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High thalamocortical theta coherence in patients with neurogenic pain

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Patients with severe and chronic neurogenic pain are known to exhibit excess EEG oscillations in the 4- to 9-Hz theta frequency band in comparison with healthy controls. The generators of these excess EEG oscillations are localized in the cortical pain matrix. Since cortex and thalamus are tightly interconnected anatomically, we asked how thalamic activity and EEG are functionally related in these patients.

During the surgical intervention in ten patients with neurogenic pain, local field potentials were recorded from the posterior part of the central lateral nucleus (CL).

The highest thalamocortical coherence was found in the 4- to 9-Hz theta frequency band (median 7.7 Hz). The magnitude of thalamocortical theta coherence was comparable to the magnitude of EEG coherence between scalp electrode pairs. Median thalamocortical theta coherence was 27%, reached up to 68% and was maximal with frontal midline scalp sites.

The observed high thalamocortical coherence underlines the importance of the thalamus for the synchronization of scalp EEG. We discuss the pathophysiology within the framework of a dysrhythmic thalamocortical interplay, which has important consequences for the choice of therapeutic strategy in patients with chronic and severe forms of neurogenic pain.

Keywords: Neuropathic pain; Central pain; Thalamocortical system; Thalamotomy; EEG oscillations; Thalamocortical dysrhythmia; Thalamus; Cortex

Introduction

Neurogenic pain arising subsequent to a variety of insults can be very difficult to treat and may evolve into a severe chronic pain disorder. Several conceptual frameworks have been proposed for the pathophysiology of neurogenic pain and pain processes in general (Treede et al., 1999; Peyron et al., 2000; Jones et al., 2003; Apkarian et al., 2005). However, no general agreement has been reached yet. A specific view has been developed that focuses on thalamocortical interplay (Llinas et al., 1998, 1999). The concept of thalamocortical dysrhythmia (TCD) for neurogenic pain is based (a) on the clinical fact that a therapeutic lesion in the central lateral nucleus (CL) relieves neurogenic pain (Jeanmonod et al., 2001a), (b) on the presence of low threshold calcium spike (LTS) bursts in the somatosensory thalamus and in CL (Lenz et al., 1989; Jeanmonod et al., 1993, 1996) and (c) on the finding of enhanced 4–9 Hz theta frequency activation in EEG/MEG in patients with neurogenic pain (Gücer et al., 1978; Llinás et al., 1999; Schulman et al., 2005; Sarnthein et al., 2006; Stern et al., 2006). The results presented here extend a first published evidence (Sarnthein et al., 2003) and provide further support for the notion that neurogenic pain originates from a disturbance in the thalamocortical interplay.

To explore the thalamocortical interplay, we recorded local field potentials (LFP) from CL in ten patients before central lateral thalamotomy (CLT). The simultaneous recording of scalp EEG with several electrodes allows investigation of both the strength and the topography of the thalamocortical interaction. We now report high thalamocortical coherence in the 4- to 9-Hz theta frequency band, which was found to be comparable in magnitude to EEG coherence between scalp electrodes. This finding suggests that thalamus and cortex are both relevant players in the synchronization of scalp EEG (Nunez et al., 2001; Schreckenberger et al., 2004).

Methods

Patients

We analyzed spontaneous brain activity intra-operatively from 10 patients suffering from severe forms of neurogenic pain, all displaying resistance to classically recognized drug treatments. The surgical procedure of CLT was approved by the Kanton Zürich Ethics committee and has been described earlier (Jeanmonod et al., 2001a). All patients were fully informed about the risks and

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benefits of the procedure and gave informed consent. Local anesthesia was applied on the frame fixation points and the penetration point. Three milligrams of the anxiolytic drug Bromazepam was given 4–5 h before recording, which neither made patients drowsy nor significantly affected their symptomatology at the moment of recording.

In a total of 28 patients, we recorded thalamic LFP and scalp EEG simultaneously with the apparatus described below. Among these, we selected a final sample of 10 patients where thalamocortical coherence exceeded 20% for further analysis. We attribute the null-finding of coherence in 18 over 28 patients to heartbeat artefacts in the LFP, uncertainties in the preparation of the LFP recording electrode and/or yet undocumented physiological factors.

LFP and EEG Recordings

Thalamic LFP was recorded in the posterior part of the CL nucleus before placing the therapeutic lesion. Some of the methods of data acquisition and analysis have been used earlier on a heterogeneous group of neurological patients with only one scalp electrode (Sarnthein et al., 2003) and on a group of patients with Parkinson's disease (Sarnthein and Jeanmonod, 2007). The recording site approximately 8 cm below the scalp was reconstructed for each patient from post-operative MRI of the lesion and projected on our stereotactic atlas of the human thalamus (Morel et al., 1997). Along the penetration in the thalamus, micro-electrode activity was recorded at several sites to confirm the localization of the therapeutic target. The tungsten micro-electrode (FHC, Maine) had a final taper angle of 10°–20° and tip diameter <1 μm. The epoxylite insulation was removed by electrolysis along 20–50 μm, and the tip was then plated with Au and Pt to obtain an impedance of <100 kΩ at 1000 Hz. This micro-electrode was used to record both LFP and single unit activity (Jeanmonod et al., 1996; Magnin et al., 2000). For LFP recordings, the uninsulated rim of the stainless steel guiding cannula served as reference. The reference was located 13 mm above the micro-electrode tip, in the ventricle or in the most dorsal part of the thalamus. The two materials produced a battery potential exceeding 0.5 V, which was eliminated with symmetric AC decoupling by capacitors on both the active and reference channels (10 nF, amplifier R_{in} = 10 MΩ, high-pass cutoff 1.6 Hz). Electrode sites on the scalp were selected from the international 10–20 system to be compatible with the surgical procedure (patients 1–5: 6 sites; patients 6–10: 15 sites). EEG was recorded with sintered Ag/AgCl electrodes (Falk Minow Services, Herrsching, Germany) against Cz as reference. Impedance was below 5 kΩ during recording. All signals were registered with a SynAmps EEG system (Neuroscan Compumedics, Houston, TX, sampling rate 20 kHz, gain 2500, range 2.2 mV, A/D conversion 34 nV/LSB, common mode rejection 100 dB, band-pass filter 0.05–3000 Hz −12 dB/octave) and continuously viewed on PC monitor. Recording lasted more than 1 min. During recording, patients were awake and had their eyes closed to reduce eye movement artefacts and to focus on resting brain activity.

Data preprocessing

The data were analyzed offline in the Matlab (The Mathworks, Natick, MA, USA) environment using EEGLAB (http://sccn.ucsd.edu/eeglab, Delorme and Makeig, 2004) and custom programming on the basis of standard mathematical and signal analysis functions. Signals were first resampled to 500 Hz for the analysis of thalamic LFP and scalp EEG. The scalp EEG was re-referenced to the mean of the signals recorded at the ear lobes. We confirmed the alertness of subjects during the recording session by checking for slowing of the alpha rhythm, slow rolling-eye movements or increasing theta power (4–9 Hz). The data were inspected in 5-s epochs, and large muscle or eye movement artefacts were removed. For editing purposes, muscle artefacts were considered significant if the underlying EEG rhythms were not clearly seen. This procedure resulted in a median EEG length of 198 s (min 50 s, max 240 s) for spectral estimates.

Spectral analysis

The spectral analysis was performed with the multi-taper method (Percival and Walden, 1993; Mitra and Pesaran, 1999,

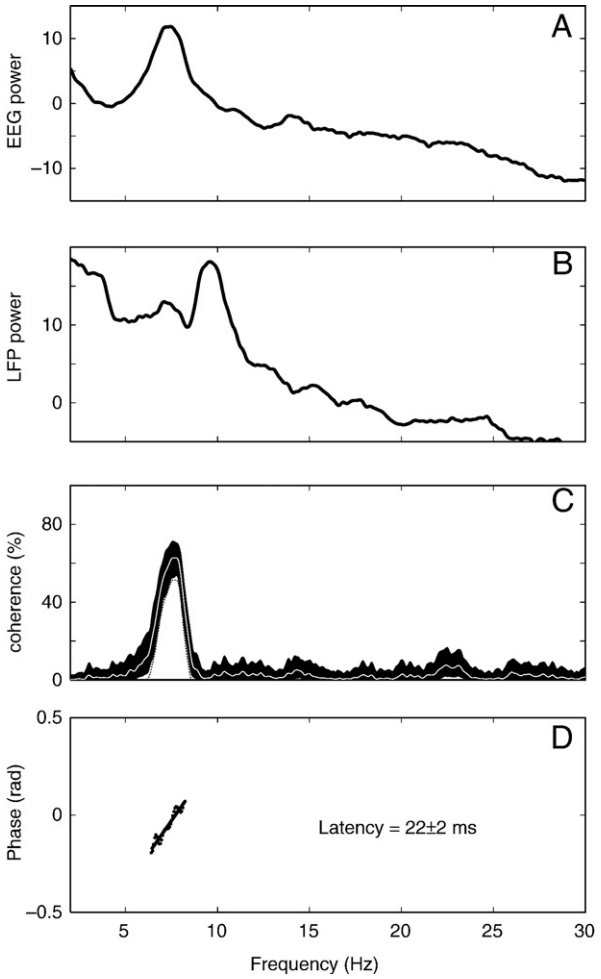

Fig. 1. Spectral analysis of EEG and LFP. Panels A and B show the power spectral density (units $10*\log10\ \mu V^2\ Hz^{-1}$) of scalp EEG at site AFz (A) and thalamic LFP (B) in patient 6. In this patient, the LFP showed a distinct alpha peak in addition to the theta peak present in all patients. (C) The coherence between EEG and LFP is significant from 6 to 9 Hz in the theta band (black ribbon, jackknife statistics, 95% confidence interval). For comparison, also the lower bound of the analytical 95% confidence interval is plotted as a dashed line. (D) Phase φ between EEG and LFP. The slope $d\varphi/df$ was transformed into latency.