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On the use of information theory for the analysis of synchronous nociceptive withdrawal reflexes and somatosensory evoked potentials elicited by graded electrical stimulation

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HIGHLIGHTS

- MI was used to quantify spinal and supraspinal activity in relation to sensory input.
- MI is a model-free approach that is not constrained by parametric assumptions.
- NWR features were in general more informative than SEP features.
- The joint information carried by pairs of features showed an overall redundancy.

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ABSTRACT

Background: To date, few studies have combined the simultaneous acquisition of nociceptive withdrawal reflexes (NWR) and somatosensory evoked potentials (SEPs). In fact, it is unknown whether the combination of these two signals acquired simultaneously could provide additional information on somatosensory processing at spinal and supraspinal level compared to individual NWR and SEP signals.
New method: By using the concept of mutual information (MI), it is possible to quantify the relation between electrical stimuli and simultaneous elicited electrophysiological responses in humans based on the estimated stimulus-response signal probability distributions.
Results: All selected features from NWR and SEPs were informative in regard to the stimulus when considered individually. Specifically, the information carried by NWR features was significantly higher than the information contained in the SEP features ($p < 0.05$). Moreover, the joint information carried by the combination of features showed an overall redundancy compared to the sum of the individual contributions.

Comparison with existing methods MI can be used to quantify the information that single-trial NWR and SEP features convey, as well as the information carried jointly by NWR and SEPs. This is a model-free approach that considers linear and non-linear correlations at any order and is not constrained by parametric assumptions.
Conclusions: The current study introduces a novel approach that allows the quantification of the individual and joint information content of single-trial NWR and SEP features. This methodology could be used to decode and interpret spinal and supraspinal interaction in studies modulating the responsiveness of the nociceptive system.

Abbreviations: EEG, electroencephalography; EMG, electromyography; fMRI, functional magnetic resonance imaging; ICA, independent component analysis; ICs, independent components; IT, information theory; MEG, magnetoencephalography; MI, mutual information; NWR, nociceptive withdrawal reflex; RMS, root-mean-square; RTh, nociceptive withdrawal reflex threshold; SEPs, somatosensory evoked potentials.

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1. Introduction

One of many ways to study the somatosensory pathways in man is by assessing electrophysiological measurements that show a relation between the applied stimulus and the evoked response. Among the different methodologies, two techniques that have been widely used in previous studies are the nociceptive withdrawal reflex (NWR) and somatosensory evoked potentials (SEPs). The NWR is a spinal polysynaptic reflex that integrates sensory input, descending modulatory signals and motor commands to evoke the proper motor response resulting in the withdrawal of the limbs from potential tissue damage in the present postural context (Andersen, 2007). The NWR is often used to study the spinal nociceptive response to diverse pharmacological and non-pharmacological interventions, in healthy volunteers as well as in patients suffering from acute and chronic pain conditions (Sandrini et al., 2005; Lim et al., 2011). SEPs are transient changes in the ongoing electroencephalogram (EEG) elicited by sensory events. When using electrical stimulation at high-intensity levels, SEPs reflect the simultaneous activations of large-diameter, lower threshold non-nociceptive fibers (Aβ) and small-diameter, higher threshold nociceptive fibers (Aδ) (Garcia-Larrea, 2006).

Previous studies that analyzed the relationship between stimulus intensity and NWR and SEP amplitudes have applied methods to measure signal covariance (e.g. correlation coefficient or general linear model) that imply a simple linear relationship between the signals (Debroucker and Willer, 1985; Dowman, 1991). A major problem of these methods is that the required assumptions (e.g. uncorrelated errors and constant error variance across observations) do not often hold (Kisley and Gerstein, 1999). In addition, these methods cannot determine if there is an overlap between the information carried by two or more signals being analyzed. Furthermore, studies that combined the simultaneous acquisition of NWR and SEPs have based their analysis on across-trial averaging of time-locked responses (Debroucker and Willer, 1985; Dowman, 1991, 2001; Danziger et al., 1997; Goffaux et al., 2007). Across-trial averaging has been the most common methodology in the analysis of SEPs to enhance the signal-to-noise ratio. The application of the averaging procedure relies on the assumption that the SEP wave is constant across trials, while the background ongoing EEG activity is not time-locked with the stimulus and should therefore cancel out during the averaging process. The use of this procedure does not take into account across-trial variability of latencies and amplitudes of the response peaks (Mouraux and Iannetti, 2008) which could contain relevant information regarding the stimulus (Iannetti et al., 2005) and modulatory effects such as attention (Lazzaro et al., 1997) and fatigue (Jarchi et al., 2011). Therefore the averaging process may also eliminate vital information that could help to explain the different processes underlying the physiological responses.

In this article, a novel approach is taken by using the analytical framework of Information Theory (IT), developed in the mathematical theory of communication (Shannon, 1948). This model-free approach allows the computation of quantities that can be interpreted as stimulus-signal and signal-signal relationships, using the stimulus-response probability distributions estimated from numerous single-trial measurements. By means of the concept of mutual information (MI), it is possible to quantify statistical non-independence between signals of interest considering linear and non-linear correlations at all orders.

The aims of this study were to test a new methodology to (1) quantify the amount of information that single-trial NWR and SEP features convey in relation to graded electrical stimuli (non-painful to painful intensities), and (2) to establish if the information carried jointly by two features is higher than their individual contributions.

2. Material and methods

2.1. Subjects

Sixteen healthy male volunteers (23.6 ± 4.6 years) participated in the experiment. All volunteers were informed about the protocol and provided written informed consent before participating. The experiment was approved by the local ethics committee (Project No. N-20110027).

2.2. Electrical stimulation

Electrical stimulation was performed through surface electrodes to evoke the NWR and SEPs. The cathode for stimulation (15 mm × 15 mm, type Neuroline 700, Ambu A/S, Denmark) was placed in the arc of the sole of the left foot, while the anode was an electrode pad (50 mm × 90 mm, type Synapse, Ambu A/S, Denmark) placed at the dorsum of the foot. The stimulus consisted of a constant current burst of 5 square-wave pulses, with 1 ms of duration each and 5 ms between pulses, delivered by a computer-controlled electrical stimulator (Noxitest IES 230, Aalborg, Denmark). The electrical stimulations were applied with an inter-stimulus interval of 15 s plus a random jitter of 1 s maximum.

2.3. EMG recordings

The NWR was assessed by surface electromyography (EMG) recordings of the tibialis anterior muscle. After shaving and cleaning the skin with isopropyl alcohol, two electrodes (30 mm × 22 mm, type Neuroline 720, Ambu A/S, Denmark) were placed on the muscle belly along the main direction, separated 20 mm each. The ground was an electrode pad (50 mm × 90 mm, type Synapse, Ambu A/S, Denmark) placed over the left bony prominence of the anterior superior iliac spine. EMG signals were sampled at 4000 Hz, amplified (up to 20,000 times), filtered (5–500 Hz, second order) and stored between 200 ms of pre-stimulus and 1800 ms after stimulation onset.

2.4. EEG recordings

Continuous EEG data were recorded by a 128-channel system, using a standard EEG cap (Waveguard cap system, ANT-Software A/S, Enschede, The Netherlands) based on the extended International 10–20 system. The recording reference was the common average of all connected unipolar electrode inputs, while the ground electrode was located along the sagital midline, between Fz and FCz electrodes. EEG data were sampled at 2048 Hz per channel and recorded by ASA 4.7.3 Software (ANT-Software A/S, Enschede, The Netherlands) for further offline analysis.

2.5. Experimental procedure

Subjects were in supine position throughout the entire experiment, with back support inclined 120° relative to the horizontal level. Pillows were placed under their knee to flex the knee joint approximately 30°.

The procedure started with a period of familiarization where the subject received 10–12 stimuli at low intensities (4–5 mA). After 5 min of rest, the NWR threshold (RTh) was obtained using a staircase procedure (Willer, 1977). The first ascending and descending staircase consisted of 2-mA steps whereas the second and third ascending and descending staircases used 1-mA steps. The RTh was defined as the average intensity of the last two peaks and troughs.

Six stimulation intensities were selected: 0.5, 0.75, 1.0, 1.25, 1.5 and 2.0 times the RTh. Each intensity level was applied at least once to familiarize the subject. Afterwards, 5 sets of 24 stimuli