group were not able to relate to the relaxation technique to a sufficient extent to increase the RIII suppression effect. Also, more than one instructed relaxation

training session might have been necessary for thorough application of the relaxation technique. However, all subjects in the relaxation group practiced the relaxation technique at home for at least 30 days before starting the RIII feedback training.

3.3 Supraspinal nociception during RIII feedback training

Notably, subjects in each of the three studies (Chapters 2.1, 2.2, 2.3) reported significant reduction of experimental pain intensity, parallel to RIII reduction, during application of cognitive-emotional strategies. In the groups that received true RIII feedback, RIII reduction and experimental pain suppression during cognitive-emotional modulation mostly correlated significantly (see Chapters 2.1 and 2.2). As described in previous publications, a parallel decrease in pain and RIII reflex is considered solid evidence of descending pain-inhibitory activity (Willer et al., 1979; Rhudy et al., 2005; Sandrini et al., 2005; Ruscheweyh et al., 2011a). Surprisingly, also the control (no feedback) and sham feedback groups of the first and second study (Chapters 2.1 and 2.2), respectively, reported significant experimental pain reduction, despite their limited, or lack of RIII suppression. This divergence between RIII reflex and pain sensation might be based on expectancy of the subjects, who maybe anticipated pain reduction due to their application of cognitive-emotional strategies or due to visualized RIII reflex reduction on the feedback screen. Accordingly, other studies also showed results with weak correlation between the RIII reflex size and pain intensity (Terkelsen et al., 2004; Piché et al., 2009). Another reason for independent pain and RIII reflex modulation might be the contribution of supraspinal processes that modulate pain intensity, independent of spinal processes.

The results of the initial study with healthy subjects (Chapter 2.1) raised the question of whether the reduction in subjective pain intensity can also be quantified by an objective method. Thus, the subsequent study with healthy subjects (Chapter 2.2) then demonstrated that supraspinal nociception, as quantified by late SEP amplitudes 100-150 ms after stimulation ($SEP_{100-150}$), was reversibly reduced during application of cognitive-emotional strategies under true RIII feedback. According to Dowman and colleagues, the $SEP_{100-150}$ component likely reflects pain-related activity in the insula and the adjacent parietal operculum (Dowman, 1994; Dowman et al., 2007). Therefore, these results suggest that the reduction of spinal nociception achieved during RIII feedback training also leads to a concomitant decrease in ascending nociceptive input to the brain. In contrast, the sham feedback group in this study did not reduce their $SEP_{100-150}$ amplitudes during RIII suppression. Their $SEP_{100-150}$ amplitudes during RIII suppression were significantly different from those of the true feedback groups. This likely indicates that the subjects in the sham feedback group did not inhibit their spinal nociception sufficiently to also decrease their ascending nociceptive input.

However, these results of the second study were not reproduced in the third study (Chapter 2.3). In the third study, the true feedback controls achieved no significant reversible reduction of $SEP_{100-150}$ amplitudes during RIII suppression, and there were no significant differences in the reduction of $SEP_{100-150}$ amplitudes between the three groups, i.e. between true and sham feedback groups, or between patient and control groups. These different results might be due to more subjects without reproducible SEPs and smaller SEP amplitudes in the third study, likely because of the older age of the subjects, as is also seen in somatosensory and contact heat evoked potentials (Kemp et al., 2014; Granovsky et al., 2016).

3.4 Efficacy of true and sham RIII feedback

As various studies stated before, the control over endogenous physiological processes is easier to learn when biofeedback about these physiological parameters is received (Birbaumer et al., 1999; Weiskopf et al., 2004; Nestoriuc and Martin, 2007). After studying true RIII feedback, as opposed to no RIII feedback, the results of the initial study with healthy subjects brought up the question of whether reduction in RIII reflex under RIII feedback is possibly due to the sheer expectancy of reducing the RIII reflex under visual feedback, which by itself might activate descending pain inhibition, as is the case during placebo analgesia (Bingel and Tracey, 2008). In the subsequent study with healthy subjects and the study with chronic pain patients (Chapters 2.2 and 2.3), therefore, subject groups were included that received sham RIII feedback, as opposed to true RIII feedback in the comparison groups. These sham feedback groups received an RIII feedback, showing the reflex course and significant RIII suppression of a subject from a previous study, suggesting a successful RIII suppression to the subjects. Since the RIII feedback on the screen visualized a successful RIII reduction, the sham feedback subjects were expecting their applied cognitive-emotional strategies to successfully reduce their RIII reflex, comparable to a placebo treatment.

The results of the second study with healthy subjects (Chapter 2.2) revealed that only the subjects that received true RIII feedback, as opposed to sham RIII feedback, achieved a significant RIII reduction during the use of cognitive-emotional strategies. This RIII reduction was significantly larger under true feedback than under sham feedback. Hence, these findings suggest that, in healthy subjects, RIII suppression is not based on an expectancy effect. Instead, they suggest that true RIII feedback is crucial, as compared to sham RIII feedback, for successful reduction of the RIII reflex, i.e. of spinal nociceptive transmission.

However, in the study with chronic pain patients (Chapter 2.3), the patient group that received sham feedback also achieved significant reversible RIII suppression, without significant difference to the RIII suppression of the true feedback patients. One possible reason for this RIII reduction in sham feedback patients might be that most of these patients had previously participated in a multidisciplinary pain treatment program, in which they had also learned to apply cognitive and emotional strategies to reduce their pain, a therapy that is regularly used for patients with chronic pain (McCracken and Turk, 2002; Turk et al., 2008). During the RIII feedback training, they then might have successfully applied these previously learned strategies, even without receiving true feedback. Another possible interpretation of the lack of significant difference between the RIII suppression in the true and sham feedback patients is that any RIII feedback has some effect on the patients. Maybe, the visual RIII feedback by itself improves the patients' body perception and thus makes it easier for them to concentrate and apply their cognitive-emotional strategies. Accordingly, the RIII suppression in the sham feedback patients might be based on a placebo effect. Further, the presented study did not include a control group of patients that received no RIII feedback, leaving the open question of whether RIII feedback is necessary at all for successful RIII suppression in patients with chronic back pain. For these reasons, the efficacy of true and sham RIII feedback in patients with chronic back pain cannot be finally concluded from the present results.

Nonetheless, despite the above stated considerations, numerous results of the studies in this thesis argue for a superior efficacy of true feedback compared to sham feedback. Reproducibly in all of the three studies, subjects that received true RIII feedback were able to significantly reversibly suppress their RIII reflex during the application of cognitive-emotional strategies. In contrast, healthy subjects that received sham feedback (Chapter 2.2) were not able to achieve RIII reduction. In addition, only those healthy subjects of the second study (Chapter 2.2)

that received true feedback, not sham feedback, showed significant reduction of $SEP_{100-150}$ amplitudes, significantly correlating with the RIII reduction. Furthermore, only those patients with chronic pain that received true RIII feedback, as opposed to sham feedback patients, significantly improved their descending pain inhibition, as quantified by the CPM effect (Yarnitsky, 2010). However, it has to be considered that only the true feedback patients exhibited a complete lack of CPM effect at baseline, potentially allowing larger improvement. Notably, consistent with previous research (Nestoriuc and Martin, 2007), only the true feedback in this thesis exerted significant analgesic effects on clinical pain and concomitantly reduced anxiety (Chapter 2.3). Sham feedback patients also reported less chronic pain intensity and anxiety after the feedback training, but these reductions were not significant (also see 3.5 Application of the RIII feedback training in patients with chronic back pain).

Taken together, based on the current state of research, true RIII feedback appears to be superior to sham RIII feedback in healthy subjects, concerning the extent of RIII reflex suppression and $SEP_{100-150}$ reduction. However, future experiments with chronic back pain patients need to prove the efficacy of true and sham RIII feedback in patients.

3.5 Application of the RIII feedback training in patients with chronic back pain

Descending pain inhibition can be impaired in patients with chronic pain (Yarnitsky, 2010; Kwon et al., 2014). Therefore, an improvement of descending pain inhibition in patients with chronic pain is an attractive and innovative approach in the therapy of pain (Yarnitsky, 2015). Before the RIII feedback training with chronic back pain patients (Chapter 2.3), it was not clear at all whether the patients would be able to activate their

impaired descending pain inhibition and reduce their spinal nociception. But, the patients were indeed able to learn cognitive and emotional strategies that worked best for each of them to reduce their individual spinal nociception, likely by activating their descending pain inhibition. In fact, patients receiving true feedback were able to suppress their RIII reflex even to a similar extent as age-matched healthy controls, with no significant difference in RIII suppression between these two groups. This finding indicates that patients with chronic back pain are able to gain control over their spinal nociception, despite their impaired descending pain inhibition.

As described in more detail in the study with chronic pain patients (Chapter 2.3), the sham feedback patients were supposedly less affected by their chronic pain disorder: they reported significantly less chronic pain than the true feedback patients and showed a less impaired CPM effect, reflecting the activity of descending pain inhibition (Yarnitsky, 2010), before the onset of the feedback training. Therefore, the sham feedback patients in the presented study did not comprise an ideal comparison group.

In the presented patient study (Chapter 2.3), patients with chronic back pain that received true feedback showed almost no CPM effect at all at baseline. However, notably, these patients exhibited a significantly improved CPM effect after the feedback training, indicating improved descending pain inhibition (Yarnitsky, 2010). This result provides strong evidence that patients indeed trained to deliberately activate their descending pain inhibition throughout the feedback training and that this recurrent activation led to easier-to-activate descending inhibiting pathways after the training.

Importantly, these true feedback patients, in contrast to sham feedback patients and patients with chronic back pain who did not participate in the feedback training, moreover experienced a significant decrease in their chronic back pain intensity and anxiety directly after the feedback

training, as was also the case in previous feedback training to treat migraine (Nestoriuc and Martin, 2007). This decrease in pain and anxiety, however, unfortunately did not sustain until three months later. These findings in the true feedback patients are in line with other research demonstrating that the CPM effect, i.e. activity of descending pain inhibition, is positively related to RIII reflex reduction and negatively related to psychological factors like anxiety and depression in patients with chronic pain (de Souza et al., 2009; Piché et al., 2011). Sham feedback patients also showed nominal reductions in their chronic back pain and anxiety after the feedback training, but these were non-significant. However, it has to be considered that the sham feedback patients reported less pain than the true feedback patients at baseline. Maybe, their pain was already at an intensity level that could not be reduced any further by the RIII feedback training. The improvements in chronic back pain intensity and anxiety further strengthen the hypothesis that descending pain-inhibiting neurons were activated during the RIII feedback training, inhibiting nociception on the spinal level, resulting in reduction in clinical back pain and in one of its comorbid psychological symptoms.

However, one cannot exclude the possibility that the attention and care the patients received from the experimenter, an expert on the topic of pain, during the feedback training contributed to the clinical pain reduction of both the true and the sham feedback patient groups after the feedback training. In a total of four experimental sessions of up to four hours each, the patients learned about (or refreshed their knowledge of) pain mechanisms, received counseling about pain management (i.e. the use of cognitive-emotional strategies) and had the opportunity to talk about their pain disorder, which contributed to establishing a relationship of trust with the experimenter. This intensive care itself, receiving encouragement and the hope of tackling their pain with their very own cognitive-emotional strategies, might have improved the patients' psychological state, e.g. feeling less left alone with their pain disorder

and, possibly, increasing their feeling of self-efficacy. Therefore, the potentially positive effect of the experimenter's care on the patients' psychological state, possibly contributing to pain reduction, should not be underestimated. Previous studies also revealed that social support like interpersonal interaction, communication involving cognitive and emotional care (e.g. positive suggestions and empathy), and trust in the health care personnel may reduce pain and stress (Krahé et al., 2013; Roberts et al., 2015; Mistiaen et al., 2016; Losin et al., 2017).

Altogether, the RIII feedback training can help patients with chronic back pain to learn control over their spinal nociception, as quantified by the RIII reflex, by deliberate activation of their descending pain inhibition, increasing the patients' self-efficacy. Furthermore, the RIII feedback training can improve the patients' impaired descending pain inhibition, as quantified by the CPM effect, and lead to a reduction of their chronic back pain and anxiety. However, as discussed above (see 3.4 Efficacy of true and sham RIII feedback), the superiority of true versus sham RIII feedback in patients with chronic back pain remains to be proven in a future study. The use of descending pain inhibition not only causes analgesia, but also protects the spinal cord and the brain from strong nociceptive input. In this way, central sensitization could be down-regulated or reversed, reducing the persistence of chronic pain (Ruscheweyh et al., 2011b). Therefore, the RIII feedback training potentially constitutes an innovative drug-saving method in pain therapy. However, currently, the RIII feedback training is time-consuming and elaborate in its experimental setup. Thus, simplification of the procedure is necessary before integrating the RIII feedback training into clinical routine (Chapter 2.3).

3.6 Limitations of the studies

Major limitations of the studies of this thesis are the lack of significant difference between the RIII suppression in the true and sham feedback patients in the third study (Chapter 2.3), and that this study did not include a patient group that received no RIII feedback (also see discussion 3.4 Efficacy of true and sham RIII feedback). Therefore, the efficacy of true and sham RIII feedback in patients with chronic back pain could not be definitely concluded from the present results. Moreover, baseline differences in chronic back pain intensity led to limitations in the comparability of the true and sham feedback patients (also see 3.5 Application of the RIII feedback training in patients with chronic back pain).

Furthermore, every data acquisition method in research has its limitations and considerations that have to be taken into account when analyzing and interpreting collected data. The limitations of the methods used in this thesis are critically discussed in the following paragraphs.

3.6.1 Considerations on the RIII reflex as a measure of spinal nociception

First of all, it should be considered that electrical stimulation of the sural nerve also excites non-nociceptive fibers, and not exclusively nociceptive fibers. The RIII reflex is primarily evoked by stimulation of nociceptive afferent Aδ-fibers (Sandrini et al., 2005). However, measurement of the RIII reflex after sural nerve stimulation can include contamination by the non-nociceptive RII reflex and the startle response, the latter of which is mediated supraspinally (Dowman, 1992; Sandrini et al., 2005). Nonetheless, analyzing the electrophysiological reflex recordings 90-150 ms after stimulation, which is the analysis window applied in the

methods presented in this thesis, should reduce the contribution of these non-nociceptive components to the RIII reflex recordings (Dowman, 1992; France and Suchowiecki, 2001).

Furthermore, it should be taken into consideration that the RIII reflex arch, besides nociceptive afferent fibers, is also comprised of non-nociceptive components, e.g. interneurons in the deep dorsal horn (Schouenborg et al., 1995) and spinal efferent motor neurons. That is why reduced RIII reflexes do not inevitably represent descending pain-inhibitory activity and/or reduced ascending nociceptive transmission (Schouenborg et al., 1995; Terkelsen et al., 2004; Piché et al., 2009) but may also imply reduction in spinal motor activity. However, the results of the second study with healthy subjects (Chapter 2.2) revealed that motor neuron excitability, as quantified by F-waves (Lin and Floeter, 2004; Baars et al., 2006) (see Figure 2), does not decrease during learned RIII suppression. This result supports the assumption that reduction of the RIII reflex during RIII feedback training likely does not rely on modulation of the motor components of the RIII reflex arch, but rather on inhibition of nociceptive transmission in the spinal cord. Further, the change in RIII reflex size correlated with the change in pain perception (Chapters 2.1 and 2.2), and with the change in $SEP_{100\text{-}150}$ amplitudes (Chapter 2.2) during modulation in the first and second studies with healthy subjects (additionally, see discussion 3.6.2 Considerations on subjective pain rating and somatosensory evoked potentials as measures of ascending nociception). These findings also support the assumption that ascending nociception indeed was affected during the RIII feedback training. Therefore, these results argue in favor of the fact that RIII suppression during the feedback training does reflect activation of descending pain inhibition, with a consecutive impact on supraspinal nociception.

Finally, a relevant aspect of the RIII reflex tool is its elaborate experimental procedure in order to obtain reliable RIII reflex recordings. It can be difficult to record stable RIII reflexes in subjects, applying

painful stimuli over the course of 8 minutes. On average, 20-40% of the subjects willing to participate need to be excluded due to instable or non-recordable RIII reflexes. This considerably high drop-out rate has to be taken into account when planning the experimental design and estimating the time-frame of a study involving the use of the RIII reflex as a tool. Furthermore, a high drop-out rate like this bears the risk of a bias in the results.

3.6.2 Considerations on subjective pain rating and somatosensory evoked potentials as measures of ascending nociception

The initial and subsequent studies with healthy subjects (Chapters 2.1 and 2.2) found significant correlations between reductions in the RIII reflex size and experimental pain intensity ratings in large parts of the studies. Partly lacking correlations between these parameters (see Chapter 2.1) might be based on the fact that subjects experienced the rating of the intensity of electrical pain stimuli as difficult. Another reason for this divergence could be that C-fibers are involved in nociceptive pathways evoking pain following sural nerve stimulation, but play a minor role in eliciting the RIII reflex (see 1.5 The nociceptive flexor reflex (RIII reflex)). An alternative explanation might be that pain perception is not exclusively determined by spinal nociception (as reflected by the RIII reflex size), but is also modulated by supraspinal processes.

Furthermore, reductions of experimental pain intensity were similar in all investigated groups, partly without concurrent RIII reflex or $SEP_{100\text{-}150}$ reduction (see control group of Chapter 2.1, and sham feedback group of Chapter 2.2). Possibly, these subjects expected their pain to decrease, as they applied cognitive-emotional strategies for activation of descending

pain inhibition or witnessed the (putative) reduction of their RIII reflex on the feedback screen, likely involving the phenomenon of placebo analgesia. This would be analogous to previous research that found that placebo analgesia has no effect on the RIII reflex (Roelofs et al., 2000). Additionally, besides its effects on spinal nociceptive transmission, the RIII feedback training may also exert direct effects on supraspinal nociceptive processing. Nonetheless, the significant correlations between modulations in RIII reflex size and presumably nociceptive $SEP_{100-150}$ amplitudes (Chapter 2.2) suggest that, at least in part, $SEP_{100-150}$ amplitudes reflect ascending nociception in healthy subjects. However, it should be noted that suppression in $SEP_{100-150}$ amplitudes may also reflect supraspinal changes in processing nociceptive input.

Just as the concurrent excitement of non-nociceptive and nociceptive fibers introduces non-nociceptive components to the RIII reflex recordings (see 3.6.1 Considerations on the RIII reflex as a measure of spinal nociception), this dual excitement also adds non-nociceptive potentials to the SEP measurements. Consistently, Dowman and colleagues (Dowman, 1994; Dowman et al., 2007) also demonstrated that late SEPs have non-nociceptive components. However, also significant nociceptive components were shown to be present starting about 75 ms post stimulation (Dowman, 1994; Dowman and Schell, 1999; Dowman et al., 2007). In line with these previous reports, the results of the second study with healthy subjects (Chapter 2.2) revealed that the evaluated $SEP_{100-150}$ amplitudes considerably increased during noxious stimulation, compared to innoxious stimulation, indicating the likely measurement of nociceptive SEP components during the RIII feedback training.

Taken together, the parallel, correlating, suppression of $SEP_{100-150}$ amplitudes and RIII reflex size in the second study with healthy subjects (Chapter 2.2) substantiates the hypothesis that RIII reduction indeed goes along with decreased nociceptive transmission ascending to the brain, reducing nociceptive input reaching supraspinal areas. However, these results could not be reproduced in the third study (Chapter 2.3), likely

due to the older age of the subjects (see 3.3 Supraspinal nociception during RIII feedback training).

3.7 Potential future research

Electrical stimuli are of short duration and of a very different sensory quality than clinical pain. Thus, many subjects perceive these "unnatural" electrical stimuli as difficult to rate. Furthermore, the unspecific electrical stimulation of the sural nerve is often criticized because, as mentioned in the limitations of the studies (Chapter 3.6), this stimulation excites nociceptive as well as non-nociceptive fibers. Therefore, in explorative experiments following the studies of this thesis, we tried to evoke the RIII reflex by painful contact heat stimuli (Iannetti et al., 2006), and by selective nociceptive electrical skin stimulation using concentric electrodes (Kaube et al., 2000). However, in our trials, none of the above methods was able to evoke stable, reproducible RIII reflexes of sufficient size in a reasonable number of healthy subjects, while applying tolerable stimuli (unpublished observations).

The results of the RIII feedback training in patients with chronic back pain (Chapter 2.3) showed no significant difference between the RIII suppression in the true and sham feedback patient groups (see 3.4 Efficacy of true and sham RIII feedback). To resolve the open question of whether RIII feedback is needed for successful RIII suppression in patients with chronic back pain, a future study should include a group of patients that does not receive any RIII feedback during the RIII suppression training. Further, a prospective study should comprise true and sham feedback patient groups that exhibit similar chronic back pain intensities at baseline, to particularly quantify the effect of the RIII feedback training on clinical outcomes.

According to previous research (Yarnitsky et al., 2012), a less efficient CPM effect at baseline argues for successful improvement in descending pain inhibition by the treatment. Therefore, another possible research approach is the evaluation of the CPM effect as a predictor of the success of the RIII feedback training in patients with chronic pain, in terms of RIII reflex reduction, and improvement of descending pain inhibition and clinical pain. To this end, two groups of patients with chronic pain should be included, one of them exhibiting a poor, and the other one a significantly better CPM effect. As treatment, both groups should receive the same (true) RIII feedback training, and the effect of the RIII feedback training on the CPM effect should be evaluated. The analysis should address whether more severely impaired descending pain inhibition, i.e. a less efficient CPM effect, at baseline predicts more successful RIII feedback training. If the results correspond to those of Yarnitsky and colleagues, the efficiency of the CPM effect at baseline could potentially pre-select suitable patients that would likely profit from the RIII feedback training by improving their descending pain inhibition.

Moreover, healthy subjects and patients with chronic pain are able to learn control over the pain-related rACC as well as their pain perception under rt-fMRI feedback (deCharms et al., 2005). These results suggest that individuals should also be able to learn control over their descending pain inhibition by deliberate selective activation of respective pain-related brain areas. Consequently, a very interesting approach would be rt-fMRI feedback training, using pain-related brain activity as an fMRI feedback parameter. To establish this rt-fMRI feedback training, first of all, those brain areas that are active during modulation of descending pain inhibition would need to be identified. To this end, subjects that have already successfully learned to use cognitive-emotional strategies in the RIII feedback training should apply these strategies under RIII feedback and reduce their RIII reflex, while their brain activity is examined by fMRI. The activity of the identified brain regions would subsequently serve as the visual fMRI feedback parameter during the

rt-fMRI feedback training. Cognitive-emotional modulation activates the PFC, ACC, or amygdala, which in turn activate descending pain inhibition (see 1.2.1 Modulation of descending pain pathways). Therefore, these brain structures could potentially qualify for rt-fMRI feedback regions. During the rt-fMRI feedback training itself, under rt-fMRI feedback, subjects should then learn to use and optimize cognitive-emotional strategies to deliberately modulate, i.e. upregulate, their brain areas that activate descending pain inhibition, and thus control their spinal nociception, as quantified by the RIII reflex. To investigate supraspinal pain-related activation in a chronic pain disorder, this rt-fMRI feedback training should subsequently also be applied to patients with chronic back pain. RIII feedback reflects spinal nociception, indirectly giving information about descending inhibitory activity. The advanced approach in the rt-fMRI feedback training would be a direct feedback about descending inhibitory activity, indicated by the activity of pain-related brain areas targeting the descending pain inhibition in the brainstem. Furthermore, this study could reveal the brain areas related to the activation of descending pain inhibition. However, the prerequisite for this rt-fMRI feedback training to be applied uniformly is consistent activation of similar brain regions during modulation across all subjects.

3.8 Conclusions

This thesis described the development and implementation of a feedback training method in which healthy subjects and patients with chronic back pain learned control over their spinal nociception, as quantified by the RIII reflex, while receiving feedback about the size of their RIII reflex. In the feedback training, individuals learn to apply and optimize cognitive-emotional strategies that likely activate descending pain-inhibiting pathways, reducing nociceptive transmission in the spinal cord, and hence suppressing the RIII reflex. The results demonstrated that, by

applying individual cognitive-emotional strategies, subjects were able to learn to deliberately significantly reduce their RIII reflex and, concomitantly, their subjective pain perception. Further, RIII reduction in healthy subjects was shown to be accompanied by reduced $SEP_{100-150}$ amplitudes, a measure of supraspinal nociception, likely reflecting reduced ascending nociceptive input from the spinal cord to the brain. Notably, also patients with chronic back pain, who exhibit impaired descending pain inhibition, were able to reduce their RIII reflex during the RIII feedback training. Furthermore, remarkably, patients with chronic back pain showed significantly improved descending pain inhibition, as quantified by the CPM effect, directly after the RIII feedback training. Patients additionally reported both significantly reduced chronic back pain and anxiety after the RIII feedback training.

Finally, taken together, the results suggest that the RIII feedback training can teach healthy subjects as well as patients with chronic back pain to control their spinal nociceptive transmission – and improve descending pain inhibition, anxiety, and chronic back pain in patients. However, further research should substantiate the advantage of true over sham and no RIII feedback in patients with chronic back pain, and establish a simplified training procedure for implementation in clinical routine. The studies of this thesis have a scientific impact and allow a better understanding of mechanisms underlying cognitive-emotional modulation of descending pain inhibition in humans. Further, the studies use an innovative clinical approach in pain therapy: learning to deliberately activate descending pain inhibition improves the patients' self-efficacy and thus potentially reduces drug-intake. Consequently, the RIII feedback training could be an attractive non-pharmacological contribution to pain therapy.

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LIST OF PUBLICATIONS

Bäumler, M., Feller, M., **Krafft, S.**, Schiffer, M., Sommer, J., Straube, A., Weinges, F., Ruscheweyh, R. Learned control over spinal nociception: Transfer and stability of training success in a long-term study. *Clin Neurophysiol* 2017;128(12):2462-2469. doi: 10.1016/ j.clinph.2017.09.109.

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Krafft S. (2016). Chronic back pain and the control over spinal nociception. *University of Miami, Miller School of Medicine, UHealth Institute for Advanced Pain Management, Miami, Florida, USA*. Guest speaker.

Krafft, S., Göhmann, H. D., Sommer, J., Straube, A., Ruscheweyh, R. (2016). Chronic back pain patients learn to control spinal nociception under feedback about their nociceptive withdrawal reflex (RIII reflex). *Neuroscience 2016*, *46th Annual Meeting of the Society for Neuroscience (SfN)*, *San Diego*, *California*, *USA*. Poster presentation.

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RR, MM, AS, JS: Conception and design.
JS: Programming and implementation of the experimental software.
FW, MS, MB, MF, SK: Data acquisition.
RR, FW, MS, MB, MF, SK: Data analysis and interpretation.
RR: Manuscript writing.

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RR, AS: Conception and design.
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München, den 29.08.2017

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EIDESSTATTLICHE VERSICHERUNG / AFFIDAVIT

Hiermit versichere ich an Eides statt, dass ich die vorliegende Dissertation “Learned Control Over Spinal Nociception In Healthy Subjects And Patients With Chronic Back Pain“ selbstständig angefertigt habe, mich außer der angegebenen keiner weiteren Hilfsmittel bedient und alle Erkenntnisse, die aus dem Schrifttum ganz oder annähernd übernommen sind, als solche kenntlich gemacht und nach ihrer Herkunft unter Bezeichnung der Fundstelle einzeln nachgewiesen habe.

I hereby confirm that the dissertation “Learned Control Over Spinal Nociception In Healthy Subjects And Patients With Chronic Back Pain“ is the result of my own work and that I have only used sources or materials listed and specified in the dissertation.

München, den 29.08.2017

Stefanie Krafft

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