

# Abstract

## Introduction

Chronic pain affects 10% of the population and has a substantial impact on quality of life. Unfortunately, effective treatments are lacking due to limited understanding of the nociceptive system. Therefore, extensive research has been conducted to observe this system and get a more profound comprehension of its functioning. For instance, the University of Twente developed a method to stimulate this system and observe cortical responses around detection thresholds. However, these protocols are hindered by long measurement duration, which impacts motivation, alertness, and attention. Hence, it affects measurement outcomes. Therefore, this research aims to develop a protocol that limits measurement duration.

The strategy used is to exclude stimulation around the detection threshold and solely stimulate supra-threshold. In addition, this study continues the investigation of undiscovered areas by measuring the cortical responses for paired-pulse facilitation and changes in detection criteria and incorporates the exclusion of novelty components and the detection of habituation by applying sets of multiple stimuli. Furthermore, this study attempted to incorporate paired probing features; however, an error in the implementation led to the investigation of independent pulses. The designed protocol includes a total of two sub-protocols, of which one incorporates the investigation of paired-pulse facilitation by using short and long inter-pulse intervals with amplitude increases for supra-threshold stimulation. The second sub-protocol includes an amplitude increase in combination with two distinct NoP. The overall design of the protocol is to utilize an experiment in which the detection threshold is determined, after which supra-threshold stimulation is applied by increasing the amplitude of the detection threshold, after which another detection threshold is measured to evaluate whether there is any change in detection criteria.

## Methodology

This study includes healthy subjects who performed each sub-protocol once in which the nociceptive system was electrically stimulated. The detection threshold is measured with the MTT method, and the average value is multiplied by 1.5 to serve as the supra-threshold stimulation amplitude. Furthermore, the cortical responses have been measured to determine the grand average evoked potential (EP).

## Results

The results show correct implementations of the usage of amplitude and instances for administered stimuli. However, for some measured subjects, extra sets of applied stimuli are demonstrated. Furthermore, results show that a change in detection criteria is indicated. However, this seems highly related to the order of executed sub-protocols. Furthermore, results regarding paired-pulse facilitation show that grand average EPs are shorter and narrower. Lastly, the results demonstrate that supra-threshold stimulation can measure cortical responses, but that the data is highly contaminated with the increasing signal-to-noise ratio (SNR) making it difficult to interpret the findings concerning novelty and habituation.

## Conclusion

The developed protocol can significantly shorten the measurement duration while maintaining the capacity to activate the nociceptive system. The study also continues the analysis of paired-pulse facilitation. Regarding this, the protocol provided valuable insights into EP characteristics, with paired-pulse facilitation relating to higher and narrower peak potentials. Furthermore, the developed protocol demonstrates promising implementation regarding the exclusion of novelty and investigation into habituation, although data analysis failed to consider the SNR necessitating further investigations. Lastly, it can be concluded that adaptation of the detection criteria seems to be indicated, and therefore there is an indication that

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the protocol may not affect the nociceptive system can activate during the measurement, although this is highly determined by the order of the conducted protocol.