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Dynamic spectral indices of the electroencephalogram provide new insights into tonic pain

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HIGHLIGHTS

- The cold pressor test provides reliable EEG spectral indices.
- Tonic pain induced widespread changes in the EEG spectrum, with theta, beta3 and gamma bands correlating to the overall perceived pain.
- Dynamic EEG analysis revealed that theta activity is associated to both inter-individual and dynamic perception of tonic pain.

ABSTRACT

Objective: This study aimed to investigate reliability of electroencephalography (EEG) during rest and tonic pain. Furthermore, changes in EEG between the two states as well as dynamics and relation to pain ratings were investigated.
Methods: On two separate days EEG was recorded in 39 subjects during rest and tonic pain (cold pressor test: left hand held in 2 °C water for 2 min.) while pain intensity was rated continuously. Dynamic spectral analysis was performed on the EEG. Between-day reliability of spectral indices was assessed and correlations to pain ratings were investigated.
Results: EEG reliability was high during both states. The relative spectral indices increased in delta (1–4 Hz; $P = 0.0002$), beta3 (18–32 Hz; $P < 0.0001$) and gamma (32–70 Hz; $P < 0.0001$) bands during tonic pain, and decreased in theta (4–8 Hz; $P < 0.0001$), alpha1 (8–10 Hz; $P < 0.0001$), alpha2 (10–12 Hz; $P < 0.0001$) bands. Theta, beta3 and gamma bands correlated significantly to the area-under-curve of pain ratings, but only theta was dynamic and correlated to the pain ratings ($R = 0.88$, $P < 0.0001$).
Conclusions: EEG assessed during tonic pain is a valid experimental pain model both in terms of reliability between days and in connection between cortical activity and pain perception.
Significance: EEG during tonic pain is more pain-specific and should be used in future basic and pharmacological studies.

1. Introduction

Experimental pain models are widely used in the pain research community and have recently also gained increasing popularity in the clinical setting. They are used to unravel pain mechanisms in acute and chronic pain conditions, and to evaluate the mechanisms of action underlying analgesic treatments. Experimental pain models are also commonly used in phase II studies where new analgesics are used as proof of concept in healthy individuals before initiation of clinical studies, as they keep down expenses and allows for fast and efficient evaluation of new analgesic compounds (Mitchell et al., 2004; Olesen et al., 2012).

Most experimental pain models are based on recordings of subjective psychophysical responses to stimuli of controlled intensity. In addition, various methods have been used to objectively

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characterize evoked pain responses. Measurements of cortical electrical activity following rapid phasic noxious stimuli have been used to quantify pain perception as time-locked electroencephalogram (EEG) potentials (Frøkjær et al., 2011; Gram et al., 2013). However, it has been speculated that such brief stimuli are not suited to simulate natural and clinical pain conditions. Hence, increased focus has been given to experimental tonic pain which simulates chronic pain better (Rainville et al., 1992; Nir et al., 2010, 2012). Thermal stimulation with hand immersion in either hot or cold water for a set amount of time are common methods to induce experimental tonic pain, In particular immersion of the hand in cold water, the cold pressor test (CP), has been widely used to induce tonic pain in experimental pain studies (Lowery, 2003).

It is generally agreed that the CP test mimic clinical pain due to its high levels of unpleasantness (Rainville et al., 1992). However, EEG recorded following tonic stimulations lack the time-locked waveforms seen in evoked potentials (Frøkjær et al., 2011). Therefore more advanced methods such as spectral analysis are required to explore and visualize the EEG activity. Spectral analysis uses time–frequency methods to compute standardized spectral EEG indices (Graversen et al., 2012a). The algorithm most commonly used is the Fast Fourier-transform (FFT), but more advanced methods such as the continuous wavelet transform (CWT) can be utilized to achieve superior time–frequency resolution and less sensitivity to noise (Akin, 2002; Gram et al., 2013).

Despite growing use of continuous EEG recorded during tonic pain, there is to date no published data on the reliability of EEG during CP pain. This is probably due to the complex nature of measuring reliability and lack of well-defined guidelines for analysis (Atkinson and Nevill, 1998; Bruton et al., 2000). However reliability measures are of importance in power estimations for future studies and also indicate whether a specific measurement is of value (Atkinson and Nevill, 1998; Bruton et al., 2000; Hanneman, 2008). We hypothesized that: (I) pain scores and EEG spectral indices during CP pain are reliable and (II) dynamics of spectral EEG indices are associated with subjective pain perception. Thus the aims of this study were to: (a) investigate reliability of pain scores during CP, (b) to investigate reliability of EEG spectral indices during resting state and tonic pain, (c) to investigate differences in EEG spectral indices between resting state and CP (i.e. static EEG indices), (d) to investigate dynamics of EEG spectral indices during resting state and CP (i.e. dynamic EEG indices) and finally (e) explore if the subjective perception of pain (psychophysics) are associated with spectral indices of the EEG.

2. Methodology

The study was conducted between November 2010 and April 2012 in the research laboratory at Mech-Sense, Department of Gastroenterology and Hepatology, Aalborg University Hospital, Denmark. The local ethics committee approved the study (reference No. N-20100046).

2.1. Study subjects

This study included 39 healthy subjects who fulfilled the following inclusion criteria: (1) aged between 20 and 65 years; (2) no previous diseases or psychiatric disorders causing pain. A medical doctor conducted a routine health examination in order to rule out any diseases before enrolment. All subjects provided written informed consent and were compensated for participation in the study.

2.2. Experimental protocol

For each subject two experimental sessions were performed separated by 7 days. Each session consisted of resting state EEG followed by EEG recordings during the CP test. Experimental procedures were done on the same time of the day. Prior to the first study day, a training session was conducted in order to introduce the subject to the laboratory environment and verify that subjects were able to tolerate the cold pressor pain. Experimental tests were carried out by well-trained experimenters in a quiet room and each participant was tested by the same experimenter on both study days. Testing in female subjects was standardized with regard to phase of the menstrual cycle in order to control for variations in hormone levels.

2.3. Cold pressor test

The CP test was performed using circulated water bath (Grant, Fischer Scientific, Slangerup, Denmark). The water was cooled to 2 °C and the subjects immersed their left hand up to the wrist for 2 min while water was circulated. Subjects rated their perceived pain on a handheld electronic device with a visual analogue scale (VAS) going from no feeling of pain to the worst imaginable pain. The pain ratings were continuously sampled electronically with a frequency of 10 Hz on a scale from 0 to 10. Subjects commonly rate their pain in discrete steps using this method, which combined with the absence of verbal communication for pain rating is thought to reduce influence on EEG recordings.

2.4. EEG recordings

On both days, EEG was recorded in a dimly lit room, first during a resting period and then during CP. During the resting state recordings, subjects were instructed to keep their eyes open while minimizing eye blinking during the 2.5 min. period. EEG was recorded during CP by starting the recording simultaneously as the subject submerges their hand in cold water. EEG was recorded from a standard 62-channel cap (Quick-Cap International, Neuroscan, El Paso, TX, USA), amplified digitally on a Synamps 2 system (Neuroscan Compumedics, El Paso, TX, USA) and recorded for later analysis (Neuroscan 4.3.1, Neuroscan, El Paso, TX, USA).

2.5. Pre-processing

The data were first pre-processed in the Neuroscan EEG software in the following steps: (1) zero-phase shift notch filtering (49–51 Hz) using a finite impulse-response filter with a slope of 24 dB/octave; (2) zero-phase shift band-pass filtering (1–70 Hz) using a finite impulse-response filter with a slope of 12 dB/octave; (3) blinded visual inspection of data quality for all channels. Channels with abnormal signals were discarded and replaced by signals interpolated from neighboring electrodes; (4) re-referencing to the average electrode; (5) finally, resting EEG was cleaned by selecting 2 min of artefact-free EEG from the 2.5 min recording where the investigator was blinded to the origin of the recording.

2.6. Spectral analysis of EEG dynamics

Spectral analysis of EEG amplitudes was carried out using Matlab 2012a (The Matworks, Inc., Natick, MA, USA) to retain information about dynamics over time. The continuous wavelet transform was applied to the EEG signals from all channels. The complex Morlet wavelet was chosen for analysis with a bandwidth of 10 Hz and a center frequency of 1 Hz. Scales for the transform were chosen to match frequencies ranging from 1 to 70 Hz, with a 0.5 Hz between-scale frequency interval. The absolute value of the obtained wavelet coefficients were used in the following analysis.

To assess the static EEG spectral indices the wavelet coefficients were split into the following eight standardized bands: delta