Received: 4 May 2023 | Revised: 30 August 2023 | Accepted: 4 December 2023

DOI: 10.1111/psyp.14505

PSYCHOPHYSIOLOGY SPR WILEY

ORIGINAL ARTICLE

How to make calibration less painful—A proposition for an automatic, reliable and time-efficient procedure

Karolina Świder[1,2] | Stephan Moratti[1,2] | Ricardo Bruña[2,3]

[1]Department of Experimental Psychology, Psychology Faculty, Universidad Complutense de Madrid, Madrid, Spain

[2]Centre for Cognitive and Computational Neuroscience (C3N), Universidad Complutense de Madrid, Madrid, Spain

[3]Department of Radiology, Universidad Complutense de Madrid, IdISSC, Madrid, Spain

Correspondence
Karolina Swider, Department of Experimental Psychology, Psychology Faculty, Universidad Complutense de Madrid, Madrid, Spain.
Email: kswider@ucm.es

Funding information
H2020 EU-funded Marie Skłodowska-Curie Individual Fellowship (MSCA-IF), Grant/Award Number: 896262

Abstract

In behavioral and neurophysiological pain studies, multiple types of calibration methods are used to quantify the individual pain sensation stimuli. Often, studies lack a detailed calibration procedure description, data linearity, and quality quantification and omit required control for sex pain differences. This hampers study repetition and interexperimental comparisons. Moreover, typical calibration procedures require a high number of stimulations, which may cause discomfort and stimuli habituation among participants. To overcome those shortcomings, we present an automatic calibration procedure with a novel stimuli estimation method for intraepidermal stimulation. We provide an in-depth data analysis of the collected self-reports from 70 healthy volunteers (37 males) and propose a method based on a dynamic truncated linear regression model (tLRM). We compare its estimates for the sensation (t) and pain (T) thresholds and mid-pain stimulation (MP), with those calculated using traditional estimation methods and standard linear regression models. Compared to the other methods, tLRM exhibits higher R^2 and requires 36% fewer stimuli applications and has significantly higher t intensity and lower T and MP intensities. Regarding sex differences, t and T were found to be lower for females compared to males, regardless of the estimation method. The proposed tLRM method quantifies the calibration procedure quality, minimizes its duration and invasiveness, and provides validation of linearity between stimuli intensity and subjective scores, making it an enabling technique for further studies. Moreover, our results highlight the importance of control for sex in pain studies.

KEYWORDS

Dynamic Truncated Linear Regression Model, Pain Calibration Procedure, Pain sex differences, Intraepidermal Electric Stimulation

1 | INTRODUCTION

Pain perception is a subjective experience involving a complex interplay of factors encompassing psychosocial, affective, cognitive, and biological dimensions (Bushnell et al., 2013; Chen & Wang, 2023; Tracy, 2017). Experimental studies that, in controlled conditions, aim to investigate pain processing, perception, modulation, and management strategies, use standardized stimuli of different modalities (e.g., electrical, mechanical, thermal, and laser) to produce pain sensation (Schmidt & Willis, 2007; Olesen et al., 2012; Reddy et al., 2012). Typically, those studies employ diverse stimulus intensities (e.g., non-painful, mid, and high painful stimulation) which can be determined through a wide range of calibration procedures. Calibration is implemented to map the objective stimulation intensity to the individual's subjective perception of pain, such as pain threshold (*T*), and align it with commonly used pain response scales, such as visual analog scales (VAS) or the numeric rating scale (NRS; Adamczyk et al., 2022; Parhizgar & Ekhtiari, 2010). Despite the efforts to find better assessment methods (Gruss et al., 2019; Lautenbacher et al., 2022; Lundeberg et al., 2001; Wang et al., 2022), subjective self-report scales remain prevalent in both laboratory and clinical settings (Karcioglu et al., 2018; Williamson & Hoggart, 2005), notwithstanding their inherent limitations and weaknesses (Wagemakers et al., 2019). A critical concern revolves around the linearity of pain scores, which hampers the use of mathematical calculations (Lazaridou et al., 2019) to extrapolate values out of the calibration range or to otherwise force translations of complex non-linear phenomena onto an inaccurate linear scale (Berger & Baria, 2022). Therefore, within the domain of pain research, consistent reporting of linearity test results conducted on stimuli–response pairs (SRP) assumes pivotal importance. Nonetheless, it is regrettable that this practice is not consistently provided in existing literature, except for a few noteworthy examples (Atlas et al., 2010; Myles & Urquhart, 2005; Price et al., 1994).

Considering the above, there is a constant need to enhance our comprehension of the assessment and prediction of pain reporting and response. In this pursuit, a synergistic combination of two components is required: the utilization of an efficient stimulus selection procedure (e.g., method of limits, method of constant stimuli, method of adjustment, minimum entropy procedures, adaptive testing, and adaptive probing procedure) and an adequate stimuli estimation method[1] (Doll et al., 2013; Ehrenstein & Ehrenstein, 1999; Gescheider, 1997). Consequently, the primary objective of this study is to propose a new calibration method relying on an automatic stimulus selection procedure and a novel stimuli estimation method based on a specific linear regression model (LRM), which paves the way to minimizing stimuli number and hence makes the calibration process less painful.

In the present study, we incorporate intraepidermal electric stimulation (IES) that is widely used in neurophysiological studies (Paul et al., 2021; Perchet et al., 2012; van den Berg et al., 2020; van den Berg, Hijma, et al., 2022; van den Berg, Manoochehri, et al., 2022; Vecchio & De Pascalis, 2021) owing to its documented capacity to preferentially activate nociceptive afferent nerve fibers in the epidermis when the stimulus intensity is kept below twice the sensation threshold (*t*) (Motogi et al., 2016; Mouraux et al., 2010; Poulsen et al., 2020). Such stimulation can be elicited via a one-needle WASP electrode that operates on a similar principle to the classical Inui (Inui et al., 2002; Inui & Kakigi, 2012) electrode and a five-microneedle electrode (Jansen et al., 2021; Steenbergen et al., 2012; van den Berg & Buitenweg, 2021; van den Berg, Hijma, et al., 2022; van den Berg, Manoochehri, et al., 2022). Discrepancies in electrode attributes (e.g., needle length and outer ring radius) and the type of the stimulation (e.g., pulse train stimulation vs single long duration stimulation) warrant distinct calibration procedures.

Regarding the first element of calibration, namely, stimulus selection procedure, both one-needle (Inui et al., 2002; Inui & Kakigi, 2012; Manresa et al., 2018; Rütgen, Seidel, Riečansky, et al., 2015; Seidel et al., 2015; Vecchio & De Pascalis, 2021) and 5-needle (Steenbergen et al., 2012; van den Berg et al., 2021) IES electrodes utilize the method of limits (Gescheider, 1997), specifically a simple staircase procedure (Cornsweet, 1962). Such a procedure conventionally entails the presentation of stimuli of gradually increasing intensity, using fixed or varying step sizes, until the participant reports the initial *t* or *T*, depending on the calibration aim and scale anchors. Subsequently, stimuli with decreasing intensity are presented until no sensation of stimulation nor pain is perceived. Such a procedure offers several advantages over other stimuli selection methods (e.g., method constant stimuli or adjustment; Gescheider, 1997; Klein, 2001; Lue et al., 2017). It is precise, individualized, efficient, and easy to administer, making it a valuable and widely accepted tool in clinical and research settings. It applies the stimuli near the threshold being measured and does not require as many stimulus applications, as is typically needed in the case of the continuous stimuli method (Watson & Fitzhugh, 1900); nevertheless, it is not without limitations (Johnson, 2016). For individuals with high or low pain sensitivity, it may lead to ceiling or floor effects, hence rendering accurate measurement of the pain threshold impossible (Adamczyk et al., 2022). Furthermore, repetitive

[1]In literature, *threshold estimation method* is commonly used. However, this is limited to only estimating the threshold, and to generalize it, we decided to use the stimuli *estimation method* instead.

stimulation may cause habituation or sensitization, which can potentially affect the accuracy of the results (Paul et al., 2021).

Considering the above, we propose to collect SRP calibration data by implementing an automatic staircase procedure for both *t* and *T*, with adjusted step size and specific NRS (where score 5 indicates first pain sensation). This methodology enables participants to subjectively assess the intensity of stimulation from non-painful to the minimum level of painful anchors and may provide enough data to reliably check for SRP linear behavior. Therefore, we hypothesize that this stimulus selection procedure will achieve linearity for stimuli estimation between *t* and *T* (hypothesis 1, *H1*). The proposed method is adequate for studies employing single long-duration stimuli of relatively low current, which is aligned with previous studies that used WASP electrodes (Rütgen, Seidel, Riečansky, et al., 2015; Vecchio & De Pascalis, 2021).

Concerning the stimuli estimation method, IES usually involves averaging stimuli intensity corresponding to *t* or *T* acquired from several (usually three) repetitions of the procedure (Chan et al., 2012; Gescheider, 1997). In the context of studies that must determine reliable electrical stimulation intensities for painful and nonpainful stimuli that are different from *t* and *T*, the common practices are as follows: (1) implementation of an analogous method of limits for scale scores higher than *t* and/or *T* (e.g., stimuli consistently rated as 2 or 7 on NRS/VAS; Rütgen, Seidel, Riečansky, & Lamm, 2015; Świder et al., 2017; Vecchio & De Pascalis, 2021); (2) in the case of regulating long-duration stimuli strength via current manipulation, specific functions are employed depending on *T* and/or *t* levels (Adamczyk et al., 2021; Bąbel et al., 2017, 2018; Bajcar et al., 2020; Colloca & Benedetti, 2009); (3) if pulse train stimulation is used to control stimuli strength to selectively stimulate delta fibers, stimuli intensity is usually set to t or less than twice *t* (Steenbergen et al., 2012; van den Berg et al., 2021).

It is worth mentioning that in the literature, we can find attempts of unbiased calibration procedures for pulse train IES. These involve repetitive measurements of *t*, in the form of yes/no responses, which are then used as arguments in a mathematical function to estimate the level of painful stimulation delivered as a pulse train. Specifically, such procedures combine selection stimuli procedures (e.g., minimum entropy procedure; Doll et al., 2013; adapted probing procedure (Doll et al., 2013, 2015; van den Berg et al., 2021) with specific estimation methods (e.g., logistic regression or Bayesian estimation) or other procedures that implement a threshold tracking technique, designed to estimate detection thresholds that may potentially drift over time (Doll et al., 2015, 2016; van den Berg et al., 2021; van den Berg, Hijma, et al., 2022; van den Berg, Manoochehri, et al., 2022). Unlike train stimulation, there is still a need for further development of stimuli estimation methods for other electric stimulation, including single-pulse IES.

Our study proposes a calibration method that systematically checks for linearity for all SRP series (in the range of lower pain or even non-painful stimuli intensities), which allows us to incorporate a stimuli estimation method that relies on LRMs. Specifically, we propose to use a truncated LRM (tLRM) which, instead of being based on all the data from the calibration procedure, uses data up to an optimal point, chosen according to the maximum goodness-of-fit (R^2) of the predictive model. We hypothesize that tLRM will have a higher R^2 than LRM (*H2*). Optimal R^2, together with a convergence parameter based on the regression line gradient, forms the basis for rejection criteria, i.e., the determination of a failed procedure. Apart from improved reliability, such calibration may minimize stimuli number and intensity and shorten experimental time. Since we truncate the calibration data, we hypothesize that the number of necessary stimuli will be significantly smaller for tLRM than LRM (*H3*). Choosing an optimal set of data can help avoid habituation to painful stimuli, which has a negative impact on the results (De Paepe et al., 2019). Finally, automation of our method not only ensures consistency and reliability but may also provide a standardized framework that can be readily adopted, regardless of the specific laboratory context.

As a means of validation, the second objective of this study is to compare the accuracy and reliability against a set of commonly used estimation methods. We compare the values of *t* and *T*, both computed via classical approaches, such as threshold method (TM), and via a family of LRM, with the values obtained using our approach. Furthermore, in laboratory studies, it is common to define the stimulation intensity using a function of *T* (Bąbel et al., 2017; Colloca et al., 2010), so we compared scores higher than *T* (Rütgen, Seidel, Silani, et al., 2015; Świder et al., 2017). For this reason, we present a comparison of mid-painful stimulation calculated using our linear regression method (LRM). It is expected that, due to habituation (Paul et al., 2021), the values of *T* calculated using TM and LRM will be higher than those calculated using the proposed tLRM (*H4*) and that TM and LRM, compared to tLRM, will overestimate the intensity of the mid-pain (MP) stimuli (*H5*).

Finally, although it is known that there are sex differences in pain sensitivity, their direction and scope are not always consistent across experimental pain modalities (Fillingim & King, 2009; Hashmi & Davis, 2014). Despite the ambiguity, the prevailing opinion is that women are characterized by higher sensitivity in detecting all modalities of perceptual stimuli including pain and touch

(Fillingim & King, 2009). Hence, we evaluate sex differences in both *t* and *T* values for WASP electrodes which, to the best of our knowledge, has not been done before. We believe that there will be differences for both *t* and *T* between both sexes (*H6*).

2 | METHOD

2.1 | Participants

Seventy healthy volunteers (37 males; age mean ± *SD*: 25.47 ± 5.34) participated in the calibration phase of an experiment realized under the Maria Skłodowska-Curie Action (MSCA) project (NeuroCon). The sample size was calculated for the planned magneto- and electroencephalography (MEG and EEG, respectively) study using a GPower 3.1.9.4 based on the previous pain (Bąbel et al., 2017, 2018) and MEG (Moratti et al., 2017) studies (medium effect size, .25 *f* value, .26 η, .8 statistical power). The analyses involved ANOVA with repeated measures and within-between interactions, employing six groups (2 sex groups × 3 design groups) and three within-subjects measurements. The optimal total sample size was shown to be between 42 and 48). However, due to the possibility of participant rejection and the necessity of additional stimuli counterbalancing, this number was increased to 60. An extra 10 measurements were collected during a pilot study. During data processing, four participants were excluded (see Section 3 below), resulting in a total subject population of 66 individuals (35 males; aged between 18 and 36, mean ± *SD*: 25.62 ± 5.34).

Participants were recruited using the project website (https://neuroconmsca.wordpress.com/) and consisted of students and staff of the Complutense University of Madrid (UCM), the Centre for Biomedical Technology in Madrid (CTB), and the Basque Center on Cognition, Brain and Language (BCBL) in San Sebastian. With respect to the MEG main experiment (calibration does not require any of the following exclusion criteria), there were specific exclusion criteria which include the following: age below 18 and above 36 years, pregnancy, chronic diseases including chronic pain or migraine, recurrent pain, neurological or psychiatric diseases, heart disease, repeated unconsciousness, external and internal tissue damage, use of any type of medication or drug (psychoactive medication/substances such as antidepressants, antiepileptics, antipsychotics, or illegal drugs), family history of epilepsy/photic epilepsy episode, claustrophobia, left-handedness, implantation of metal elements (e.g., endoprostheses, implants, and metallic staples) and active implants (e.g., pacemaker, neurostimulator, insulin pump, and ossicle prosthesis), and metal wire behind teeth and tattoos. Additionally, only participants who scored less than 8 on the Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983) and did not undergo a magnetic resonance scan in the last 48 h before the experiment could sign up to the study.

The calibration procedure design was approved by the Ethics Committee of UCM, the Universidad Politécnica de Madrid (UPM), and BCBL, and followed the Helsinki Declaration and National and European Union regulations as part of the MSCA project. All participants were encouraged to ask questions, were informed that they could resign from participation at any moment during the study, and were guaranteed to receive 10 euros as compensation. Finally, none of the participants showed any signs of tissue damage nor reported genuinely adverse experiences as a result of undergoing the calibration procedure.

2.2 | Stimulation hardware

We decided to provide an in-depth laboratory set up description as the calibration procedure should be performed in similar conditions to the main experiment. Furthermore, the readers can design their experimental setup by replicating ideas presented in this article.

The stimulation was controlled from a Debian PC running a MATLAB script with the use of the Psychtoolbox library. Painful stimulation was controlled via the Elekta Stimulus Trigger Interface (STI102) StimBox, which is equipped with 16 binary input/output channels (BNC sockets) which generate a set of 16 5 V analog signals. We used two channels to control the stimulation strength. The complete stimulation hardware setup included the following: (1) PC with Windows 10 and LabVIEW, (2) NI myDAQ with Florida Research Instruments Inc. myDAQ BNC adapter for ×10 oscilloscope probes with connectors, (3) Digitimer DS5 Bipolar Constant Current Stimulator, (4) WASP electrodes with connection cables, and (5) three BNC cables. The way all the hardware pieces were connected is shown in Figure 1 and described below.

We employed one-needle WASP electrodes (Brainbox, United Kingdom) to administer electrocutaneous stimulation. The electrode features an outer and inner ring of 6.5 and 2 mm diameter, respectively, and in the center, it incorporates a 0.5-mm-long platinum pin. The WASP electrode and the stainless steel concentric bipolar needle electrode developed by Inui's (Inui et al., 2002, 2003; Inui & Kakigi, 2012) work on the same principle. Specifically, by pressing the WASP electrode against the skin, the pin is inserted into it, adjacent to the free nerve endings of the thin myelinated fibers in the epidermis and superficial part of the dermis (Lefaucheur et al., 2012; Rütgen, Seidel, Silani, et al., 2015). The WASP electrode requires

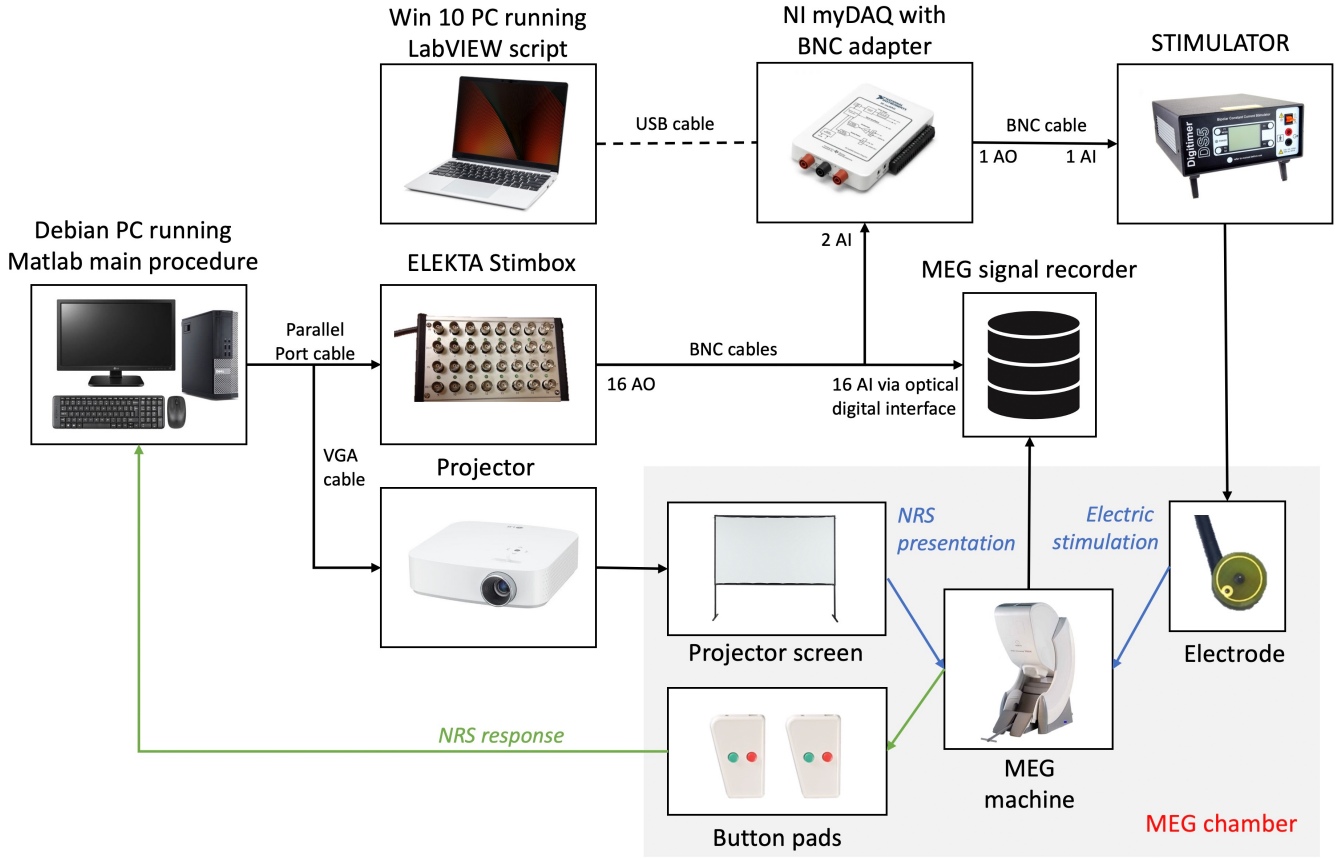

FIGURE 1 Laboratory set up used at CTB. For 24 participants that participated in the study at the BCBL, the Vipxx system (https://vpixx.com/) for stimulation was used instead of StimBox, and a Windows computer was used instead of the Debian 10 system.

minimal stimulation intensity to activate Adela nociceptors, typically up to 1.6 mA (for 300-ms stimuli duration), which corresponds to 1.5 times the individual pain threshold (Kaube et al., 2000). The stimulus strength can be modified via temporal summation of a long continuous or pulse-train simulation of fixed low intensity (Inui et al., 2002; Rütgen, Seidel, Silani, et al., 2015). For this reason, WASP electrodes have a lower probability of generating adverse secondary effects such as skin irritation.

During calibration, two WASP electrodes were attached to the dorsum of the left hand with a spacing of 8 cm (Seidel et al., 2015), but only one electrode was active and used to deliver 300-ms stimulations of increasing and decreasing intensities (see Figure 2b).

A Digitimer DS5 Bipolar Constant Current Stimulator was used owing to the ability to control its output via an analog voltage input. The stimulator was placed outside the MEG chamber to avoid electromagnetic interference. It was driven by an NI myDAQ Data Acquisition Device (National Instruments, Austin, TX, USA) in combination with a myDAQ BNC adapter (Florida Research Instruments Inc., Cocoa Beach, FL, USA), as it accepted these TTL (transistor-to-transistor logic) signals of 5 V as input and generated a varying voltage output. The NI myDAQ was controlled via USB by a PC running a LabVIEW (National Instruments, Austin, TX, USA) script, which was running continuously, listening to the input channels at a 1 kHz sampling rate and generating the requested output, if any (see Table S1 and Figure S1).

2.3 | Procedure

To facilitate the design of future studies, we present a detailed procedure description. Although our procedure was designed for an MEG experiment, it is easily adaptable to any type of pain study.

The participants were asked to enter a magnetically shielded room, take a seat in the MEG chair, facing a projector screen approximately 132 cm away, and have their hands placed on a board in front of them. They were informed that they would receive multiple increasing and decreasing intensities of electrical stimuli, starting from 0 mA, and that they would need to score their sensation according to an 11-point NRS using two 2-button response pads (Current Design, USA). In the meantime, the operator cleaned their skin with a cloth soaked in alcohol and attached the WASP electrodes to the dorsum of the left

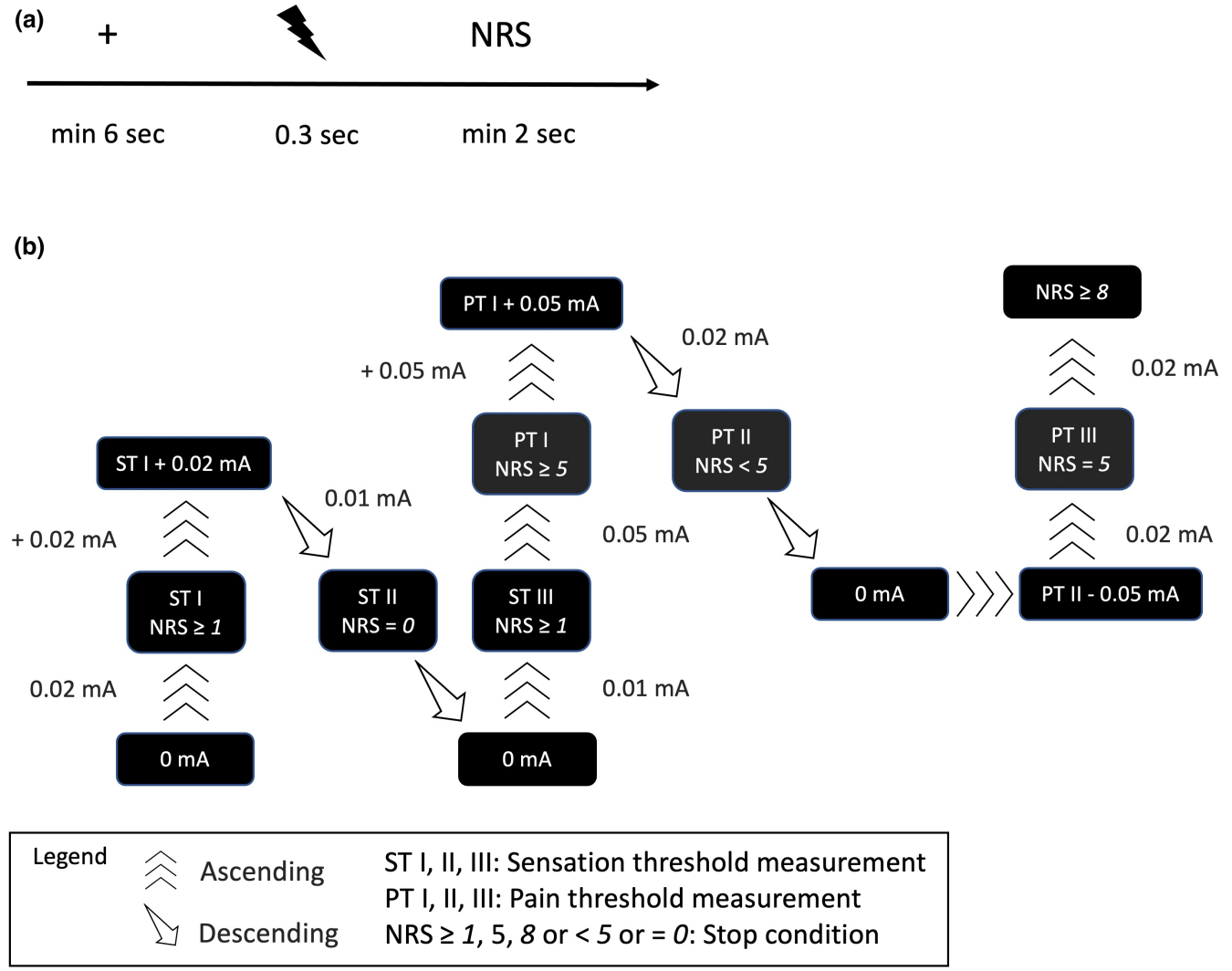

FIGURE 2 First step of the calibration procedure—stimulus selection procedure. (a) Calibration timeline; (b) Staircase stimuli selection procedure, which used three increasing or decreasing intensities steps (small: 0.01 mA, medium: 0.02 mA, and large 0.05 mA). Sensation (*t*) and pain threshold (*T*) intensities were established by taking an average of the three readings (ST I, STII, and STIII for t and PT I, PTII, and PTIII for T) corresponding to NRS rating 1 and 5, respectively.

hand(Seidel et al., 2015). After that, the participants were left alone in the MEG chamber, but with permanent visual and verbal contact via a video system during the calibration procedure.

The procedure began with the NRS practice exercise in which the participants learned how to use 2-Button Response Pads to choose the correct number on the NRS. First, they were provided with a written description of the exercise on the projector screen, and then they were given four practice trials during which they needed to choose four numbers (e.g. 2, 5, 7, and 4) on the scale. If they made a mistake, the trial was repeated. After the exercise, the participants underwent the calibration procedure which was completely automatic. The procedure applied electrical stimuli according to the timeline presented in Figure 2a. We used a variant of a simple staircase procedure, shown in detail in Figure 2b, similar to the one used in other studies that used WASP electrodes (Rütgen, Seidel, Riečansky, et al., 2015). The objective was to establish the sensation and pain thresholds so that reliable electrical stimulation intensities for painful and non-painful stimuli could be selected using a linear regression equation of SRP for the further main experiment.

First, participants were presented with a fixation cross for a minimum of 6 seconds. Then, the electric stimulation, with an adequate current intensity, was applied, which is indicated in Figure 2a by a bold lightning icon. Thereafter, participants were asked to rank the stimulus pain level, if any. After each stimulus, participants scored their sensations on the 11-point NRS ranging from 0 = *No electric sensation at all*, 1 = *I start to feel something*, 5 = *It*

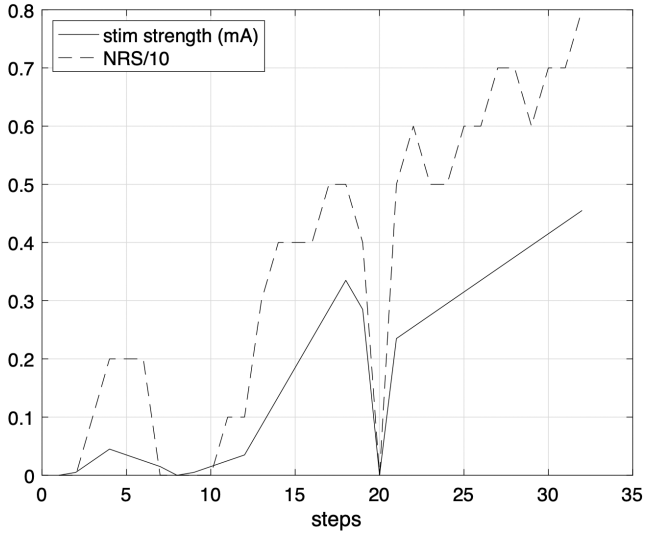

FIGURE 3 An example output provided at the end of the calibration procedure. The *x*-axis represents the number of steps and *y*-axis is the simulation current in mA (black line) and the response NRS divided by 10 (black dashed line).

starts to be painful to 10 = *The strongest painful sensation imaginable*, using the response pads. The numbers 1, 5, and 10 on the scale indicated the sensation threshold (t), the pain threshold (T), and the maximum pain tolerance (PT), respectively. These scale anchors resemble the ones used in the other studies (Roa Romero et al., 2013; Świder et al., 2017) and allow clear identification of the transition from non-painful to a painful perception.

Finally, the current intensity of the stimulation was increased or decreased, depending on the participant's response. To reduce the probability of attenuation and to reduce the number of steps required to achieve t and T values, we used three different ascending/descending steps (.01, .02, and .05, see Figure 2b). The interstimulus interval (ISI) was kept at a minimum of 8 s, to further minimize the probability of habituation.

Figure 3 presents an example of the output of the data collected during the calibration procedure.

The graph was presented to the experimenter and served as a visual cue to check if the data exhibited a habituation pattern. The maximal stimulation that the participants received was that corresponding to an NRS of 8. In a post-test, 4 min after the completed calibration, to verify if the correct stimuli intensities were calculated for each participant, three intensities of different strength were delivered in ascending order. Participants were asked to verbally rate stimuli intensity using the same NRS scale. The stimuli intensities were calculated based on LRM and the following equation based on the estimated thresholds: $3t$ mA for tactile, $1.5T + 0.02$ mA for low-pain (LP), and LP × 1.5 mA for MP.

2.4 | Stimuli estimation methods

We calculated the t and T values using four methods: TM, LRM to the whole dataset, and two versions of the truncated linear regression method (tLRM), based on the LRM.

2.4.1 | Threshold method

The TM calculates t by averaging three stimulation intensities (ST I, ST II, and ST III) rated as 1 on the NRS (Figure 2b), replicating a procedure used in previous studies (Bąbel et al., 2017; Świder & Bąbel, 2013). ST I was achieved in the first ascending curve, selecting the first stimulation current with an NRS equal to 1. ST II was taken in the first descending curve, just before the first NRS rating equal to 0. ST III was achieved in the second ascending curve, when NRS reached 1.

Analogously, T was calculated by averaging three stimulation currents (PT I, PT II, and PT III) scored as 5 on the NRS (see Figure 2b). PT I was achieved in the second ascending curve, selecting the stimulation current corresponding to an NRS equal to 5. PT II was taken in the second descending curve, just before an NRS equal to 4. PT III was achieved in the third ascending curve, selecting the stimulation current corresponding to an NRS equal to 5.

2.4.2 | Linear regression method

We used a linear regression to model NRS ratings as a function of the stimulation intensity. We used the Matlab function *fitlm*, which fits a LRM to variables in the entire dataset and returns a relation $NRS = m \cdot I + c$, where I is the stimulation current, m is the gradient, and c is the intercept. We also obtained R^2 as a statistical measure to determine the proportion of variance in the dependent variable that can be explained by the independent variable.

2.4.3 | Truncated linear regression method

In this work, we propose two novel stimuli estimation methods, namely, tLRMm and tLRMmc, truncated linear regression method with variable intercept obtained by modifying the LRM method to use only a specific part of the calibration data. The difference between both methods is that tLRMm assumes that the c intercept is 0, while tLRMmc does not. As previously, we used the Matlab function *fitlm* to create the regression models.

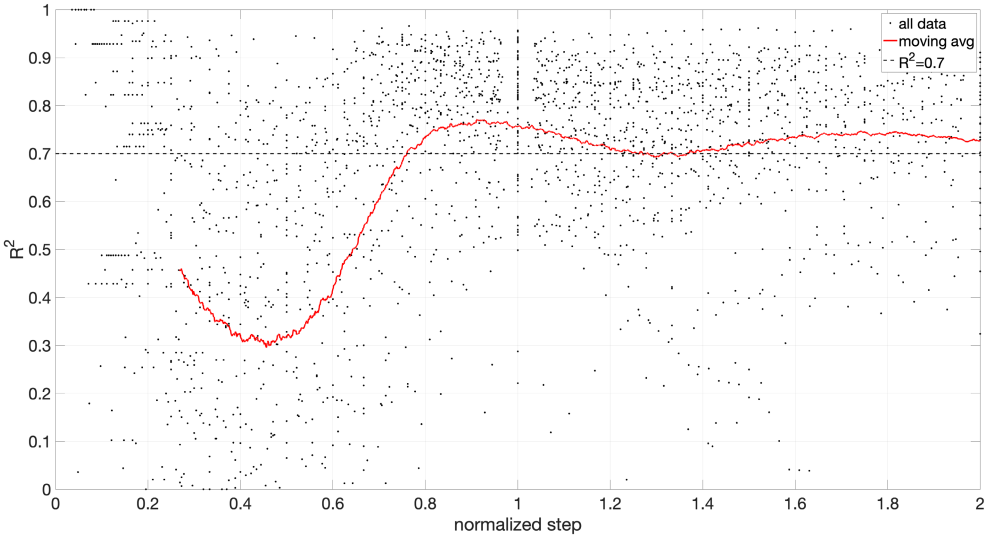

FIGURE 4 R^2 values against the number of steps normalized with the zero current simulation. The black dots represent all the R^2 values, the red line moving average over 250 points and dotted line the $R^2 = .7$.

In both, the linear model is obtained not once, as in the case of LRM, but iteratively when a new SRP is collected, starting from the second stimulation. As a result, m, c, and R^2 are dynamically obtained as a vector of size $n-1$, where n is the total number of stimulations. Later, we truncate the vector based on the position of maximum R^2, given that calibration was run for sufficiently many steps. To determine it, the R^2 vectors for all the participants were plotted against the steps normalized with the second time a zero current stimulation was delivered. A moving average window of 250 data points was applied for better data interpretation (Figure 4).

According to Figure 4, the maximum R^2 occurs at a normalized step .91 and is equal to 0.77. For simplicity, the second zero current stimulation, i, was chosen as the reference point, corresponding to normalized step 1 with R^2 equal to .76. Additionally, to ensure optimal performance, a step range was defined between $i-3$ and $i+3$, and the optimal step for tLRM corresponded to the maximum R^2 (see an example shown in Figure 5). Such design minimizes the number of painful stimuli and limits the highest pain sensation NRS rating to approximately 5, the pain threshold.

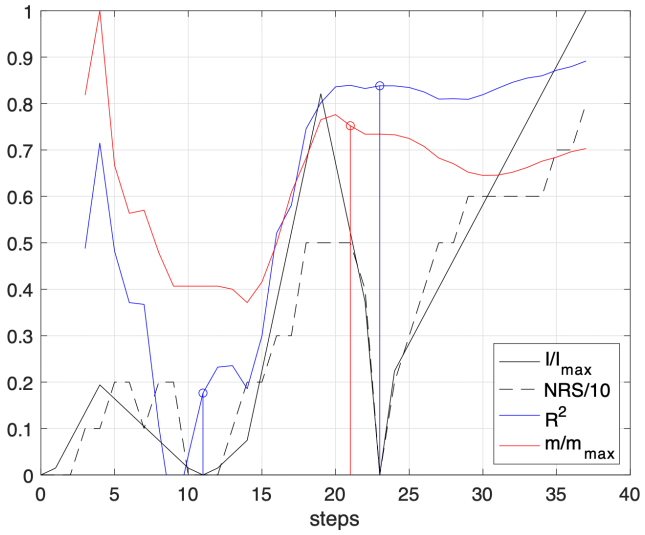

FIGURE 5 An example of truncated linear regression model (tLRM) output. The x-axis represents calibration steps, starting from 0. The y-axis corresponds to: stimuli strength, I, normalized by its maximum value (black line); corresponding NRS rating divided by 10 (black dashed line); evolution of the coefficient R^2 for the linear regression (blue line); and linear regression equation gradient, m, normalized by its maximum value (red line). Blue vertical lines represent points where zero current stimulation was applied, and the red vertical line represents the optimal truncation point.

3 | DATA ANALYSIS

3.1 | Rejection criteria

To ensure that only good-quality data were analyzed, we quantitatively checked which participants "failed" the calibration procedure. This verification was performed for the tLRMmc and tLRMm, as the evaluation of these methods is the object and novelty of this study.

We propose three rejection criteria with their corresponding thresholds. The first one is based on R^2 where high values indicate good data linearity. A recent study on thermal stimulation (Amir et al., 2022) established that for a successful calibration procedure, R^2 should be at least .4. The second is related to the convergence

of the parameters. We can say that the calibration procedure has converged at a point where the regression model parameters are invariant when further data are incorporated. As a measure of convergence, we propose to modify the classical Cauchy's criterion based on the gradient m:

$$\sum_{i=o}^{o+r-1} \frac{m_{i+1} - m_i}{m_o} < \epsilon$$

where o subscript symbolizes the optimal truncation step and ϵ is a limit which we propose to set to 0.25. Finally, the third criterion limits the stimulation current to prevent participants from receiving multiple pain stimulations of very high intensity and habituation). In our case, we chose an upper limit to the pain sensation (NRS = 5) as 0.635 mA.

3.2 | Statistical analysis

We investigated if there are differences in the goodness of fit for the three LRMs (LRM, tLRMm, and tLRMmc). R^2 distributions were negatively skewed (−1.41, −1.24, and −1.31, respectively) and did not satisfy the Anderson–Darling test for normality ($p < .005$). To mitigate the skewness, a set of 40 different power transformations were tested, which concluded that power 4.69 yielded optimal normalization results (skewness of 0.24, −0.30, and −0.35, respectively and Anderson–Darling normality test $p = .054$, .040, and .055, respectively). Next, we performed a mixed-effects repeated measure ANOVA for R^2 with *Linear Regression Type* (LRM, tLRMm, and tLRMmc) as a within- and *Sex* as between-subject factor (females and males).

To indicate which stimuli estimation method requires fewer stimuli, we used a nonparametric Wilcoxon signed rank test on the stimuli number required by LRM versus tLRM (by definition, the tLRMm and tLRMmc require the same number of stimuli).

Afterward, we investigated if there were differences between the four tested stimuli estimation methods. We performed a mixed-effects repeated measure ANOVA for the calculated values of T and t with *Threshold Type* (sensation and pain threshold) and *Sex* (females and males) as between- and *Estimation Type* (TM, LRM, tLRMm, and tLRMmc) and *Threshold Type* (t and T) as within-subject factors.

Next, we compared the intensity of MP stimulation calculated for each of the stimuli estimation methods. For TM, it was obtained by $1.5 \times T$ used in previous studies (Bąbel et al., 2018; Colloca et al., 2010). For linear models, the intensity leading to an NRS of 8 was used. Then, we performed a repeated measures ANOVA for mid-pain intensity (mA) with *Estimation Type* (TM, LRM, tLRMm, and tLRMmc) as within- and *Sex* (females and males) as between-subject factor.

If necessary, Greenhouse–Geisser correction was applied for violations of sphericity, and in the case of interaction effects, the repeated measure ANOVA was followed by multiple comparison tests, using Bonferroni correction for multiple comparisons, to indicate the meaning of the effect. Data analysis was performed using MATLAB (R2020b Update 2), and statistical analyses were performed using IBM SPSS (Version 26).

4 | RESULTS

According to the rejection criteria, we determined that four participants (5.7%) needed to be excluded from further analysis due to low R^2 (below .4, see Figure 6a,d), stimulation currents above 0.635 mA for NRS of 5 (see Figure 6b), or lack of convergence (see Figure 6c,d).

For the LRM and tLRM (both methods), R^2 values were above .75. No patterns could be observed in the residual plots, suggesting a random distribution of residuals, implying no bias. Furthermore, the residuals' mean is close to 0% and 80% of the residuals are normally distributed. The relation between stimuli intensity and NRS ratings is, therefore, linear, which is in line with our hypothesis (*H1*).

Results of repeated measure ANOVA for R^2 revealed a statistically significant main effect of the *Linear Regression Type* ($F_{(2,65)} = 17.25$, $p < .001$, $\eta_p^2 = .21$) and no effects of *Sex* ($F_{(1,64)} = .06$, $p = .81$, $\eta_p^2 = .16$) nor interaction effect *Linear Regression Type* × *Sex* ($F_{(1,64)} = 2.10$, $p = .15$, $\eta_p^2 = .02$). The pairwise comparisons of *Linear Regression Type* indicated statistically significant differences between LRM vs. tLRMm, LRM versus tLRMmc, and tLRMm versus tLRMmc. The results indicate that the tLRM models (tLRMmc reported higher R^2 than tLRMm, as would be expected due to a higher number of degrees of freedom) ensure the highest degree of linearity, as was hypothesized (*H2*; Table 1).

The Wilcoxon signed rank test for the number of stimuli required by the LRM versus tLRM revealed a statistically significant difference ($p < .001$). tLRM takes on average 17.2 steps less than the LRM (36%), which is in line with our hypothesis (*H3*). Descriptive statistics of the number of steps for each estimation method are presented in Table 1.

The results of repeated measures ANOVA for individual threshold values of T and t are presented in Table 2. We found statistically significant main effects of *Estimation Type*, *Threshold Type*, and *Sex*, as well as interaction effects of *Estimation Type* × *Threshold Type* and *Threshold Type* × *Sex*.

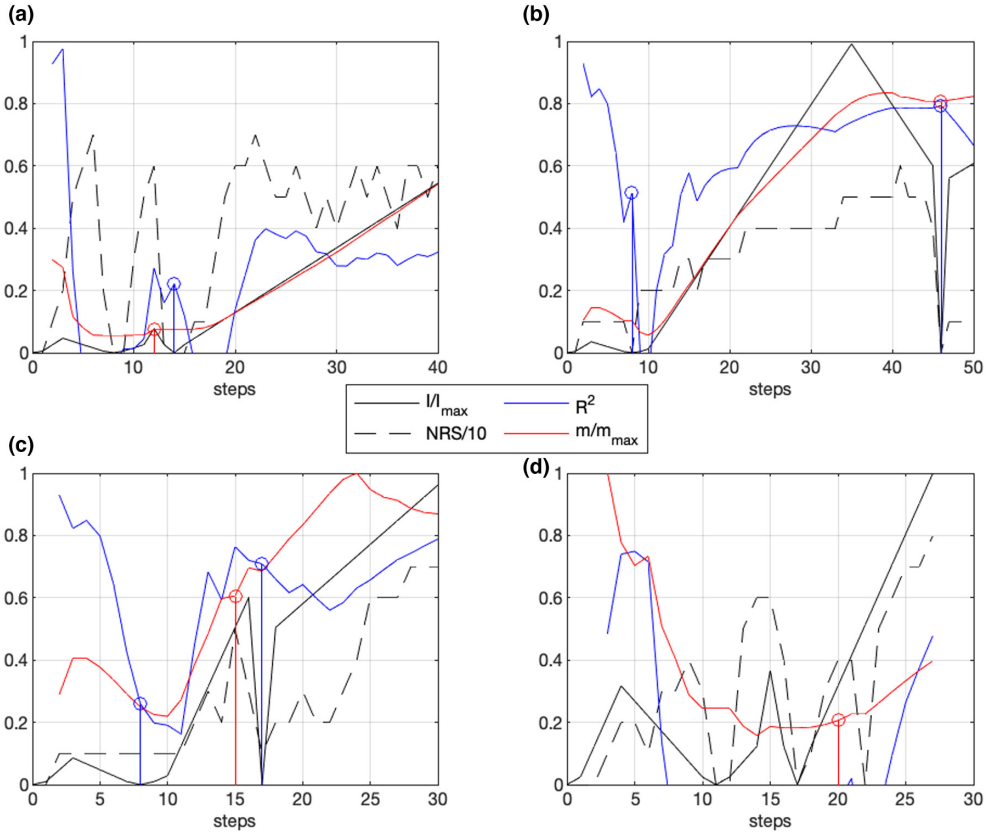

FIGURE 6 Participants rejected from further analysis. For plot description refer to Figure 5. Blue vertical lines represent points where zero current stimulation was applied; the red vertical line represents the optimal truncation point. Rejection reasons: (a) low R^2 (blue line) indicating lack of data linearity and high number of delivered stimuli (steps on *x*-axis); (b) high stimuli current and high number of delivered stimuli; (c) lack of convergence (the gradient, red line, changes constantly) and mistake in 0 mA stimulus scoring; (d) lack of convergence, low R^2 and mistake in 0 mA stimuli scoring.

The within-factor multiple comparison tests for the interaction *Estimation Type* × *Threshold Type* for the *T* values showed a statistically significant difference between LRM versus TM, tLRMmc versus TM, tLRMm versus TM, tLRMm versus LRM, and tLRMmc versus LRM (see Table 2 and Figure 7), which is in line with our hypothesis that *T* values calculated for longer-lasting TM and LRM may be higher than ones calculated based on the tLRM (*H4*). An analogous exploratory analysis performed for *t* values revealed that there was a statistically significant effect in the comparison between TM and the three types of LRM (see Table 2 and Figure 7). It is interesting to note that for the four participants, the LRM method predicted negative stimuli intensity for *t*.

The pairwise comparison between the tLRMm and tLRMmc for *t* and *T* found no differences. For this reason, both models will be from now on described as tLRM.

The ANOVA analysis for mid-painful stimulation indicated statistically significant main effects of *Estimation Type* ($F_{(3,64)}=19.38$, $p<.001$, $\eta_p^2=.23$) and *Sex* ($F_{(1,64)}=10.63$, $p>.01$, $\eta_p^2=.14$), but no interaction effect *Estimation Type* × *Sex* ($F_{(1,64)}=0.93$, $p>.05$, $\eta_p^2=.01$; see Figure 8 and Table 1).

The pairwise comparisons indicate a statistically significant difference ($p<.05$) between TM versus LRM, TM versus LRMm, TM versus LRMmc, LRM versus LRMm, and LRM versus LRMmc. These results are in line with our hypothesis that the TM and LRM may overestimate the intensity of the pain stimuli (*H5*). The post-test revealed that, for most of the participants, mid-painful stimulation was indicated for NRS scores between 6 and 9, low-painful between 3 and 6, and tactile between 2 and 3.

Finally, the within-factor multiple comparison tests showed sex differences as reflected by the interaction *Threshold Type* × *Sex*. For both *T* and *t*, we found statistically significant differences between both sexes, which is in line with our hypothesis of the existence of sex differences in *t* and *T* (*H6*). The results are presented in Table 2 and Figure 9.

5 | DISCUSSION AND CONCLUSIONS

Our main aim was to address challenges posed by nonlinear behavior of pain scores which hamper an accurate

TABLE 1 Descriptive statistics of investigated variables for all four estimation methods: TM, tLRMm, tLRMmc, and LRM.

Estimation method	Sex	t[a] (mean ± *SD*)	T[b] (mean ± *SD*)	Mid-painful stimulation[c] (mean ± *SD*)	Step number[d] (mean ± *SD*)	R^2[e]	N[f]
TM	Female	0.02 ± 0.01	0.26 ± 0.32	0.40 ± 0.23	37.68 ± 2.64	N/A	31
	Male	0.03 ± 0.02	0.37 ± 0.15	0.56 ± 0.22	46.56 ± 2.49		35
	Total	0.02 ± 0.02	0.32 ± 0.16	0.48 ± 0.24	42.38 ± 1.88		66
LRM	Female	0.04 ± 0.03	0.23 ± 0.16	0.38 ± 0.23	37.68 ± 2.64	0.80 ± 0.09	31
	Male	0.07 ± 0.05	0.35 ± 0.16	0.56 ± 0.22	46.56 ± 2.49	0.75 ± 0.15	35
	Total	0.05 ± 0.05	0.29 ± 0.17	0.47 ± 0.23	42.38 ± 1.88	0.78 ± 0.13	66
tLRMm	Female	0.04 ± 0.02	0.19 ± 0.10	0.30 ± 0.14	23.55 ± 0.75	0.81 ± 0.12	31
	Male	0.05 ± 0.02	0.27 ± 0.11	0.43 ± 0.16	26.69 ± 1.1.7	0.81 ± 0.13	35
	Total	0.05 ± 0.02	0.23 ± 0.11	0.36 ± 0.16	25.21 ± 0.73	0.81 ± 0.12	66
tLRMmc	Female	0.04 ± 0.02	0.19 ± 0.10	0.30 ± 0.14	23.55 ± 0.75	0.83 ± 0.11	31
	Male	0.05 ± 0.03	0.27 ± 0.11	0.43 ± 0.16	26.69 ± 1.1.7	0.83 ± 0.13	35
	Total	0.04 ± 0.03	0.23 ± 0.11	0.37 ± 0.16	25.21 ± 0.73	0.83 ± 0.12	66

Abbreviations: tLRMm, truncated linear regression method that assumes that the coefficient c (the y-intercept) is 0; tLRMmc, truncated linear regression method where the coefficient c is not equal to 0; TM, threshold method.

[a]Sensation threshold.

[b]Pain threshold.

[c]Pain stimulation corresponding to 1.5 × T for TM and NRS of 8 for all linear models.

[d]Number of steps/stimuli of each calibration procedure.

[e]Coefficient of determination.

[f]Participant number.

and comprehensive evaluation of pain perception. We have achieved it by designing a stimuli estimation method that ensures SRP linearity, measured using R^2 and achieving values above .75, and allows for a significant reduction in the number of delivered stimuli during the calibration (36% fewer compared to LRM), making the calibration procedure less painful to the participants. It also allowed for quantifying the quality of the procedure and for establishing automatic rejection criteria. Finally, we have made a thorough analysis of our stimuli estimation method's accuracy and reliability against a set of commonly used estimation methods.

Consistent with our first hypothesis, SRPs were shown to be highly linear, which is indicated by high R^2 values for the LRM and both tLRM models. These findings support results of earlier research (Oliveira et al., 2014; Van Der Heide et al., 2009). Linearity of SRPs has been a topic of debate, with previous studies showing inconsistent results (Hartrick et al., 2003; Price et al., 1994). The observed variability may be linked to the type of laboratory stimulation and the specific clinical pain condition under investigation (Myles & Urquhart, 2005).

Furthermore, the tLRM shows higher R^2 values than the LRM (*H2*), indicating that considering only an optimal dataset gives better results than a complete one, likely due to habituation effects in the latter. In our study, we utilized an 11-point NRS to assess both painful and non-painful stimuli, following the methodology of earlier research (Colloca et al., 2010; Roa Romero et al., 2013; Świder et al., 2017). This, together with the tLRM, allows for performing estimations on SRP. Finally, truncating data has another advantage, namely, decreasing the number of delivered stimuli (*H3*). This means that the tLRM required on average 17.2 fewer stimuli than the complete staircase procedure, making it less painful and less uncomfortable for the participant, and possibly mitigating habituation.

Since data linearity has been shown, R^2 can be used to quantify the correctness and reliability of the calibration procedure. This allows for an automatic (no human labor required) and instant (immediately after calibration end) procedure for rejection of participants according to the three proposed criteria. As a result, the experimenter can avoid perpetuating errors in further stages of the experiment, which can save time and financial resources.

Further reliability investigations involved threshold comparisons between the methods. On the one hand, the LRM and tLRM yield statistically similar results for t, which are higher than for the TM method. This means that either the LRMs overestimate the required stimulus, or the TM underestimates it. We suspect that the latter is more probable, due to a higher sensitivity to stimuli at the beginning of the procedure when t is predicted by TM. On the other hand, T estimated by the tLRM is lower than for the TM and LRM. This is in line with our hypothesis (*H4*) that, in general, the TM and LRM would indicate higher stimuli intensity as they require more stimuli application

TABLE 2 The results of repeated measures ANOVA for pain and sensory thresholds.

	F	*df*	*p*	η_p^2
Main and interactions effects				
Estimation type	19.06	3,64	**<.001**	.23
Threshold type	326,74	1,64	**<.001**	.83
Sex	11.34	1,64	**.001**	.15
Estimation type × Threshold Type	37.42	3,64	**<.001**	.37
Estimation Type × Sex	1.5	3,64	.21	.02
Threshold Type × Sex	9.89	1,64	**<.01**	.13
Estimation Type × Threshold Type × Sex	1.51	3,64	.23	.02
Within-factor multiple comparison tests for T[a] values				
Estimation Type × Threshold Type				
LRM versus TM			**<.001**	
tLRMm versus TM			**<.001**	
tLRMmc versus TM			**<.001**	
tLRMm versus tLRMmc			.10	
tLRMm versus LRM			**.001**	
tLRMmc versus LRM			**<.01**	
Within-factor multiple comparison tests for t[b] values				
Estimation Type × Threshold Type				
LRM versus TM			**<.001**	
tLRMm versus TM			**<.001**	
tLRMmc versus TM			**<.001**	
tLRMm versus tLRMmc			.42	
tLRMm versus LRM			.81	
tLRMmc versus LRM			.14	
Between-factor multiple comparison				
Threshold Type × Sex				
T[a] female versus males	10.90	1,64	**<.01**	.15
t[b] females versus males	8.07	1,64	**<.01**	.11

Bold font indicates statistical significance.

Abbreviations: tLRMm, truncated linear regression method that assumes that the coefficient *c* (the *y*-intercept) is 0; tLRMmc, truncated linear regression method where the coefficient *c* is not equal to 0; TM, threshold method. Bold font indicates statistical significance.

[a]Pain threshold.

[b]Sensation threshold.

and therefore participants can suffer from habituation. Habituation can be minimized by using an adequate ISI, which in our study was at least 8 s. In studies using analogous intra-epidermal electrodes, rest time between three stimulation sets was 1 min (Tanaka et al., 2021) or an ISI between 2.5 and 3.5 s (Poulsen et al., 2020). Consequently, the chosen ISI was sufficient but, in future studies, including breaks between ascending/descending curves can further mitigate those effects. Next, increasing/decreasing stimulation intensity during the staircase procedure can be predicted by the participants, introducing bias to the results (Ehrenstein & Ehrenstein, 1999; Levitt, 1970). A future verification method could include applying an extra set of random stimuli and comparing their ratings with the predictions.

Next, since the tLRMm and tLRMmc yield statistically similar results for *t*, *T*, and mid-painful stimuli, we propose to use the tLRMm method, as it is described by only one parameter, *m*, and forces the condition that for no stimulation the NRS is 0. This, in turn, makes comparisons between participants and experiments easier and avoids unrealistic situations where negative stimulation is predicted for low NRS, as was observed for a few cases of the LRM.

The investigation into the assumption that non-painful stimuli can be used to make predictions about painful

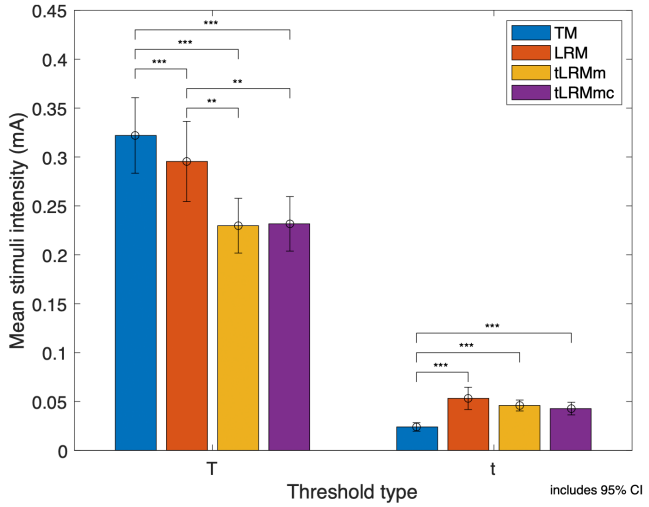

FIGURE 7 Pain (*T*) and sensation threshold (*t*) values in mA for each of the four tested stimuli estimation methods. TM, Threshold Method; tLRMm, truncated linear regression method that assumes that the coefficient *c* (the *y*-intercept) is 0; tLRMmc, truncated linear regression method where the coefficient *c* is not equal to 0; ** and *** correspond to $p < .01$ and $p < .001$, respectively.

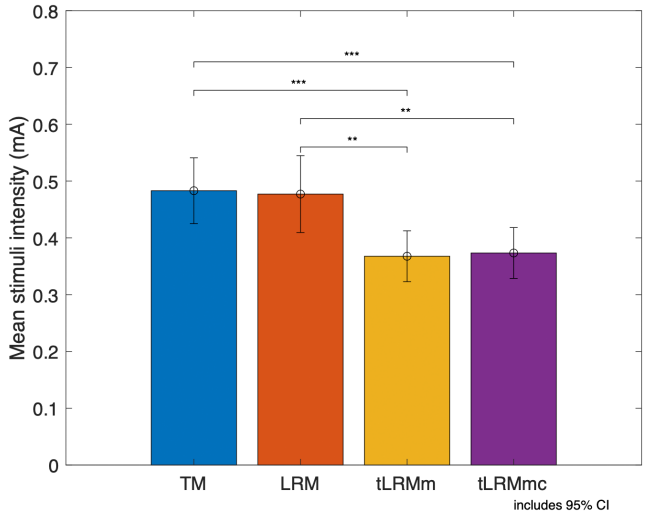

FIGURE 8 Mid-painful stimulation estimated for each of four estimation methods. TM, threshold method; tLRMm: truncated linear regression method that assumes that the coefficient *c* (the *y*-intercept) is 0; tLRMmc, truncated linear regression method where the coefficient *c* is not equal to 0; For TM the equation 1.5 T was used to set mid-painful stimulation; ** and *** correspond to $p < .01$ and $p < .001$, respectively. For TM, the equation 1.5 T was used to set mid-painful stimulation.

stimuli involved a comparison between predicted levels for mid-painful stimulus. There is no statistically significant difference between the TM based on $1.5 \times T$ and the LRM. However, they are different to the intensity levels predicted by the tLRM, which are significantly lower,

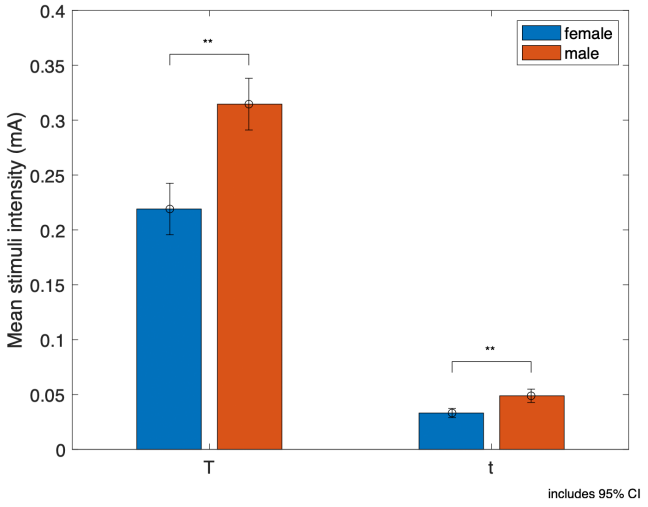

FIGURE 9 Pain (*T*) and sensation (*t*) threshold values for males and females. **$p < .01$.

possibly due to habituation of the former (*H5*). However, we cannot exclude that the tLRM mid-painful intensity is underestimated, as the post test for the LRM validated its correctness with low- and mid-painful stimulations. A possible way of mitigating this effect could be using an adaptive staircase procedure (Atlas et al., 2010). This method first applies several stimuli, which serves to create the initial linear model, followed by a set of stimuli with random order and strength, aimed to refine that model. Such refinement, based on random stimuli, could be added to the tLRM to verify the possibility of underestimating the threshold-related stimuli. Nevertheless, the higher degree of linearity in the tLRM is a strong indication that non-painful stimulation calibration can be extrapolated to provide predictions of painful stimulation. To further improve the proposed calibration reliability, a random strength stimulation verification of reliability should be performed *a posteriori*. This could be used to check if the calibration results are consistent over time, as was done before for thermal stimulation (Amir et al., 2022). Afterward, it is recommended to compare our method to the results obtained using the random staircase procedure. This method involves using a predetermined set of amplitudes to randomly select stimuli. Studies have shown that the random staircase procedure achieves higher precision compared to the standard method of stimulus selection (Doll et al., 2013).

Finally, regarding sex differences, our results indicate that females require a lower stimulation intensity than men to reach both the sensation and pain thresholds (*H6*). This may suggest that women have a higher sensory acuity, at least in response to electric stimulation via WASP electrodes. This conclusion is not consistent across other studies (Racine et al., 2012a, 2012b); however, the predominant view is that women have a greater pain responsiveness for

most pain modalities (Sorge & Totsch, 2017). This is not unique to pain, as there is evidence that women are often more perceptive across multiple sensory domains (Hashmi & Davis, 2014), exhibiting greater detection and discrimination sensitivity to tactile (Boles & Givens, 2011), olfactory (Bontempi et al., 2021), and visual stimuli (Shaqiri et al., 2018). These findings are also consistent with the clinical reality that has shown sex differences in pain tolerance and thresholds, as well as a higher prevalence of chronic pain conditions in females (Meints et al., 2018; Sorge & Totsch, 2017; Templeton, 2020). Finally, sex differences in pain perception and modulation exists at the molecular, cellular, and system level (Presto et al., 2022). According to our results, sex difference in pain perception induced via WASP electrodes should be considered when designing further experiments. In studies that control for sex (which include both men and women as within-study design), this sex difference may not be as significant as in between-study design when examining only one sex. Next, controlling for the influence of sex hormones, including estrogens, is an important factor to consider in pain perception research. The present study did not take this into account, despite ample evidence demonstrating the impact of sex hormones on pain perception (Amandusson & Blomqvist, 2013).

In relation to the above, the calibration procedure in our study was automated to enhance standardization and minimize experimenter biases (Engskov et al., 2021). Moreover, to control the effect of experimenter characteristics and sex, a woman and a man were always present in the laboratory. The literature on this topic is marked by significant ambiguity, and it is possible that pain modality may play a crucial role. For instance, higher thresholds for pain were determined in the presence of a female investigator with regard to participant sex (Engskov et al., 2021). Another study, where pressure stimuli were used, shows that men showed higher average pain thresholds when tested by a female experimenter (Gijsbers & Nicholson, 2005). Interestingly, heat pain thresholds were not shown to be significantly influenced by experimenter sex (McDougall et al., 2021). Therefore, future studies should investigate the impact of experimenter sex on pain induced by WASP electrodes.

Another important aspect to discuss is other electrical stimulation types. Failure to account for the specific properties of the electrical stimulation type and the electrodes utilized may impact the final calibration results (e.g., number of steps and threshold estimates). First, previous studies indicate that sensation produced by needle electrode stimulation and surface electrode stimuli are distinct. The former is often described as pricking and tingling, while the latter is labeled as touch or shock (Mouraux et al., 2010). Next, various characteristics of the electrodes, such as impedance or charge density, can impact the quality and intensity of the stimulus. Also, the temporal properties of rectangular-wave current stimuli, such as adjusting the pulse-width, number of pulses, and inter-pulse interval, can also be important and influence the calibration results (Doll et al., 2016; Van Der Heide et al., 2009). Depending on the location and parameters of stimulation (e.g., frequency, intensity, and duration), different types of fibers are activated. Electrocutaneous stimulation is often less specific in its targeting of a certain type of afferent nerve fibers compared to other methods (Bromm & Lorenz, 1998). Specifically, standard electrocutaneous stimulation was shown to activate mechanoreceptors Aβ (Inui et al., 2003). According to Motogi et al. (2016), IES can activate cutaneous nerve fibers (Aδ) with less current compared to conventional co-axial planar electrodes that lack a needle tip, due to the high density of electrical fields surrounding the needle tip in the epidermis. As was mentioned before, IES are delta fiber-specific (Inui et al., 2002, 2003) when stimuli intensity is lower than two detection thresholds (Kodaira et al., 2014; Mouraux et al., 2010; Poulsen et al., 2020). IES electrode parameters like dimensions of the outer ring, needle length, as well as skin surface condition (e.g., sweating may increase skin surface conductivity) can influence the electric field distribution and can apply varying pressure to the skin, which could impact the perceived intensity of the stimulus (Motogi et al., 2016). Concluding, it is essential to test and compare the proposed calibration using other types of electrocutaneous stimulation.

The possibility of using our method for other nociceptive stimulation should also be addressed. Certain stimulation modalities require adequate calibration procedures, specifically stimuli selection methods, that consider the specificity of a given pain stimulation. Electric stimulation is characterized by a rapid onset and offset compared to laser and heat stimulation. Furthermore, it obviates the need to measure skin temperature at the stimulation site and to employ an adequate reaction time as a criterion to differentiate between A delta- and C-fiber responses (Churyukanov et al., 2012). However, the novelty of this article does not lie within the stimulus selection procedure and its subsequent application, but in the stimuli estimation method where linear models are used. For this reason, we suggest that our method could be extended to other modalities; nevertheless, the physiological differences across nociceptive stimuli should be carefully considered and proper adjustment to the stimuli selection procedure should be ensured. Those adjustments can include additional reliability tests and modification of certain stimuli parameters like ISI and stimuli duration. Furthermore, the relationship between the intensity of a heat pain stimulus and the subjective pain experience may differ from the relationship between the intensity of an electric stimulus and the subjective pain experience

which may require certain mathematical transformations to make them linear.

Finally, the results obtained from our calibration procedure may not be consistent across different pain modalities since individuals may have distinct pain thresholds for different stimuli modality—pain thresholds obtained for different stimuli modality may or may not be correlated (Bhalang et al., 2005; Harris & Rollman, 1983; Rainville et al., 1992). Nevertheless, pain thresholds cannot be simply viewed in terms of stimuli and/or pain scale because it is a subjective experience due to the unique nature of nociception. The transmission and regulation of the pain threshold for a particular modality are likely influenced, to some extent, by similar pathways and mechanisms, but multiple psychological, contextual, and physiological variables contribute to the central nervous system's neural integrative capacity (Coghill, 2010, 2020; Fillingim, 2005; Koban et al., 2019). Future attempts should be made to test the proposed calibration using other pain modalities.

In conclusion, we established an alternative method for stimuli estimation based on the LRM using single-pulse IES that can be adapted to any type of laboratory environment, which improves automation of the calibration procedure. We emphasize the significance of verifying the quality of calibration data, compare various stimuli estimation methods, and provide a comprehensive laboratory setup and software (Matlab and LabView scripts) that can benefit other researchers. We believe that the replicability of the laboratory setup is crucial for further comparison of study results and development of reliable psychophysiological pain studies using advanced equipment, such as MEG and/or EEG, in combination with WASP electrodes. The importance of the proposed calibration also encompasses clinical studies where experimental pain models are used, for instance, to test the effectiveness of analgesic compounds (Reddy et al., 2012). Furthermore, according to a multi-modal approach in human pain research (Neziri et al., 2011), this method also allows for a standardized comparison between different stimulation modalities, facilitating translation of their result to clinical settings. Furthermore, linear regression satisfies the definition of the International Association for the Study of Pain, which recommends that the pain threshold should be at the level at which 50% of stimuli would be recognized as painful instead of the least stimulus intensity at which pain is perceived (Raja et al., 2020).

5.1 | Limitation

Our method is not free from limitations and the need for further refinements. Reliability tests are required for future experimental studies on WASP electrodes and studies where pain biomarkers or signatures are evaluated (Davis et al., 2020; Pleil et al., 2018). It is crucial to demonstrate whether the calibrated stimuli induced pain that truly corresponded to the NRS ratings. Therefore, we suggested that a calibration check is run when stimulus intensities for different pain levels are calculated. Furthermore, the intra-epidermal electrodes, such as WASP, have been found to be sensitive to their positioning relative to the location of the nerve fiber (Poulsen et al., 2020), which could have influenced the calibration. Next, the use of a non-standard scale (ranging from 0 = *No electric sensation at all*) in this study may limit the generalizability of the results. However, given the method by which the electrode was attached to the skin, we specifically wanted to measure the absence of electric sensation, as was done in a previous study (Świder et al., 2017). Also, more research is needed to determine the factors influencing the sex-based differences in t and T, such as possible differences of electrode attachment or sex physiological, chemical, and biophysical skin differences (Rahrovan et al., 2018). For future studies, it is suggested that the VAS, which is commonly used in clinical practice (Bielewicz et al., 2022) and often described as a ratio scale (Myles & Urquhart, 2005; Price et al., 1994), is used. However, there are data indicating a high correlation between both the VAS and NRS (Williamson & Hoggart, 2005), suggesting that the choice between the mentioned scales for pain assessment can be based on subjective preferences (Breivik et al., 2008).

AUTHOR CONTRIBUTIONS

Karolina Swider: Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; resources; software; validation; visualization; writing – original draft; writing – review and editing. **Stephan Moratti:** Supervision; writing – review and editing. **Ricardo Bruña:** Methodology; software; supervision; writing – review and editing.

ACKNOWLEDGMENTS

We would like to thank all the participants and Gabriel Delojo Pradas for his enthusiasm and practical support in conducting the study. Also, we would like to thank Steve Baker for the help with proofreading.

FUNDING INFORMATION

This work was supported by H2020 EU-funded Marie Skłodowska-Curie Individual Fellowship (MSCA-IF), Grant agreement ID: 896262.

CONFLICT OF INTEREST STATEMENT

The authors have no competing interests to declare that are relevant to the content of this article.

DATA AVAILABILITY STATEMENT

The datasets analyzed during the current study and the code used for their analysis are available under https://github.com/Karolina-Swider/CalibrationProcedure.git.

CONSENT TO PARTICIPATE

All subjects signed informed consent to participate in the study.

ORCID

Karolina Świder https://orcid.org/0000-0003-1855-7416

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

Table S1. Input signal and its corresponding action performed by the LabVIEW script.

Figure S1. Calibration LabVIEW design.

How to cite this article: Świder, K., Moratti, S., & Bruña, R. (2024). How to make calibration less painful—A proposition for an automatic, reliable and time-efficient procedure. *Psychophysiology*, *61*, e14505. https://doi.org/10.1111/psyp.14505