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Micropatterned surface electrode for massive selective stimulation of intraepidermal nociceptive fibres

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HIGHLIGHTS

- A new surface electrode for selective stimulation of nociceptive afferents is presented.
- The electrode is characterized by a micropattern with 150 μm gaps covering large areas without loss of selectivity.
- Only late SEP responses can be recorded with our electrode.
- Conversely, with a wider gap electrode, early and medium SEP components can be recorded.
- Lack of early and medium SEP components show selectivity of our electrode, which is an alternative to laser stimulation.

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ABSTRACT

Background: No satisfactory neurophysiological test for nociceptive afferents is available to date. Laser stimuli present risks of skin damage, whilst electrical stimulation through specially designed electrodes is not selective enough.
New method: We present a new electrode designed according to critical issues identified in preliminary computer simulations concerning electric field gradient through the skin. To provide selective stimulation the activating electric field must be limited to intraepidermal free nerve endings. To this end, a new interdigitated electrode (IDE) was made of conductive rails arranged in a comb-like micropattern, situated only 150 μm apart from each other (150 IDE) and alternately connected to the opposite poles of the stimulator.
Results: Evoked potentials recorded from the scalp were obtained after stimulation with the 150 IDE and with a similarly designed, but more widely spaced electrode (1000 μm, or 1000 IDE). Small amplitude early and medium latency components were recorded with the 1000 IDE, suggesting activation of Aβ fibres. On the other hand, the 150 IDE only evoked late responses, confirming sufficient selectivity in small fibre activation.
Comparison with existing method(s): The main differences with existing electrodes are: 1) Microspaced interdigitated conductive rails. 2) The potentially unlimited surface of stimulation and high efficiency per surface unit, resulting in large numbers of activated nociceptors.
Conclusions: A new electrode providing selective stimulation of nociceptive nerve free endings is presented. It is non-invasive, and its surface can be enlarged at will. It is expected that it may greatly help in neurophysiological assessment of conditions affecting the nociceptive pathway.

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Acronyms

150 IDE 150 μm interdigitated electrode
1000 IDE 1000 μm interdigitated electrode
LEP laser evoked potential
PREP pain related evoked potential
SEP somatosensory evoked potential

1. Introduction

One of the mainstays of clinical electrophysiology is the ability to record activity of the nervous system evoked by suitable stimuli delivered to peripheral nerves or receptors. Refinements of hardware and software have brought important advances in detecting very small signals, even when embedded within undesired noise, provided that stimulus synchronization is feasible. Most of the techniques used so far allow objective and very reliable assessment of the nervous transmission, completely independent from the subject's alertness.

Unfortunately, such highly sophisticated tests are only suitable to explore the fast conducting fibres. So far, no electrophysiological method allows similar precision nor independence from the subject's collaboration when the transmission through small myelinated (Aδ) or unmyelinated (C) fibres is concerned.

Two challenges are to be overcome. First, the selective stimulation of these two groups of fibres. Second, the recording of action potentials that are thousands of times smaller than those of the large fibres (unless they are "amplified" by the associative areas of the cortex, but this is another story).

In this paper we address the first challenge, that is selective stimulation. The best method developed so far is an infrared laser pulse, irradiating thermal energy in a short period of time, from 5 to 50 ms, and absorbed by the superficial layer of the skin, where only the free nerve endings of Aδ and C fibres are situated. Long latency evoked responses are thus recorded from the scalp, related to the stimulus (Treede et al., 2003). However, there are several drawbacks: the heat pulse damages the skin, so it can only be repeated a few times, and never on the same spot; the device is costly, and, because the irradiated spot has very limited area, only a few afferents can be excited. In addition, the selectivity of solid state lasers has been questioned, as their radiation penetrates deep enough to also activate non-nociceptive receptors and fibres (Leandri et al., 2006). A simpler, but even more debated method, is represented by electrical pulses delivered through electrodes designed so that the generated field would stay superficial enough (Katsarava et al., 2006; Inui and Kakigi, 2012). Unfortunately, the performance of the electrodes so far proposed has been challenged by a number of experiments, questioning their selectivity (Perchet et al., 2012). The electric stimulus in principle has optimal characteristics of control, ease of generation and delivery, instantaneous propagation (so that a number of fibres or receptors can be depolarized at the same time) and ease of synchronization with recording devices. We thought that the properties of the electric stimulus could be exploited provided the stimulating electrode could be designed in a more sophisticated manner. We investigated the existing electrodes, tested them with computer simulations as to the generated electric field, and here propose a new electrode which according to our simulation and experimental tests generates electric fields superficial enough to be selective for free nerve endings and at the same time able to activate a large number of receptors.

2. Materials and methods

2.1. Computer simulation

Finite element analysis of the electrode performance was carried out using Comsol Multiphysics® 4.3b (electric currents module) with an Intel® Core™ i7-3820 CPU @3.6 GHz equipped with 64 Gb of RAM.

We studied the static response of the electrode considering a pure resistive model of the human skin adapted from one previously proposed (Mørch et al., 2011). It consisted of 4 layers: stratum corneum (thickness 29 μm), epidermis (60 μm), dermis (1300 μm) and hypodermis (5000 μm) having different conductivity values (stratum corneum $\sigma = 5 \times 10^{-4}$ S/m, epidermis $\sigma x = 0.95$ S/m $\sigma y = 0.15$ S/m, dermis $\sigma x = 2.57$ S/m $\sigma z = 1.62$ S/m, hypodermis $\sigma = 2 \times 10^{-2}$ S/m). The conductivity of the stratum corneum was set to match the resistance of our 150 μm and 1000 μm interdigitated electrodes (see Section 2.3) measured in real experimental conditions. The voltage polarization and the ground conditions were applied to cathode and anode line regions with same dimension as the electrodes and which rested on the upper boundaries of the stratum corneum. Continuity conditions for current were set in the inner boundaries (interfaces between the layers), while electric insulation conditions were set for the external boundaries. Free triangular meshes were employed for all layers, with maximum and minimum element size of 5 μm and 0.2 μm and 10(x):1(y) aspect ratio (y-direction scale = 10) for both the stratum corneum and epidermis layers. Free triangular meshes with 1:1 aspect ratio and predefined "extremely fine" conditions were used for the dermis and hypodermis layers.

2.2. Subjects

All recordings were performed on ten healthy volunteers, 8 males and 2 females, ranging in age from 24 to 35 years, from the medical personnel of the Department of Neuroscience. All of them gave informed consent for the procedure and data treatment. The procedures were totally non-harmful and the study was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. The study had been approved by the local ethics committee.

2.3. Electrodes

Three types of stimulating electrodes were used in the real experiments: i) a micropatterned interdigitated electrode with inter-rail distance and rail width of 150 μm (from now on named 150 IDE) (Fig. 1, bottom left), which was intended to stimulate the intraepidermal free nerve endings only; ii) a micropatterned interdigitated electrode with inter-rail distance of 1000 μm and rail width of 150 μm (from now on named 1000 IDE) (Fig. 1, bottom right), intended to stimulate deeper intradermal nerve fibres and iii) traditional, self-adhesive electrodes for surface stimulation of peripheral nerves, which will be referred to as "classic electrodes" in the text to follow.

The 150 IDE is the main object of this paper. It was designed and built as a prototype by three of the authors (M. Leandri, L. Pellegrino and A. Siri). The invention has been registered as Italian Patent n. 1425199, also published as WO/2015/186087, joint property of the University of Genova and Italian National Research Council (CNR). The 150 IDE and the 1000 IDE used in the experiments were made under licence by Bionen (Florence, Italy). They were made of a glass epoxy substrate with a micropattern of gold conductor rails which interdigitated in a double comb-like fashion. Each of the two "combs" was connected to one of the stimulator poles. The area covered by these electrodes was in either case 10 × 10 mm.