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Introduction and validation of a less painful algorithm to estimate the nociceptive flexion reflex threshold

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ABSTRACT

The nociceptive flexion reflex (NFR) is a widely used tool to investigate spinal nociception for scientific and diagnostic purposes, but its clinical use is currently limited due to the painful measurement procedure, especially restricting its applicability for patients suffering from chronic pain disorders. Here we introduce a less painful algorithm to assess the NFR threshold. Application of this new algorithm leads to a reduction of subjective pain ratings by over 30% compared to the standard algorithm. We show that the reflex threshold estimates resulting from application of the new algorithm can be used interchangeably with those of the standard algorithm after adjusting for the constant difference between the algorithms. Furthermore, we show that the new algorithm can be applied at shorter interstimulus intervals than are commonly used with the standard algorithm, since reflex threshold values remain unchanged and no habituation effects occur when reducing the interstimulus interval for the new algorithm down to 3 s. Finally we demonstrate the utility of the new algorithm to investigate the modulation of nociception through different states of attention. Taken together, the here presented new algorithm could increase the utility of the NFR for investigation of nociception in subjects who were previously not able to endure the measurement procedure, such as chronic pain patients.

1. Introduction

The nociceptive flexion reflex is a spinal withdrawal reflex that can be assessed by electromyographic recording of the biceps femoris muscle during electrocutaneous stimulation of the ipsilateral sural nerve (Sandrini et al., 2005; Skljarevski and Ramadan, 2002). The strong correlation of the reflex threshold with the subjective pain threshold has made the NFR a widely used tool to investigate pain processing, pharmacological and psychological modulation of nociception as well as chronic pain conditions (Lim et al., 2011).

However, the applicability of the method is currently limited to subjects who are willing to endure the repeated painful stimulations required for assessing the reflex threshold.

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This poses a significant restriction for the method, especially when applied on patients suffering from chronic pain disorders, who exhibit a higher degree of pain sensitivity and pain catastrophizing (Ruscheweyh et al., 2013, 2012; Osman et al., 2000). To increase the utility of the method, an optimisation of the measurement procedure towards a lower pain induction seems necessary.

The standard procedure to assess the NFR threshold is an adaptive testing algorithm that increases the stimulation intensity when no reflex is detected and decreases it when a reflex occurs (Sandrini et al., 2005). While this standard algorithm is usually applied with variable stimulation intensity step sizes, the up and down steps are equal in size.

Here we propose a less painful algorithm, which in contrast uses an up/down ratio of 1:4, meaning that upon detection of a reflex the stimulation intensity is reduced four times as much as it is increased when no reflex occurs. This stimulation paradigm inherently leads to lower average stimulation intensities compared to the standard 1:1 algorithm, as the reduction of the stimulation intensity after every reflex occurrence is four times larger. Besides this direct effect, the 1:4 algorithm utilizes the probabilistic nature of the reflex occurrence (Sandrini et al., 2005) to provoke reflex responses below the reflex threshold. Since the 1:4 algorithm reduces the stimulation intensity in larger steps than it increases it back again, its application results in repeated stimulations below the reflex threshold. Single stimuli at such subthreshold intensities are unlikely to elicit reflex responses. However, because the overall probability to elicit a reflex cumulates with repeated stimulation, the application of multiple subthreshold stimuli increases the total probability of reflex responses already below the reflex threshold. Since the stimulation intensity is reduced after every reflex occurrence, such reflex responses at stimulation intensities below the reflex threshold prevent the algorithm to reach painful suprathreshold stimulation intensities. Therefore application of the 1:4 algorithm can be expected to induce less subjective pain than the standard 1:1 algorithm.

Here we demonstrate that (i) the 1:4 algorithm leads to less painful stimuli than the standard 1:1 algorithm, while (ii) agreement of the reflex thresholds estimated by the two algorithms is sufficient to allow them to be used interchangeably. We show that (iii) the new 1:4 algorithm allows for stimulating at shorter interstimulus intervals than at which the standard algorithm is commonly applied. Finally we show that (iv) the 1:4 algorithm can be used to investigate modulation of nociception.

2. Results

2.1. *General results*

56 (28 male/28 female) of 60 participants completed all measurement blocks and were included in the analysis. All 4 excluded participants did not tolerate the stimulation at an interstimulus interval of 1 s and aborted the respective blocks. The remaining 56 participants had a median (IQR) age of 23 (22–25), a median height of 177 (170–184) cm and a median weight of 69 (60–80) kg.

2.2. *Differences in subjective pain ratings, stimulation intensities and reflex threshold estimates between the standard 1:1 and the new 1:4 algorithm*

The new 1:4 algorithm led to lower average pain ratings, lower average stimulation intensities and yielded lower reflex threshold estimates compared to the standard 1:1 algorithm (Fig. 1). Population average reduction of the subjective pain ratings between the two algorithms amounted to 34% and

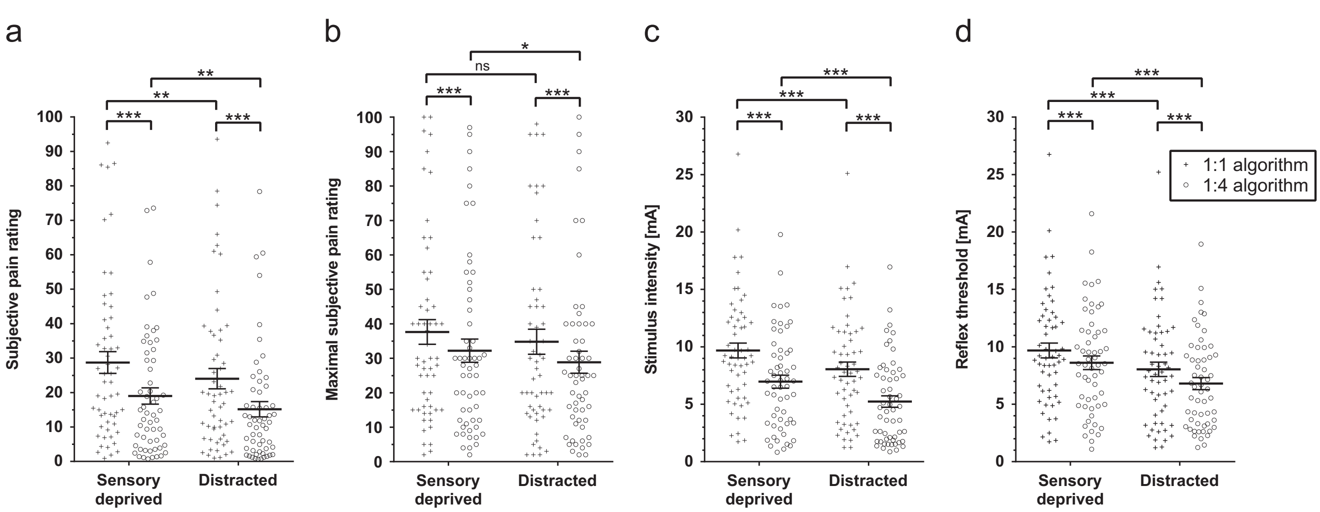

Fig. 1 – Comparison of subjective pain ratings, stimulation intensities and reflex threshold estimates between the new 1:4 and the standard 1:1 algorithm. Shown are (a) the individual average subjective pain ratings, (b) the individual maximal subjective pain ratings, (c) the individual average applied stimulation intensities and (d) the individual average reflex threshold estimates during application of the standard 1:1 algorithm (crosses) and the new 1:4 algorithm (circles), each at interstimulus intervals of 6 s, separated between the attention state of sensory deprivation and the state of distraction. Lines represent the population means and the respective standard errors. Stars mark significant differences between the states and the algorithms (ns: not significant; *: $p<0.05$; **: $p<0.01$; ***: $p<0.001$; *post hoc* test with Bonferroni correction).