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BRAIN RESEARCH

Research Report

Introduction of a continual RIII reflex threshold tracking algorithm☆

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ABSTRACT

Introduction: The RIII reflex is used in fundamental and clinical pain research. Here we introduce a continual reflex threshold tracking algorithm to facilitate investigations of the time courses of influences on the threshold. Methods: First we investigated the probability of reflex occurrence at the threshold estimated by the continual algorithm and the changes of the threshold over the time during continual recordings of 100 min duration in 10 subjects. Secondly we compared the threshold estimates of the continual algorithm with those of a standard algorithm of threshold estimation in 52 subjects and compared the differences between the two methods with the test–retest-variability of each method. Results: The average probability of reflex occurrence at the threshold estimated by the continual algorithm was 48.7% (SD = 3.2%). Changes of the RIII reflex threshold over the time were not significant (Friedman test, $p>0.05$). The variability between the thresholds determined by the different algorithms (test: SD = 2.50 mA, retest: SD = 1.80 mA) was lower than the variability between test and retest (standard algorithm: SD = 4.32 mA, continual algorithm: SD = 4.44 mA). Discussion: The continual algorithm can be used for a continuous estimation of the reflex threshold at the 50% probability of reflex-occurrence. No evidence of habituation was detected. This allows for investigations of the time courses of pharmacological and physiological influences on the reflex threshold by using this algorithm. The lower variability between the continual algorithm and the standard algorithm compared to the variability between tests and retests of the methods allows for interchangeable conclusions drawn from data obtained with both methods.

1. Introduction

The nociceptive flexion reflex (NFR) is a polysynaptic spinal withdrawal reflex that is elicited through activation of nociceptive A-delta afferents. To assess the reflex and the nociception-specific RIII component, biceps femoris muscle activity is monitored using an electromyogram (EMG) during the application of electrocutaneous stimuli to the ipsilateral sural nerve. Based on the observed EMG response, the stimulus intensity required to elicit the reflex is used as an objective measure of the individual nociceptive threshold (Willer 1977; Chan and Dallaire 1989). Since the method of

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investigation has been standardized (Skljarevski and Ramadan 2002; Sandrini et al., 2005), the NFR has been used increasingly in fundamental and clinical pain research to investigate pharmacological modulation of nociception (Willer 1985; Piletta et al., 1990; Sandrini et al., 1992; Arendt-Nielsen et al., 1995; Remy-Neris et al., 1999; Paradiso et al., 2002; Bossard et al., 2002; France et al., 2007; Escher et al., 2007; Arnold et al., 2008), spinal and supraspinal influences on nociception (Garcia-Larrea et al., 1993; Arendt-Nielsen et al., 1994; Leroux et al., 1995; Rossi et al., 1996; Rhudy et al., 2007; McIntyre et al., 2007; Emery et al., 2008; Ring et al., 2008) as well as individual differences in nociceptive processing in participants with or without pain disorders (Willer et al., 1986; Dahl et al., 1992; Sandrini et al., 1993; Desmeules et al., 2003; Bouhassira et al., 2003; Banic et al., 2004; Campbell et al., 2008). Especially under conditions where subjective ratings of nociception cannot be obtained, such as during anesthesia, an objective measure such as the nociceptive flexion reflex is of particular value.

However, up to now the estimation of the reflex threshold is usually limited to singular events, following differing algorithms (Sandrini et al., 2005). Here we propose a reflex threshold tracking algorithm based on the objective criteria suggested by Rhudy (Rhudy and France 2007) that allows for a continual estimation of the reflex threshold, facilitating investigations of the time course of threshold changes for pharmacokinetic–pharmacodynamic modelling or other time dependent mechanisms.

In the first part of this study we assessed the reliability of the threshold as estimated by the continual algorithm, at the 50% probability of occurrence of the RIII reflex. This was done for serial measurements over a period of 100 min. During these, we also investigated the stability of the reflex threshold over the time to investigate a possible drift of the RIII reflex threshold due to a possible habituation or wind-up of the RIII reflex. Both effects have been reported for the RIII reflex at different stimulation frequencies (Arendt-Nielsen et al., 1994; Dimitrijevic and Nathan 1970). A systematic drift of the RIII reflex threshold due to interaction of the continually applied stimuli would not allow a useful continual threshold estimation.

In the second part of the study we compared the threshold estimates of the continual algorithm with estimates obtained by application of a standard algorithm of threshold estimation and compared the variability between the two algorithms with the test–retest-variability of each algorithm.

2. Results

2.1. *Probability of RIII reflex occurrence at the threshold estimated by the continual algorithm*

For the first part of the study, all 10 subjects completed the experimental procedure successfully. The median number of control stimuli at the RIII reflex threshold estimated by the continual algorithm amounted to 50 for all subjects (range: 39–54). The average probability of reflex occurrence for the control stimuli amounted to 48.7% (SD=3.2%, 95% confidence interval=42.4%–54.9%) (Table 1).

Table 1 – Individual probabilities of RIII reflex occurrence at the estimated thresholds

Subject	RIII occurrence at the control stimuli		Total number of control stimuli
	Total number	Percentage (%)	
A (male)	25	50.0	50
B (male)	24	44.4	54
C (male)	25	50.0	50
D (male)	20	51.3	39
E (male)	22	45.8	48
F (female)	23	46.0	50
G (female)	26	52.0	50
H (female)	22	47.8	46
I (female)	27	54.0	50
K (female)	23	46.0	50
Mean	23.7	48.7	48.7
SD	2.1	3.2	3.9

Each individual that participated in the first part of the study received approximately 600 stimuli during the course of 100 min. At randomized intervals of 10 to 14 stimuli, a control stimulus was delivered at the estimated threshold. Here shown are the total number of control stimuli for each individual and the total number and percentage of control stimuli on which a RIII reflex occurred.

2.2. *Stability of the RIII reflex threshold over time at a constant level of distraction*

The changes of the threshold over time for the 10 individuals tested were not significant (Friedman test, $p>0.05$). The absolute mean deviation of the threshold from its mean over the time amounted to 1.04 mA±0.16 mA (mean±SE).

2.3. *Variability between the thresholds estimated by the continual algorithm and the thresholds estimated by the standard algorithm compared to the test–retest-variability of each algorithm*

For the second part of the study, all 52 subjects completed the first session (Test), but only 35 subjects participated in the second session (Retest), mainly due to scheduling problems. The groups for Test and Retest did not differ in any of the parameters age, height, weight, BMI or Trait-STAI scores (student *t*-tests with Bonferroni corrections for each parameter, $p>0.3$). Also, the State-STAI scores for Test and Retest did not differ for the individual subjects (repeated measures student *t*-test, $p>0.05$).

The average reflex threshold (data for Test and Retest condition combined) for the standard algorithm amounted to 9.18 mA (SE=0.89 mA) for the male and to 7.23 mA (SE=0.73 mA) for the female subjects. For the continual algorithm the average reflex thresholds amounted to 8.99 mA (SE=0.91 mA) for the male and to 7.76 mA (SE=0.82 mA) for the female subjects. For both algorithms, the difference of the thresholds between male and female subjects was statistically not significant (student *t*-test with Bonferroni corrections for each, $p>0.05$).

As a result of the Bland–Altman-analyses to compare the thresholds estimated by the standard algorithm with those estimated by the continual algorithm, the average differences