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Reliability of conditioned pain modulation for the assessment of endogenous pain control pathways

Tanja Bossmann[a,*,1], Torsten Brauner[a], Heiko Lowak[b], Fernand Anton[c], Clemens Forster[d], Thomas Horstmann[a,e]

[a] Technische Universitaet Muenchen, Faculty of Sports and Health Sciences, Department of Conservative and Rehabilitative Orthopedics, Georg-Brauchle-Ring 60/62, 80992 Munich, Germany
[b] Physical Therapy Practice Rothschwaige, Gruenlandstraße 16, 85757 Karlsfeld, Germany
[c] Institute for Health and Behavior, University of Luxembourg, Maison des Sciences Humaines 11, Porte des Sciences, L-4366 Esch-sur-Alzette, Luxembourg
[d] Institute of Physiology and Pathophysiology, Friedrich-Alexander University Erlangen-Nuernberg, Universitätsstraße 17, 91054 Erlangen, Germany
[e] Medical Park Bad Wiessee, Klinik St. Hubertus, Sonnenfeldweg 29, 83707 Bad Wiessee, Germany

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ABSTRACT

Introduction: Conditioned pain modulation test paradigms are commonly used in humans for the convenient non-invasive testing of endogenous pain control pathways. In this context, interdigital web pinching has recently been proposed as a conditioning stimulus avoiding confounding with cardiovascular pain modulation effects. Reliability of this test paradigm has, however, not been sufficiently examined. The aim of this study was to examine inter-rater reliability of conditioned pain modulation assessment using interdigital web pinching.
Methods: Twenty healthy subjects were independently examined on two days by two different raters. The pressure pain threshold, measured at the thenar eminence of the dominant hand, served as the test stimulus before and after a two-minute period of conditioning using interdigital web pinching applied between the index and middle finger of the non-dominant hand. The intraclass-correlation-coefficient, coefficient of variation and standard error of measurement were calculated. Agreement was assessed using the Bland and Altman approach.
Results: The intraclass-correlation-coefficient and standard error of measurement of our conditioned pain modulation test paradigm was 0.76 and 1.6 N respectively. The limits of agreement were −6.4 to 5.6 N (mean difference −0.4 N).
Discussion: Our conditioned pain modulation test paradigm might be useful as an alternative method for the assessment of pain inhibitory pathways.

1. Introduction

Experimental pain models have been widely used to evaluate the physiological and pathophysiological processing of nociception and pain (Arendt-Nielsen & Yarnitsky, 2009; van Wijk & Veldhuijzen, 2010). Test paradigms known under the term *conditioned pain modulation* (CPM, formerly: diffuse noxious inhibitory control, DNIC) use heterotopic combinations of noxious stimuli to study the modulation of pain sensitivity (Yarnitsky, Granot, & Granovsky, 2013).

These kinds of psychophysical dynamic stimulation protocols might be useful for the determination of pro- or anti-nociceptive pain profiles of individuals (Granovsky & Yarnitsky, 2013; Yarnitsky et al., 2013). There is growing evidence that impaired pain inhibitory pathways, expressed by a reduced CPM effectivity and pro-nociceptive pain profile, are associated with chronic pain conditions (Lewis, Rice, & McNair, 2012; Yarnitsky, 2010). In this context, CPM test paradigms have been shown to be promising for the prediction of persistent post-operative pain (Yarnitsky et al., 2008; Yarnitsky, 2010) as well as for assessing benefits from analgesic treatments, for example the prediction of the efficacy of pregabalin in patients with painful chronic pancreatitis and the efficacy of duloxetine in patients with painful diabetic neuropathy (Olesen et al., 2013; Yarnitsky, Granot, Nahman-Averbuch, Khamaisi, & Granovsky, 2012).

* Corresponding author.
E-mail address: tanja.bossmann@tum.de (T. Bossmann).
[1] www.kro.sp.tum.de.

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CPM determines the effectiveness of pain inhibition induced by pathways descending from the brainstem (Le Bars, Villanueva, Bouhassira, & Willer, 1992; Villanueva & Le Bars, 1995). Effective descending pain inhibition implies that the pain sensitivity at some remote body region decreases when a constant painful conditioning stimulus is applied at another body region (van Wijk & Veldhuijzen, 2010).

In studies on CPM, a broad spectrum of conditioning stimulation modalities have been used, including thermal, mechanical, ischemic and electrical, which have mainly been assessed with psychophysical scaling techniques (Lewis, Heales, Rice, Rome, & McNair, 2012; Oono, Wang, Svensson, & Arendt-Nielsen, 2011; Pud, Granovsky, & Yarnitsky, 2009). The commonly applied thermal and ischemic conditioning stimuli may, however, induce pronounced cardiovascular responses and inherent baroreflex activity which may in turn confound the expected CPM-mediated pain inhibitory effect (Chalaye, Devoize, Lafrenaye, Dallel, & Marchand, 2013; Streff, Kuehl, Michaux, & Anton, 2010; Streff, Michaux, & Anton, 2011). Accordingly, experimental baroreceptor stimulation and hypertension have been shown to be accompanied by reduced pain sensitivity (Bruehl & Chung, 2004). Interdigital web pinching has recently been introduced as an alternative conditioning stimulus (Streff et al., 2011). It induces hypoalgesia while largely avoiding the aforementioned cardiovascular responses (Streff et al., 2011).

The reported consistency of the different CPM test paradigms varies considerably, with intraclass-correlation-coefficients (ICCs) ranging from 0.1 to 0.71 (Biurrun Manresa et al., 2014; Cathcart, Winefield, Rolan, & Lushington, 2009; Lewis et al., 2012a; Martel, Wasan, & Edwards, 2013; Olesen, van Goor, Bouwense, Wilder-Smith, & Drewes, 2012; Valencia, Kindler, Fillingim, & George, 2013; Wilson, Carvalho, Granot, & Landau, 2013). Most of these studies, however, have only used measures of relative reliability, namely ICC analyses, and have not determined absolute methods of reliability assessment, namely Bland-Altman analysis and the coefficient of variation (CV) (Biurrun Manresa et al., 2014). Thus the absolute reliability of the conditioned pain modulation test paradigm using interdigital web pinching has not been examined yet.

The aim of the present study was to examine inter-rater reliability of the CPM test paradigm using interdigital web pinching as a model for the assessment of endogenous pain inhibitory pathways.

2. Material and methods

This study used a repeated measures design to evaluate between-rater agreement in pressure pain thresholds determined prior to and following application of interdigital web pinching to induce endogenous pain inhibition.

2.1. Participants

Twenty healthy pain-free adults volunteered to participate in the study (male: 9, female: 11; age: 34.4 ± 10.2 years, height: 175.4 ± 9.4 cm, weight: 69.9 ± 13.3 kg). Written informed consent was obtained from all participants. Study exclusion criteria included any acute or chronic pain condition, impaired sensory perception and current medication use (Lewis et al., 2012a). All participants were independently examined on two separate occasions by two raters of different sex in randomized order. The average time interval between the two measurement sessions was three days. Participants were required to abstain from caffeine and physical exercise for at least two hours prior to each appointment. Alcohol consumption was prohibited 12 h before the tests. Both raters were trained regarding the standardized examination procedure, participant instructions and outcome variables and were blinded to the findings of the other rater.

The study was conducted in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans and was approved by the local ethics committee of the faculty of medicine, Technische Universität München (TUM) (project number: 5498/12). The examination procedures used were consistent with guidelines on pain research published by the International Association for the Study of Pain (IASP, 2005). This study is part of a larger clinical trial indexed within the German Clinical Trials Register (DRKS00005147).

2.2. Test stimulus (pressure-pain threshold)

In our CPM test paradigm, we used pressure-pain algometry as the test stimulus (Fig. 1a) before and after the application of the conditioning stimulus, which consisted of tonic interdigital web pinching (Fig. 1b).

The pressure-pain threshold (Wagner Pain Test FPN 100; 1 cm^2 rubber tip) was analyzed twice; before and after a two-minute period of interdigital web pinching. The pressure-pain threshold was determined with three series of ascending stimulus intensities applied to the thenar eminence of the dominant hand. In accordance with the method outlined by Rolke et al. (Rolke et al., 2006), each stimulus was administered manually at a rate of 1 N/s until the participant experienced the first sensation of pain. Stimulation series were separated by rest periods of 15 s. The mean of the three consecutive pressure measurements was calculated and defined as the final pressure pain threshold (Geber et al., 2011).

2.3. Conditioning stimulus (interdigital web pinching)

Interdigital web pinching was used as the conditioning stimulus. Previous studies have shown that a pain intensity of 4 to 6 on a ten point visual analog scale (VAS; 0 = no pain, 10 = worst pain) is necessary to induce the CPM effect (Lewis et al., 2012b; Yarnitsky et al., 2008; Yarnitsky et al., 2010; Yarnitsky, 2010). To identify the individually required compression force, the interdigital web between the index and middle finger of the non-dominant hand was placed in a custom-built stimulation device using a digital force gauge (PCE-FM50, PCE Instruments, Germany; probe area: 1 cm^2; full scale: 49.03 N; resolution: 0.01 N). After positioning the hand, the force gauge was raised at 2.4 mm/s (mini actuator HG2-0527, T.E.A. Transmissions Pty Ltd., Australia) until the participant rated their pain intensity as 6 on the VAS scale. Mechanical stimulation was then maintained for two minutes to induce the pain inhibitory effect and was continued throughout the application of the test stimuli (pressure-pain thresholds, described above). The effectiveness of endogenous pain inhibitory pathways was quantified by computing the difference in pressure-pain thresholds recorded during baseline and following interdigital web pinching protocols. Positive values reflect an increase in pressure-pain threshold from baseline and, as such, endogenous pain inhibition.

2.4. Statistical analysis

All data were analyzed using the Statistical Package for the Social Sciences version 20 (IBM Germany GmbH, Ehningen). The normal distribution of all variables was tested with a Kolmogorov-Smirnov analysis. All variables were found to be normally distributed. Means, standard deviations and coefficients of variation (CV) were used as summary statistics. The CV is a measure of relative variability and is defined as the ratio of the standard deviation to the mean. The CV represents the extent of variability in relation to the group mean. The higher the CV, the