Chronische therapie-resistente neurogene Schmerzen: Pathophysiologie und Behandlung durch die inzisionslose transkranielle MR-gesteuerte fokussierte Ultraschalltechnik

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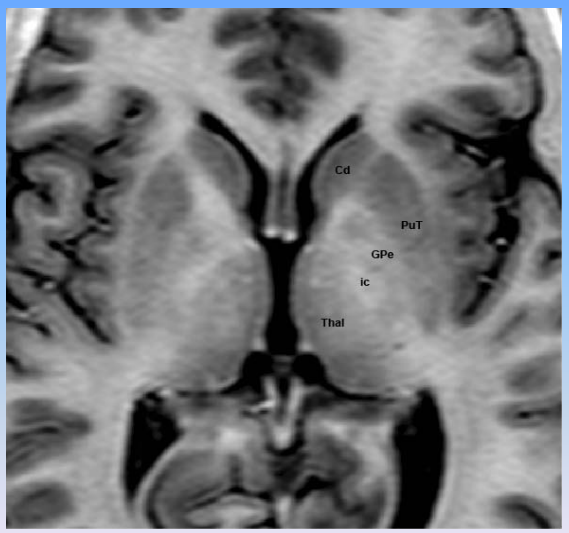
Neurogene, oder neuropathische Schmerzen

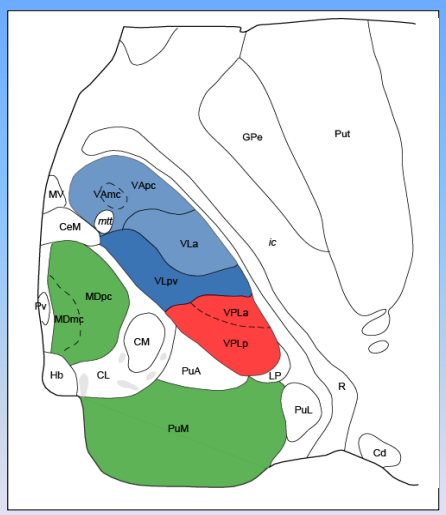
Alle Schmerzsituationen, die als Ursache eine Beschädigung des Schmerzsystems von den Nerven bis zum Kortex haben: Phantomschmerzen (nach Amputation), Nerven- und Wurzelschäden (Kompressionen oder Trennungen), Schmerzen nach Diskushernie-Operationen, Trigeminus-Neuralgie, postherpetische Neuralgie, Polyneuropathien, Plexusabriss, Paraplegieschmerzen, Schmerzen nach Hirninfarkt (thalamisches Syndrom), etc.

Unser Konzept

Wir verwenden ein multidimensionales, klinisches, wissenschaftliches und technologisches Konzept:

- Ein grundlegendes Verständnis der **Mechanismen** der erwähnten Hirnfunktionsstörungen: die thalamokortikale Dysrhythmie.
- Die quantitative **Elektroenzephalographie** (**EEG**) für die pre- und postoperative Beurteilung dieser Dysrhythmie.
- Ein selektives, regulierendes/schonendes Konzept der Behandlung der Dysrhythmie.
- Eine Integration der menschlichen **psychemotionellen** Dimension.
- Die inzisionlose transkranielle MR-gesteuerte Hochenergie fokussierte **Ultraschalltechnik** für eine non-invasive Intervention mit höchst signifikanter Risikoreduktion und erhöhter Genauigkeit.

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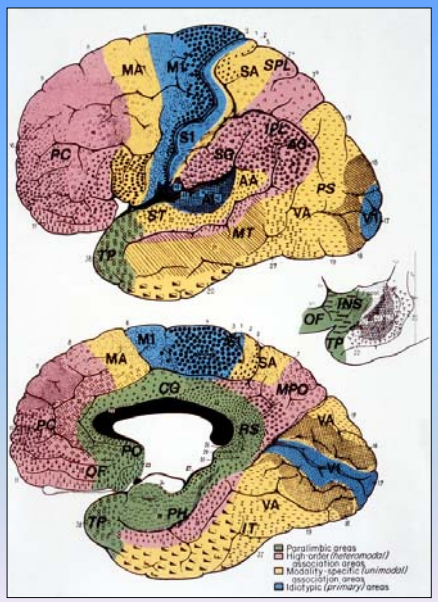
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Paralimbic areas
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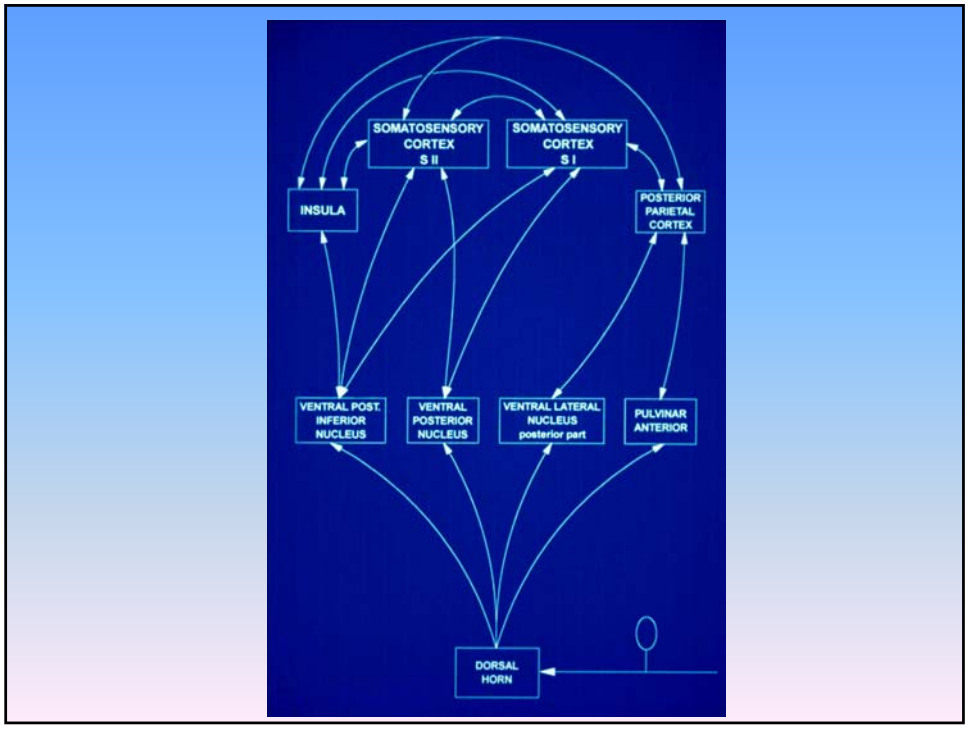
Modality-specific (unimodal) association areas
Idiotypic (primary) areas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SOMATOSENSORY CORTEX S I
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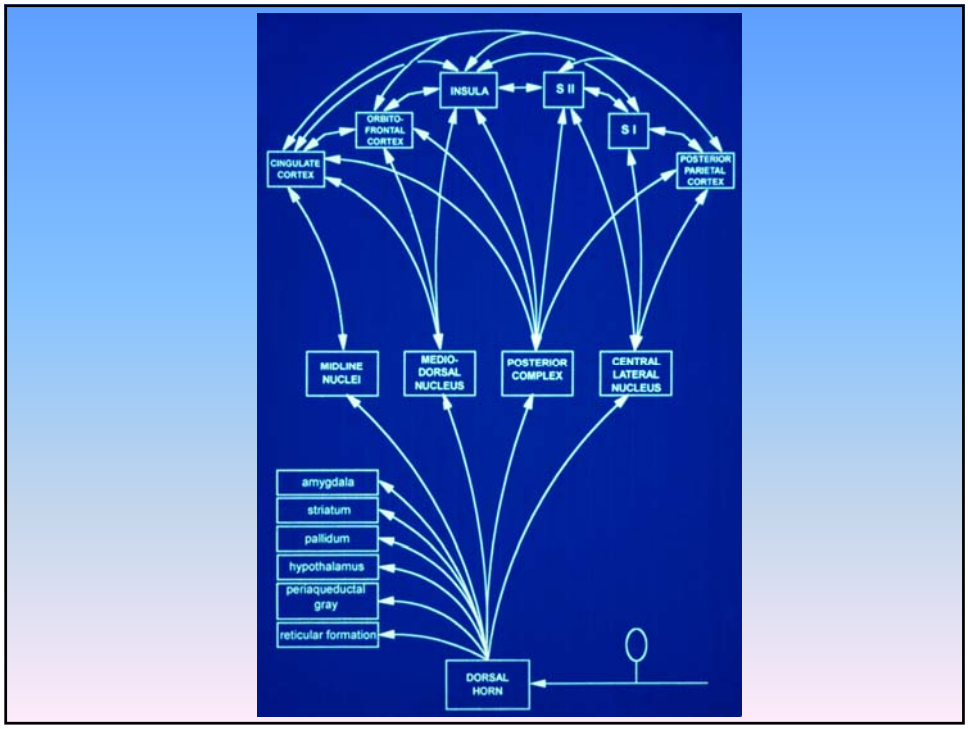
VENTRAL POST. INFERIOR NUCLEUS
VENTRAL POSTERIOR NUCLEUS
VENTRAL LATERAL NUCLEUS posterior part
PULVINAR ANTERIOR
DORSAL HORN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POSTERIOR COMPLEX
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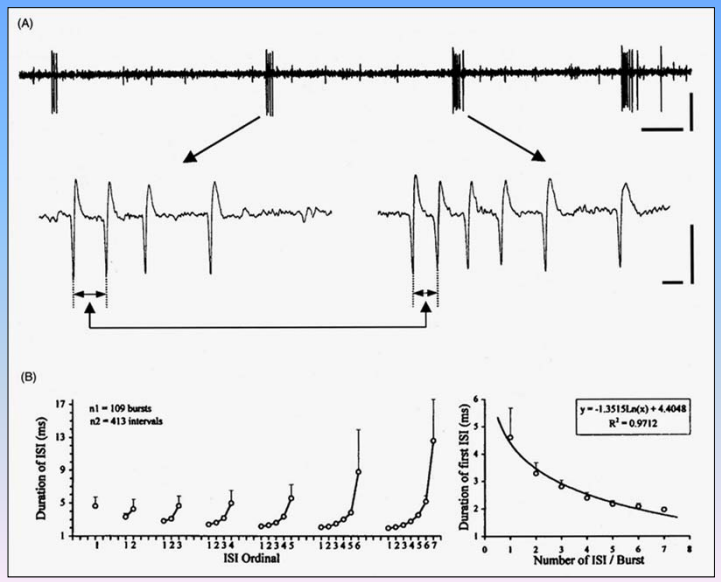
hypothalamus
periaqueductal gray
reticular formation
DORSAL HORN

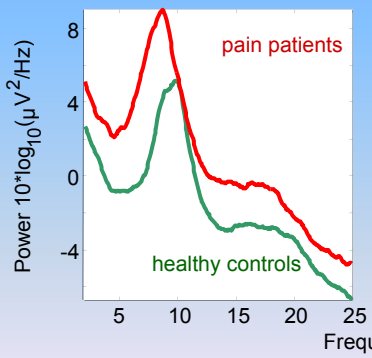
Thalamic Bursting Activity



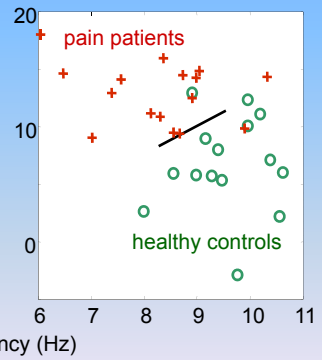
EEG in Neurogenic Pain

15 patients, 15 hc

Group spectra



Alpha peak frequency against alpha peak power for individual subjects



Discriminant analysis:
87% correct

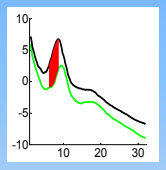
Sarnthein et al., Brain 2005

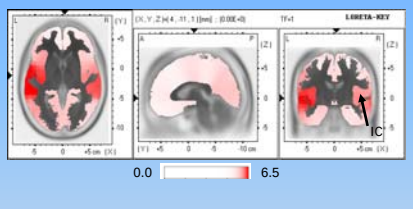
Stern et al. NeuroImage 2006

EEG source localization LORETA

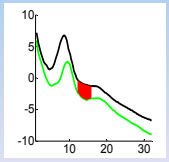
N=15 patients with neurogenic pain vs. N=15 healthy controls

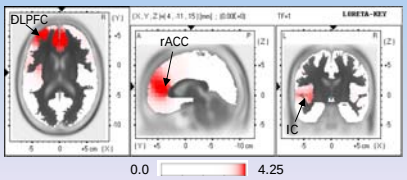
Green curves are for controls, black curves for patients





6-9 Hz



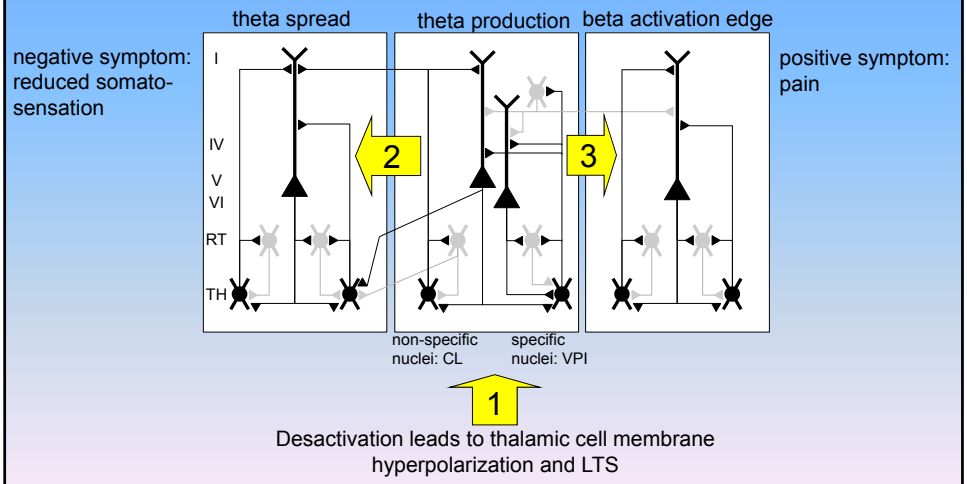


12-16 Hz

IC insular cortex ACC anterior cingulate cortex PFC prefrontal cortex

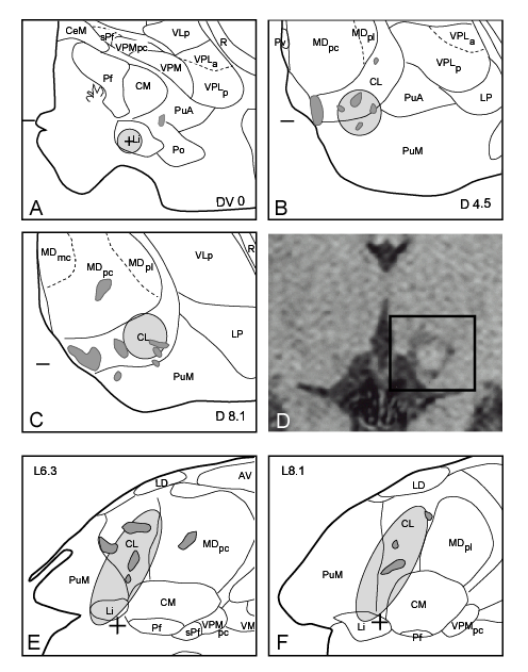
Thalamocortical Dysrhythmia (TCD)

Thalamocortical loops and their interaction in neurogenic pain patients

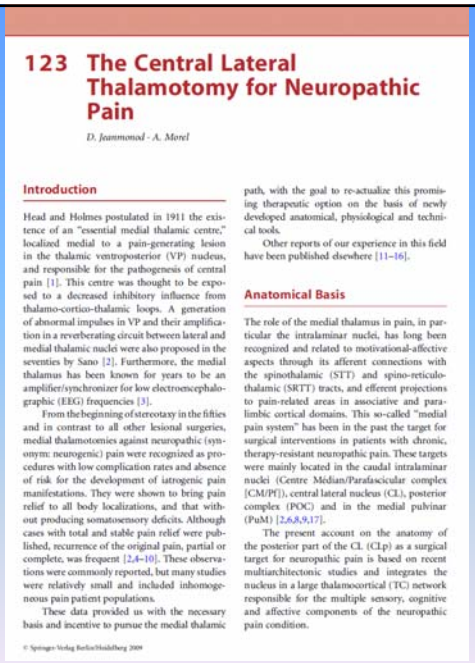


Desactivation leads to thalamic cell membrane hyperpolarization and LTS

The Central Lateral Thalamotomy



Jeanmonod et al.
Thalamus and Related Systems 2001



123 The Central Lateral Thalamotomy for Neuropathic Pain

D. Jeanmonod · A. Morel

Introduction

Head and Holmes postulated in 1911 the existence of an "essential medial thalamic centre," localized medial to a pain-generating lesion in the thalamic ventroposterior (VP) nucleus, and responsible for the pathogenesis of central pain [1]. This centre was thought to be exposed to a decreased inhibitory influence from thalamo-cortico-thalamic loops. A generation of abnormal impulses in VP and their amplification in a reverberating circuit between lateral and medial thalamic nuclei were also proposed in the seventies by Sano [2]. Furthermore, the medial thalamus has been known for years to be an amplifier/synchronizer for low electroencephalographic (EEG) frequencies [3].

From the beginning of stereotaxy in the fifties and in contrast to all other lesional surgeries, medial thalamotomies against neuropathic (synonym: neurogenic) pain were recognized as procedures with low complication rates and absence of risk for the development of iatrogenic pain manifestations. They were shown to bring pain relief to all body localizations, and that without producing somatosensory deficits. Although cases with total and stable pain relief were published, recurrence of the original pain, partial or complete, was frequent [2,4–10]. These observations were commonly reported, but many studies were relatively small and included inhomogeneous pain patient populations.

These data provided us with the necessary basis and incentive to pursue the medial thalamic path, with the goal to re-actualize this promising therapeutic option on the basis of newly developed anatomical, physiological and technical tools.

Other reports of our experience in this field have been published elsewhere [11–16].

Anatomical Basis

The role of the medial thalamus in pain, in particular the intralaminar nuclei, has long been recognized and related to motivational-affective aspects through its afferent connections with the spinothalamic (STT) and spino-reticulo-thalamic (SRTT) tracts, and efferent projections to pain-related areas in associative and paralimbic cortical domains. This so-called "medial pain system" has been in the past the target for surgical interventions in patients with chronic, therapy-resistant neuropathic pain. These targets were mainly located in the caudal intralaminar nuclei (Centre Médian/Parafascicular complex [CM/Pf]), central lateral nucleus (CL), posterior complex (POC) and in the medial pulvinar (PuM) [2,6,8,9,17].

The present account on the anatomy of the posterior part of the CL (CLp) as a surgical target for neuropathic pain is based on recent multiarchitectonic studies and integrates the nucleus in a large thalamocortical (TC) network responsible for the multiple sensory, cognitive and affective components of the neuropathic pain condition.

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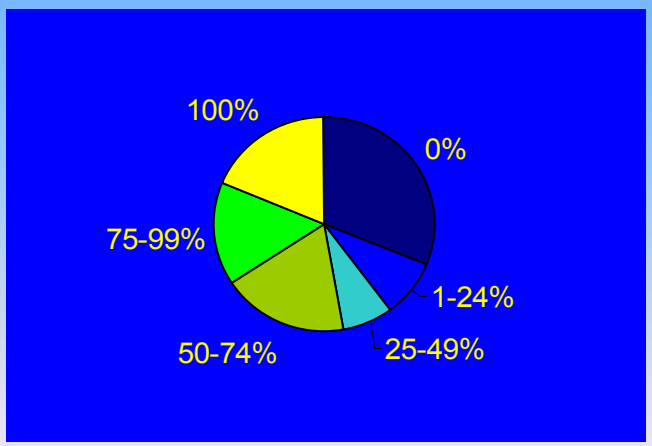
Textbook of Stereotactic and Functional Neurosurgery (2009), Springer, Eds. Lozano, Gildenberg and Tasker

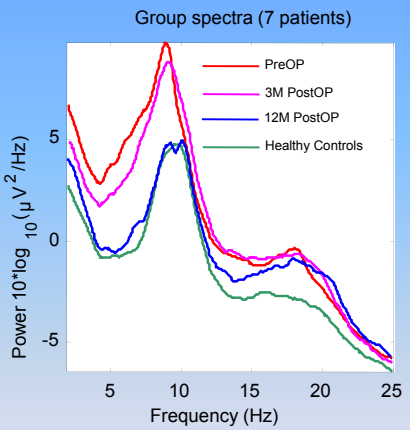
CLT and neurogenic pain

Group of N=96 patients, mean follow-up 3 years 9 months
Satisfactory to complete (50-100%) pain relief in 53% of the patients



Jeanmonod et al., Thalamus and Related Systems 2001

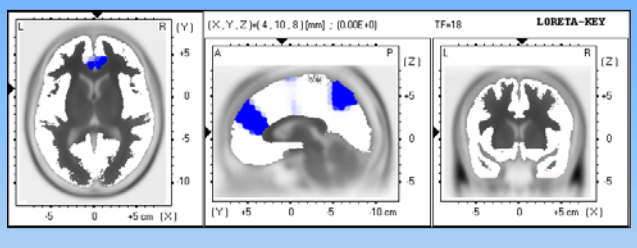
Zeitliche Entwicklung der EEG-Veränderungen nach stereotaktischer Radiofrequenz-CLT



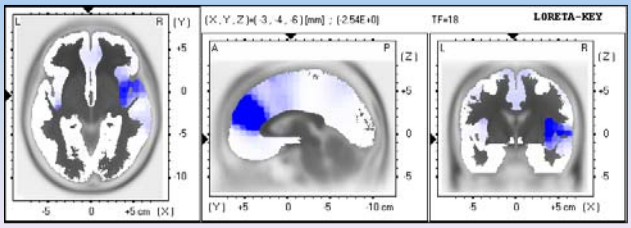
Sarnthein et al., Brain 2005

Neurogenic pain patients
Pre-post surgery comparison
Blue areas display reduced EEG activity after surgery

3 months follow-up
8.5Hz, n.s.
n=14



1 year follow-up
8.5Hz, t=3.5
n=6



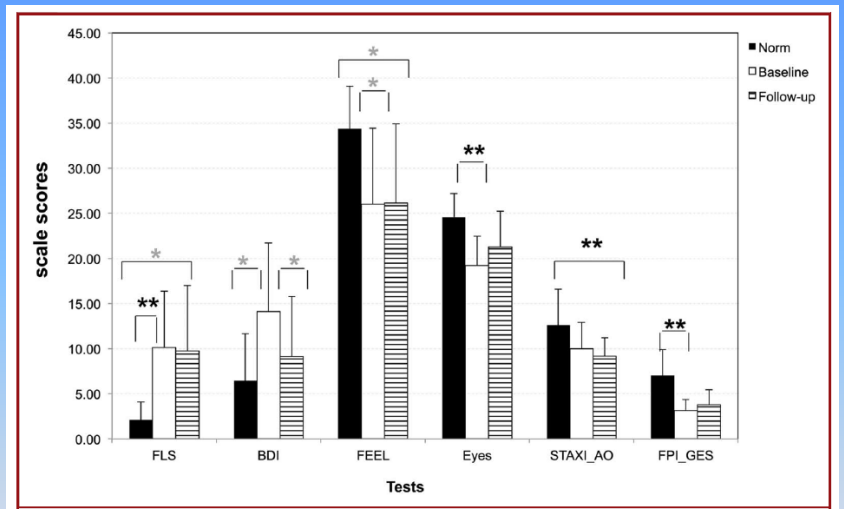
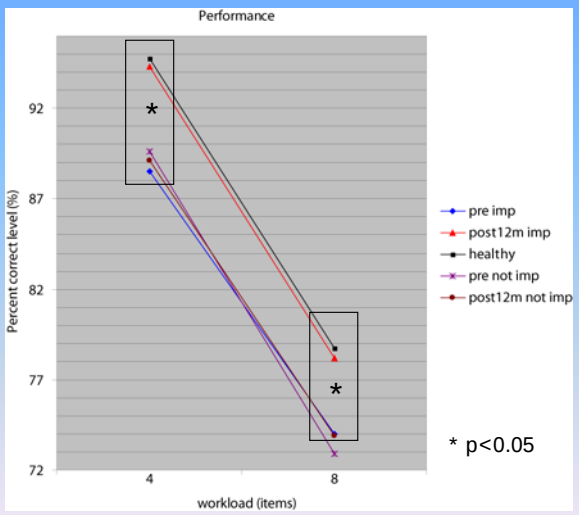


FIGURE 1. *Plots of the significant mean differences and standard deviations observed in the patients with chronic pain in comparison with the test's norm or in the comparison between baseline and follow-up. FLS, Frontal Lobe Score; BDI, Beck Depression Inventory; FEEL, Facially Expressed Emotion Labeling test; Eyes, Eyes Test; STAXI_AO, State-Trait Anger Inventory Anger out; FPI_GES, Freiburger Personality Inventory_health concern. *(light gray asterisk) P < .05, *(dark gray asterisk) significant at a Bonferroni-corrected α of.016, **P< .01.*

Pirrotta et al. Neurosurgery 2013

Behavioral data WM task



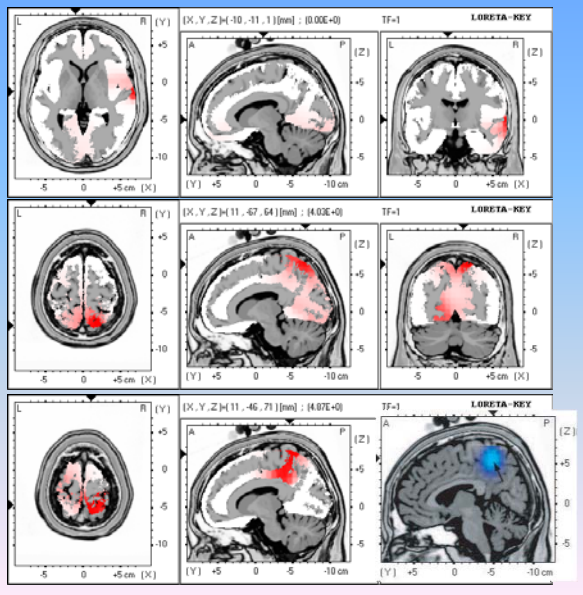
Before and 12 months after surgery

LORETA (WM)

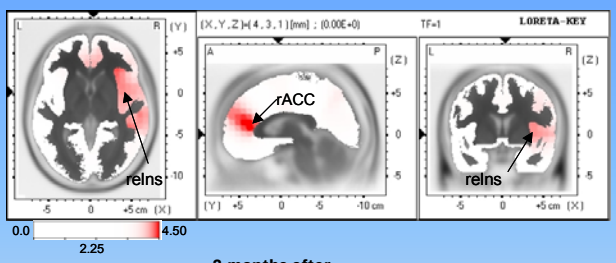
ss4-ss8 (pre), n.s.

ss4-ss8 (post12m), P < 0.05

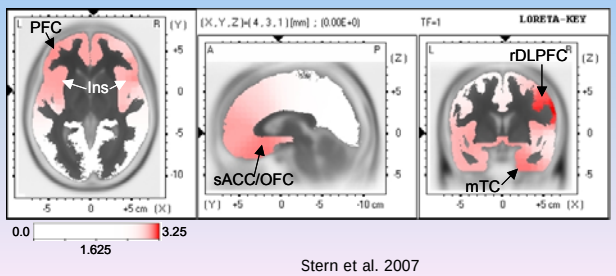
ss4-ss8 (HC), P < 0.01



Before surgery

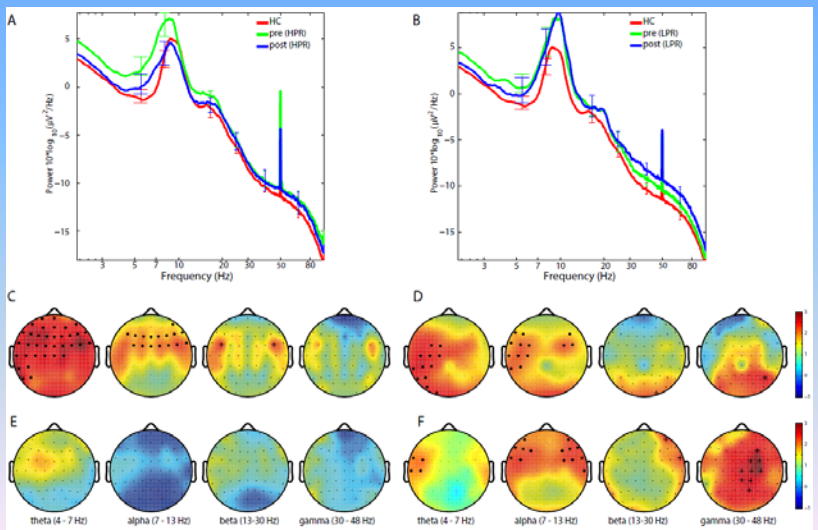


3 months after surgery

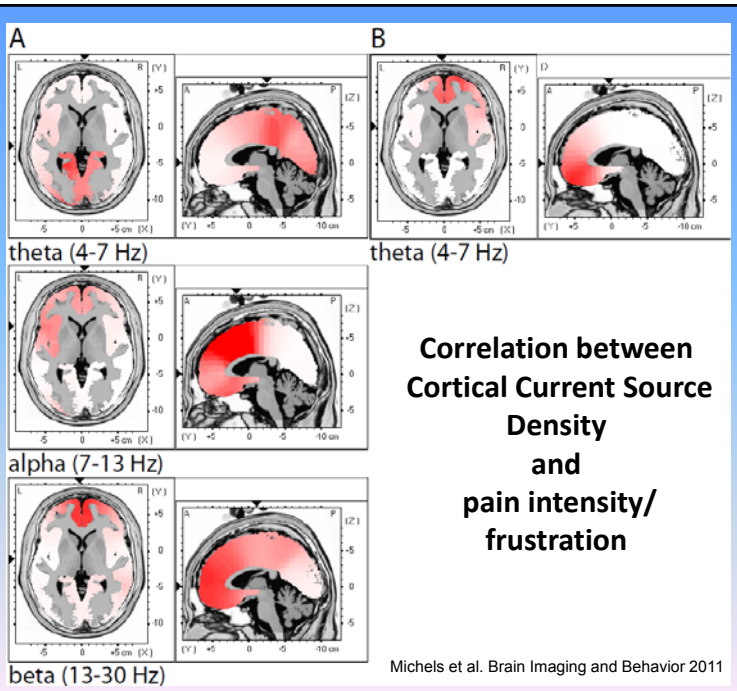


Stern et al. 2007

Neurogenic pain: EEG spectral evolution for high and low pain relief



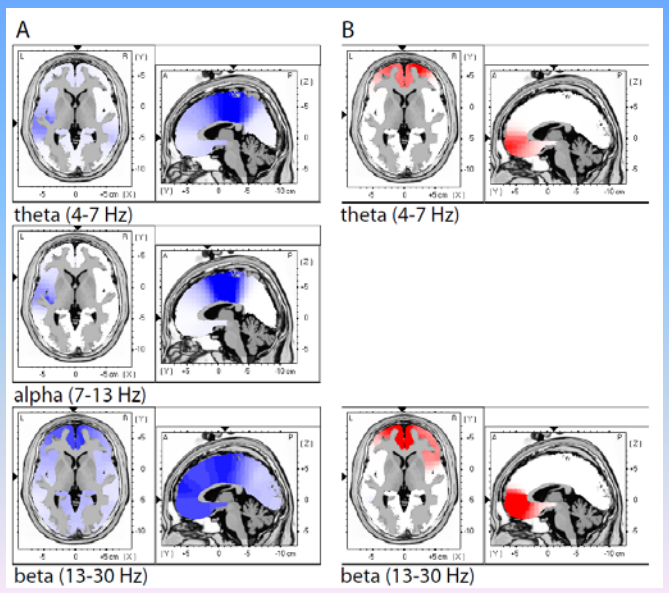
Michels et al. Brain Imaging and Behavior 2011



Correlation between Cortical Current Source Density and pain intensity/ frustration

Michels et al. Brain Imaging and Behavior 2011

Correlation between Cortical Current Source Density and pain relief/frustration in high and low pain relief patients



Michels et al. Brain Imaging and Behavior 2011

Incisionless MR-guided Focused Ultrasound Surgery

- **High Intensity Focused Ultrasound system**
  Heats and ablates targeted tissue (thermo-coagulation), without skin incision. Creation of a focal point (focusing principle)
- **Magnetic Resonance Imaging guidance**
  Enables visualization of patient anatomy to define target but also guide the whole ablation process: optimization of safety, accuracy and efficacy in real time/closed loop
- **MR Thermal Imaging monitoring**
  Enables real time temperature measurement in tissue (thermal spot) to guide progress of the ablation process: optimization of safety, accuracy and efficacy in real time/closed loop

Incisionless MR-guided Focused Ultrasound in Functional Neurosurgery

Incisionless tissue ablation as alternative option to stereotactic radiofrequency ablation (SRFA)

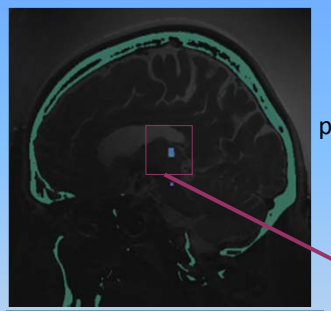
Advantages:

1) No brain tissue shift/trauma on the way (centimeters) to the target: lesion restricted to the target tissue (millimeters)
2) Suppression of the risk of infection
3) No trajectory constraints, allowing optimization of target coverage
4) Real time continuous monitoring of proper targeting and thermal effects
5) Optimized targeting precision
6) Possibility of reduced bleeding risk

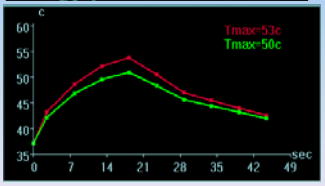
Treatment Procedure

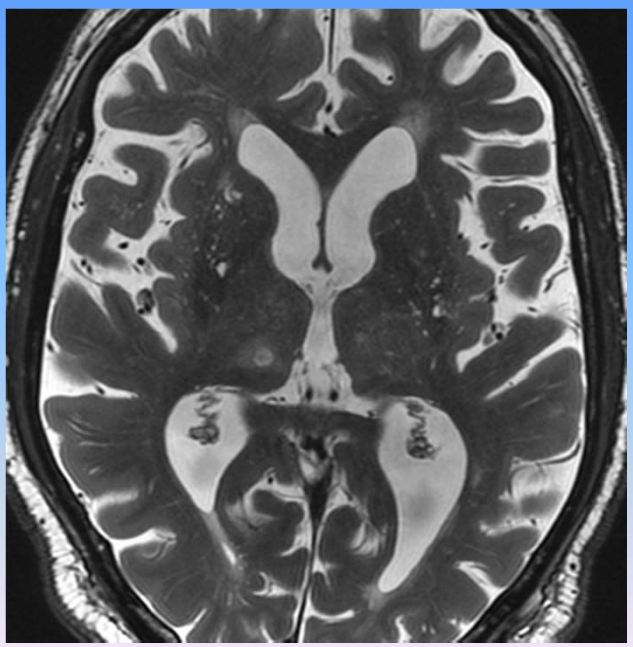
- **Patient preparation on treatment day before entry into the MR bore**
  - Head full and close shave
  - Stereotactic frame fixation for head immobilization
  - A helmet-like hemispheric ultrasound transducer is placed around the patient's head. The space between head and transducer is closed by a silicone membrane and then filled with degassed and cooled water
- **Treatment Preparation**
  - Mechanical centering of the transducer
  - Tuning of the central frequency of the MR system
  - CT/MR co-registration and exclusion of no-pass regions
  - MR stereotactic target position determination using the Morel Stereotactic Atlas of the Human Thalamus and Basal Ganglia
- **Treatment**
  - Sonication adjustment (user's manual correction of targeting) to ascertain thermal spot localization at low temperatures (below 45°) known to cause reversible tissue effects
  - Gradual increase of energy delivery guided by tissue response (temperature/energy curve)
  - The physician is constantly updated with real-time imaging showing the thermal rise and its location
  - Patient is monitored and questioned to assess changes during procedure (therapeutic effects, absence of side-effects, stimulation effects)

Thermal spot

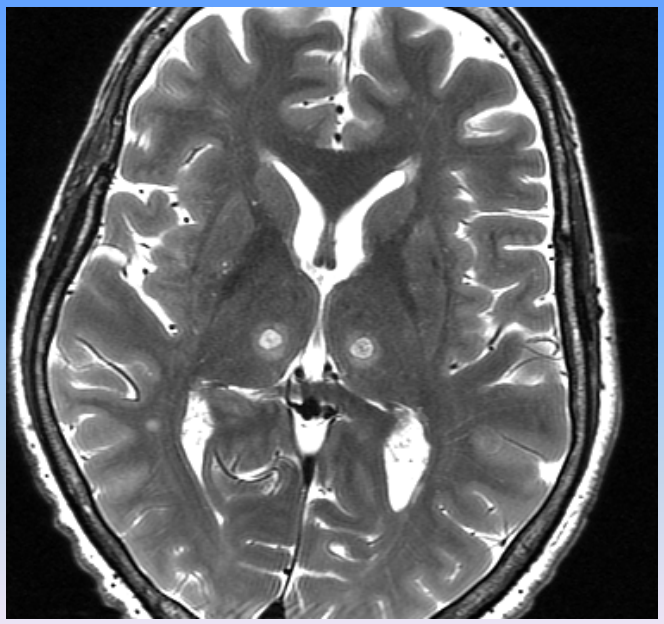


Thermal spot within planned target coordinates

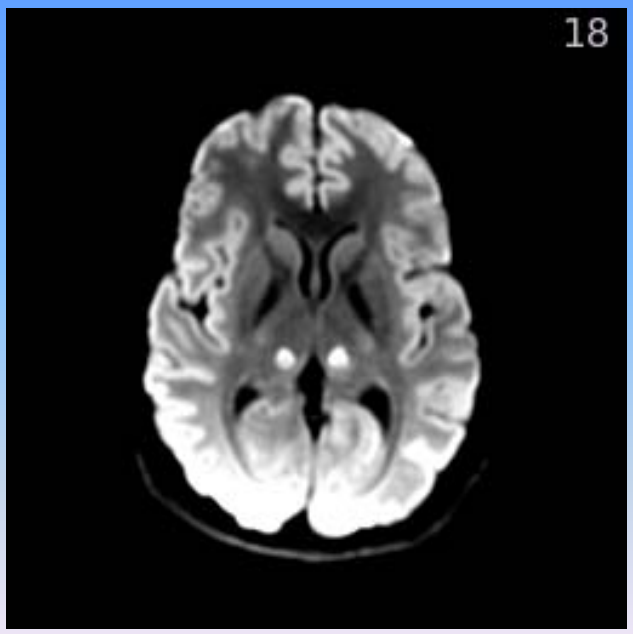




Central Lateral Thalamotomy



Central Lateral Thalamotomy



Central Lateral Thalamotomy

Neurosurg Focus 32 (1):E1, 2012

Transcranial magnetic resonance imaging–guided focused ultrasound: noninvasive central lateral thalamotomy for chronic neuropathic pain

Daniel Jeanmonod, M.D.,[1,2] Beat Werner, M.Sc.,[2] Anne Morel, Ph.D.,[1,3] Lars Michels, Ph.D.,[1,3] Eyal Zadicario, M.Sc.,[2] Gilat Schiff, B.Sc.,[2] and Ernst Martin, M.D.[3]

[1]Department of Functional Neurosurgery and [2]Center for Clinical Research, University Hospital Zurich; [3]Center of Ultrasound Functional Neurosurgery, Solothurn; [4]MR-Center, University Children's Hospital, Zürich, Switzerland; and [5]InSightec, Ltd., Tirat Carmel, Israel

Object. Recent technological developments open the field of therapeutic application of focused ultrasound to the brain through the intact cranium. The goal of this study was to apply the new transcranial magnetic resonance imaging–guided focused ultrasound (tcMRgFUS) technology to perform noninvasive central lateral thalamotomies (CLTs) as a treatment for chronic neuropathic pain.

Methods. In 12 patients suffering from chronic therapy-resistant neuropathic pain, tcMRgFUS CLT was proposed. In 11 patients, precisely localized thermal ablations of 3–4 mm in diameter were produced in the posterior part of the central lateral thalamic nucleus at peak temperatures between 51°C and 64°C with the aid of real-time patient monitoring and MR imaging and MR thermometry guidance. The treated neuropathic pain syndromes had peripheral (5 patients) or central (6 patients) origins and covered all body parts (face, arm, leg, trunk, and hemibody).

Results. Patients experienced mean pain relief of 49% at the 3-month follow-up (9 patients) and 57% at the 1-year follow-up (8 patients). Mean improvement according to the visual analog scale amounted to 42% at 3 months and 41% at 1 year. Six patients experienced immediate and persisting somatosensory improvements. Somatosensory and vestibular clinical manifestations were always observed during sonication time because of ultrasound-based neuronal activation and/or initial therapeutic effects. Quantitative electroencephalography (EEG) showed a significant reduction in EEG spectral overactivities. Thermal ablation sites showed sharply delineated ellipsoidal thermolesions surrounded by short-lived vasogenic edema. Lesion reconstructions (18 lesions in 9 patients) demonstrated targeting precision within a millimeter for all 3 coordinates. There was 1 complication, a bleed in the target with ischemia in the motor thalamus, which led to the introduction of 2 safety measures, that is, the detection of a potential cavitation by a cavitation detector and the maintenance of sonication temperatures below 60°C.

Conclusions. The authors assert that tcMRgFUS represents a noninvasive, precise, and radiation-free neurosurgical technique for the treatment of neuropathic pain. The procedure avoids mechanical brain tissue shift and eliminates the risk of infection. The possibility of applying sonication thermal spots free from trajectory restrictions should allow one to optimize target coverage. The real-time continuous MR imaging and MR thermometry monitoring of targeting accuracy and thermal effects are major factors in optimizing precision, safety, and efficacy in an outpatient context.

(http://thejns.org/doi/abs/10.3171/2011.10.FOCUS11248)

Key Words • central lateral thalamotomy • neuropathic or neurogenic pain • transcranial magnetic resonance imaging–guided focused ultrasound

Considering the inherent risks related to neurosurgical procedures, such as infections and hemorrhages, there is an obvious demand for less invasive alternative procedures. Following extensive preclinical investigations,[4-8,10,11,13,15,24,25,31,32] a clinically relevant prototype of a tcMRgFUS device for thermal ablation was developed.[9,12,14] Because of its noninvasiveness, focused ultrasound technology eliminates the risk of infection, reduces the risk of bleeding, and limits collateral damage to nontargeted tissue. Magnetic resonance imaging allows precise intraprocedural localization of the ablation target, definition and verification of safety margins for the ultrasound treatment, real-time monitoring of thermal ablation dynamics, and intra- and posttreatment assessment of intervention results.[1,2,23] The tcMRgFUS technique involves the transformation of sonic into thermal energy and the production of a thermolesion. The possibility of

Abbreviations used in this paper: CLp = posterior part of the thalamic central lateral nucleus; CLT = central lateral thalamotomy; DT = diffusion tensor; EEG = electroencephalography; tcMRgFUS = transcranial magnetic resonance imaging–guided focused ultrasound; VAS = visual analog scale; VLp = posterior part of the thalamic motor ventral lateral nucleus.

Moser et al. Journal of Therapeutic Ultrasound 2013, 1:3
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RESEARCH Open Access

MR-guided focused ultrasound technique in functional neurosurgery: targeting accuracy

David Moser[1*], Eyal Zadicario[2], Gilat Schiff[2] and Daniel Jeanmonod[1]

Abstract

Background: The purpose of this study was to describe targeting accuracy in functional neurosurgery using incisionless transcranial magnetic resonance (MR)-guided focused ultrasound technology.

Methods: MR examinations were performed before and 2 days after the ultrasound functional neurosurgical treatment to visualize the targets on T2-weighted images and determine their coordinates. Thirty consecutive targets were reconstructed: 18 were in the central lateral nucleus of the medial thalamus (central lateral thalamotomies against neurogenic pain), 1 in the centrum medianum thalamic nucleus (centrum medianum thalamotomy against essential tremor), 10 on the pallido-thalamic tract (pallido-thalamic tractotomies against Parkinson's disease), and 1 on the cerebello-thalamic tract (cerebello-thalamic tractotomy against essential tremor). We describe a method for reconstruction of the lesion coordinates on post-treatment MR images, which were compared with the desired atlas target coordinates. We also calculated the accuracy of the intra-operative target placement, thus allowing to determine the global, planning, and device accuracies. We also estimated the target lesion volume.

Results: We found mean absolute global targeting accuracies of 0.44 mm for the medio-lateral dimension (standard deviation 0.35 mm), 0.38 mm for the antero-posterior dimension (standard deviation 0.33 mm), and 0.66 mm for the dorso-ventral dimension (standard deviation 0.37 mm). Out of the 90 measured coordinates, 83 (92.2%) were inside the millimeter domain. The mean three-dimensional (3D) global accuracy was 0.99 mm (standard deviation 0.39 mm). The mean target volumes, reconstructed from surface measurements on 3D T1 series, were 68.5 mm^3 (standard deviation 39.7 mm^3), and 68.9 mm^3 (standard deviation 40 mm^3) using an ellipsoidal approximation.

Conclusion: This study demonstrates a high accuracy of the MR-guided focused ultrasound technique. This high accuracy is due not only to the device qualities but also to the possibility for the operator to perform on-going real-time monitoring of the lesioning process. A precise method for determination of targeting accuracy is an essential component and basic requirement of the functional neurosurgical activity, allowing an on-going control of the performed therapeutic work indispensable for any target efficiency analysis and the maintenance of a low risk profile.

Keywords: Anterior commissure, Posterior commissure, Stereotactic atlas, Targeting accuracy, Thalamo-ventricular border, Transcranial MR-guided focused ultrasound

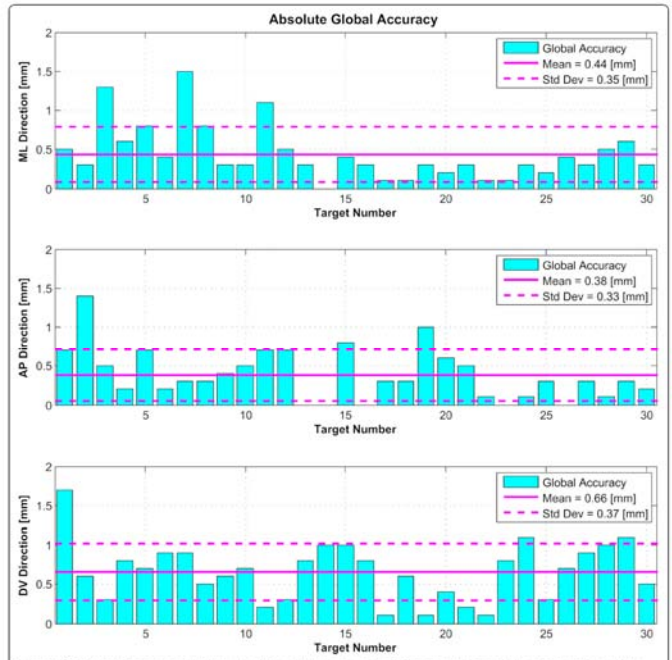

Figure 4 Global targeting accuracy. Absolute value of the global accuracies of the 30 reconstructed targets in the three directions, with the mean and standard deviation (*Std Dev*) for each. *ML* stands for medio-lateral, *AP* for antero-posterior, and *DV* for dorso-ventral.

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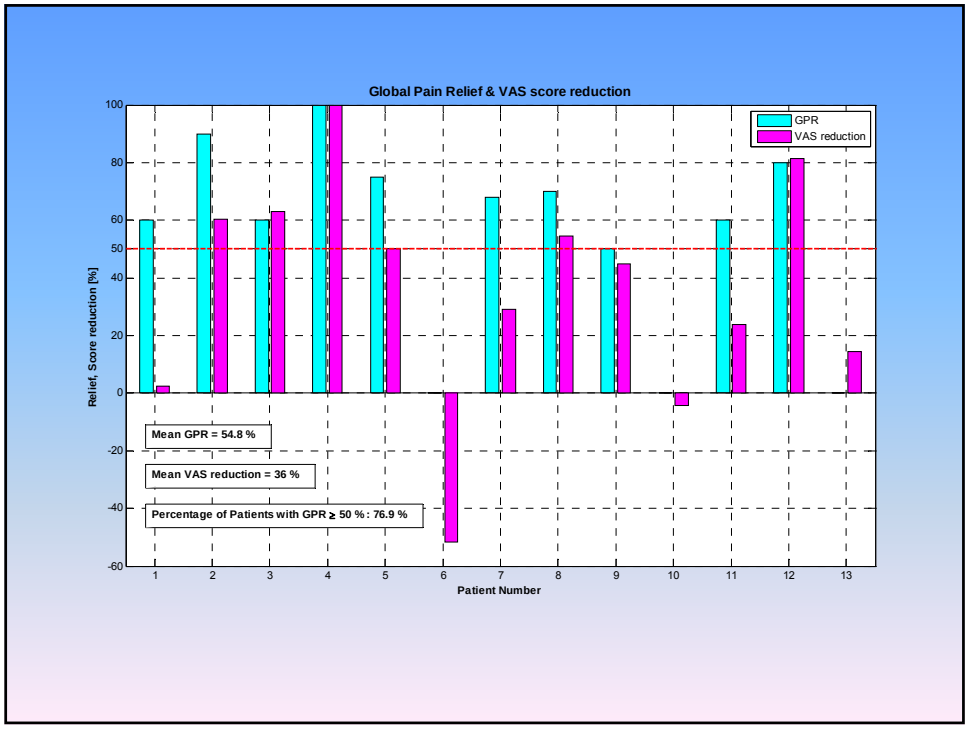
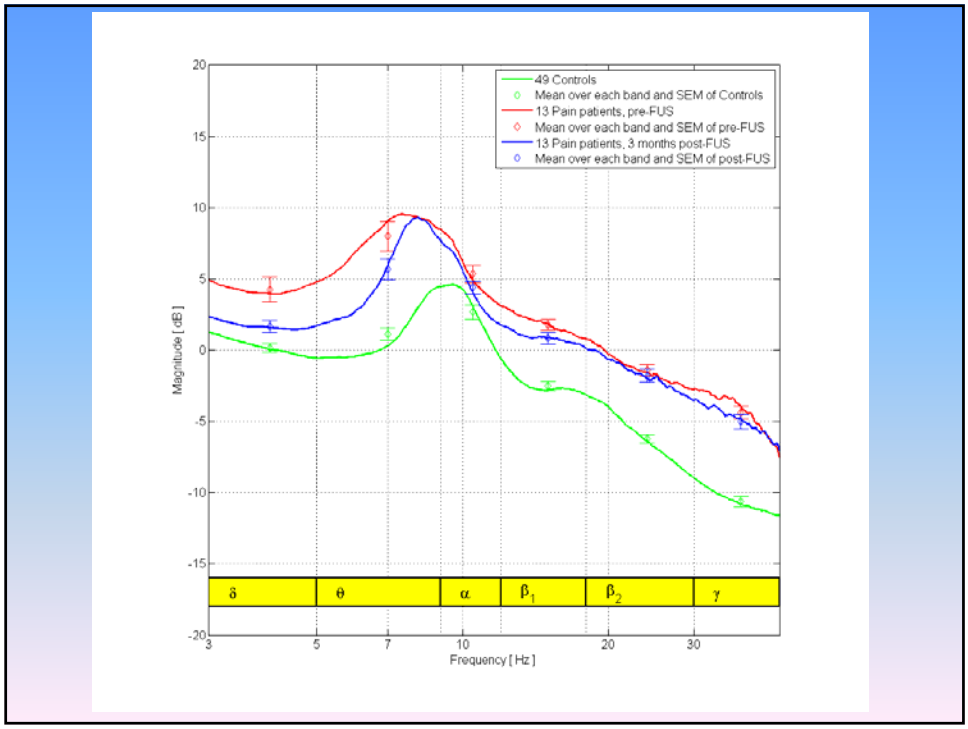
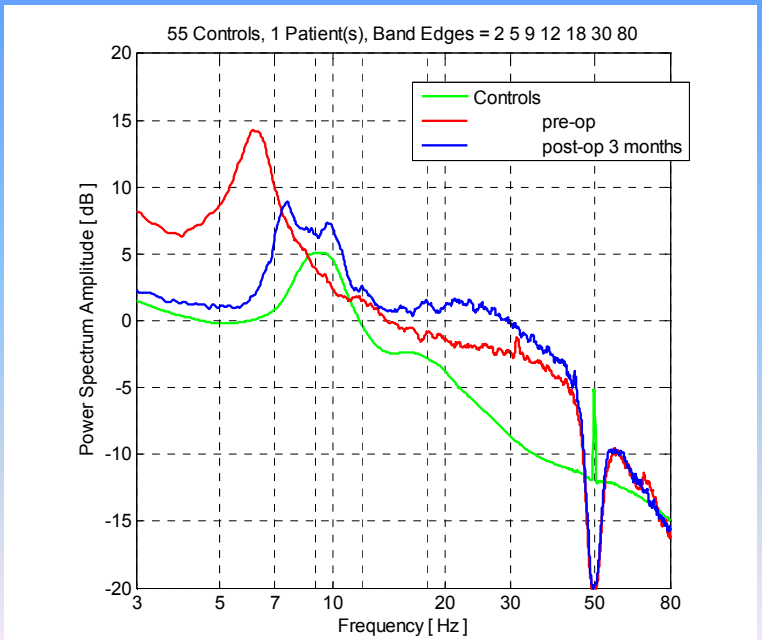
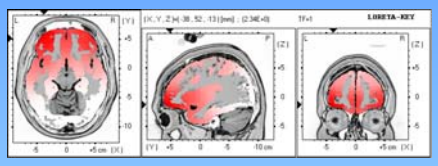

Global Pain Relief & VAS score reduction
GPR
VAS reduction
Relief, Score reduction [%]
Patient Number
Mean GPR = 54.8 %
Mean VAS reduction = 36 %
Percentage of Patients with GPR ≥ 50 % : 76.9 %


49 Controls
Mean over each band and SEM of Controls
13 Pain patients, pre-FUS
Mean over each band and SEM of pre-FUS
13 Pain patients, 3 months post-FUS
Mean over each band and SEM of post-FUS
Magnitude [dB]
Frequency [Hz]
δ
θ
α
β1
β2
γ

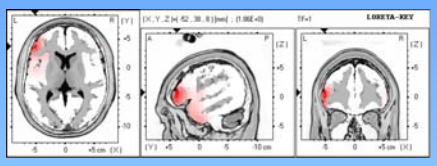


Pre-surgery

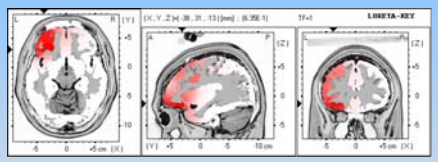
Post-surgery (3 month)



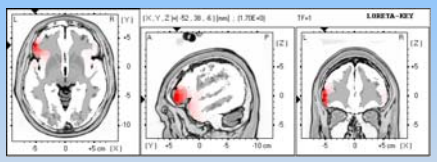
4-8 Hz, p < 0.01



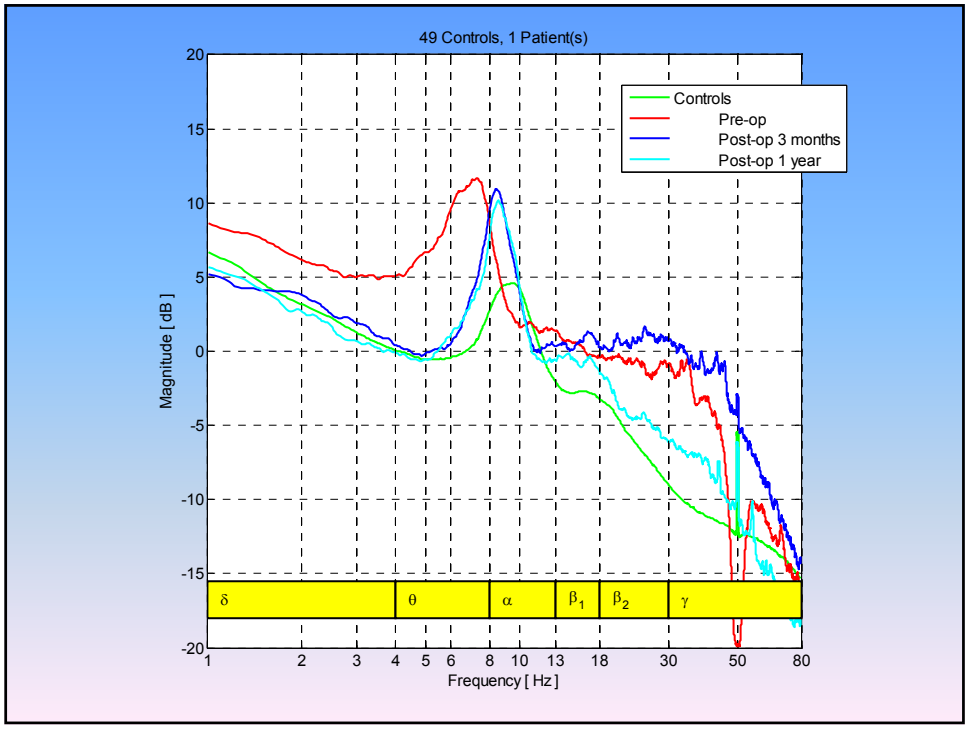
4-8 Hz, n.s.



8-12 Hz, n.s.



8-12 Hz, n.s.



Mitarbeiter

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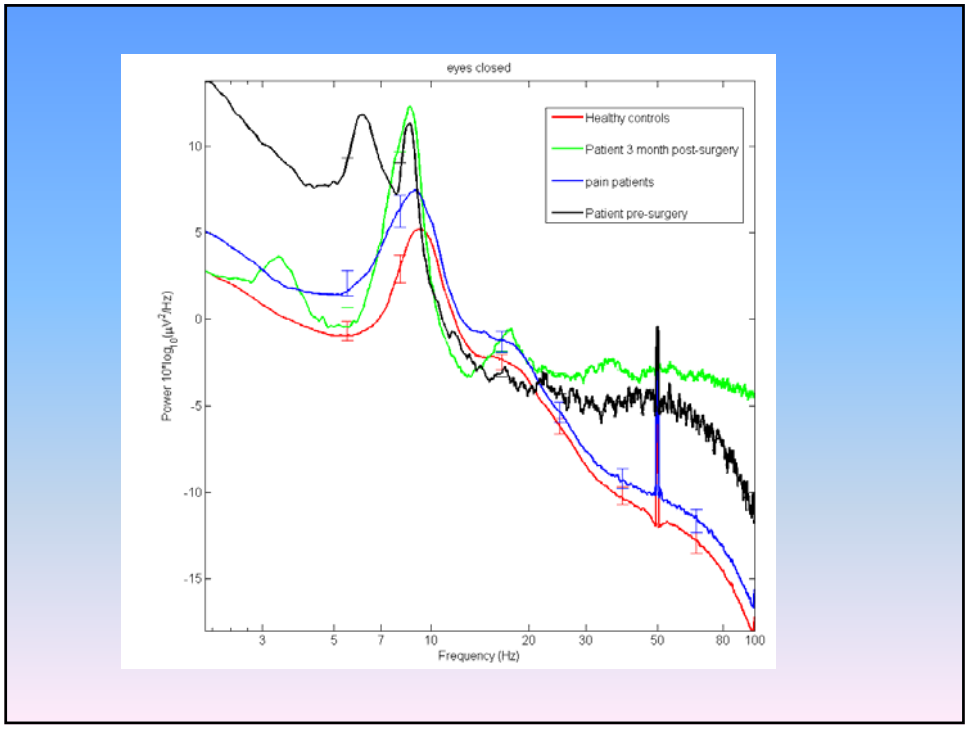
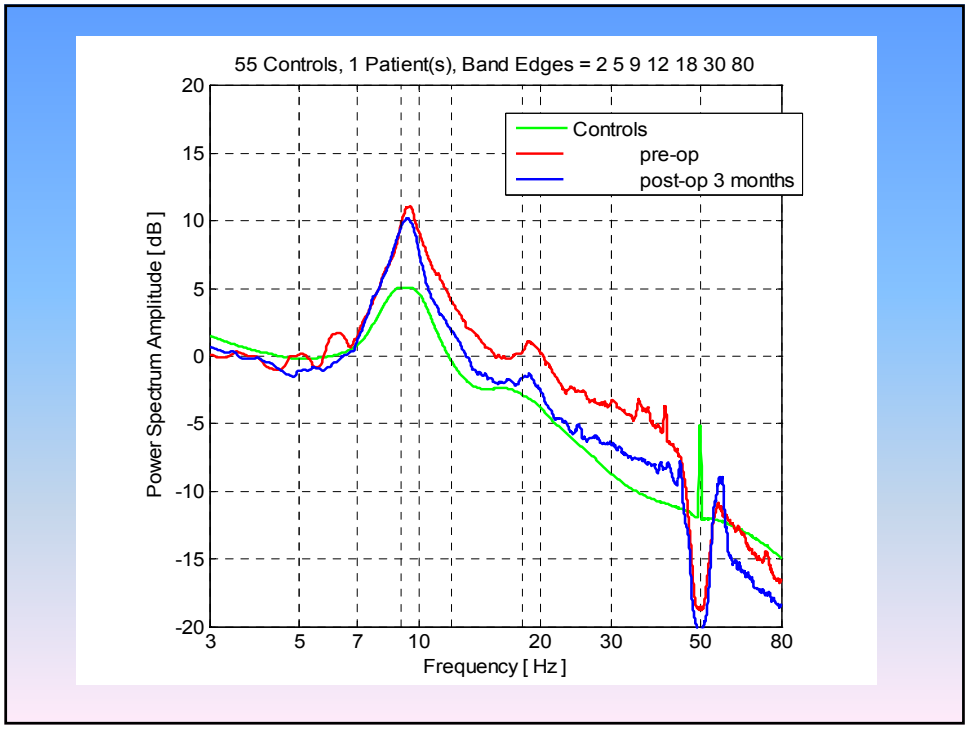
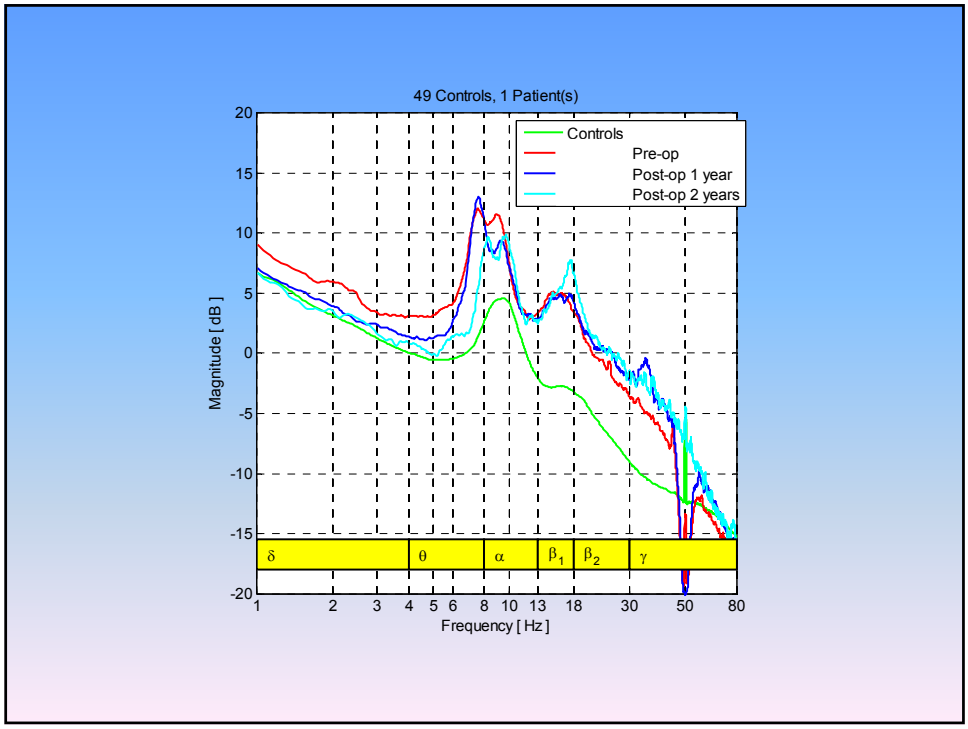
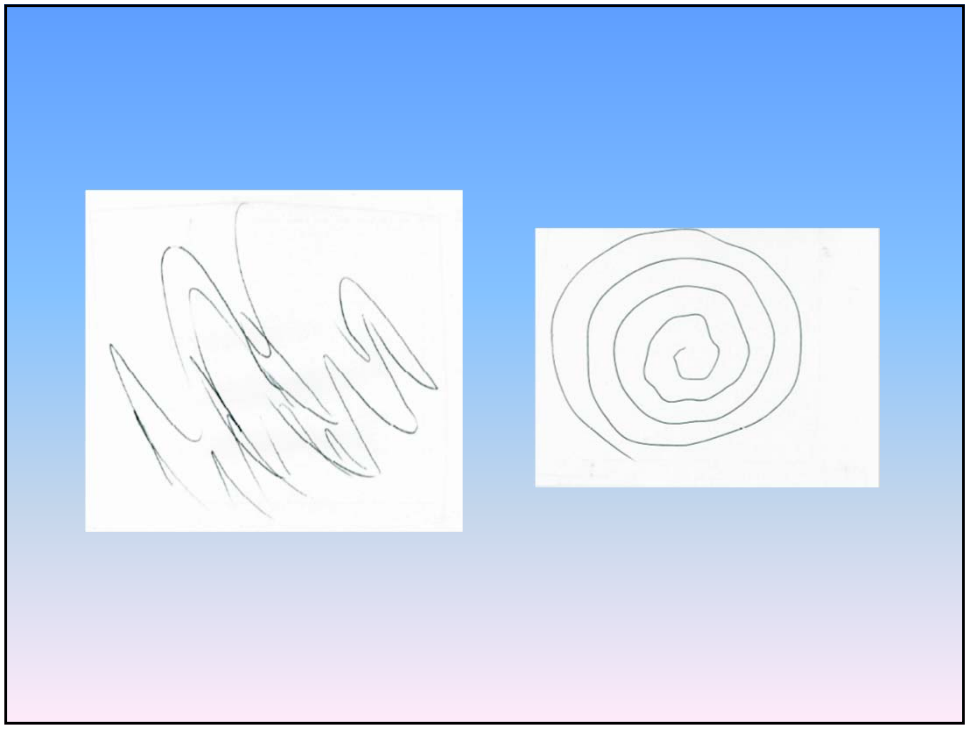
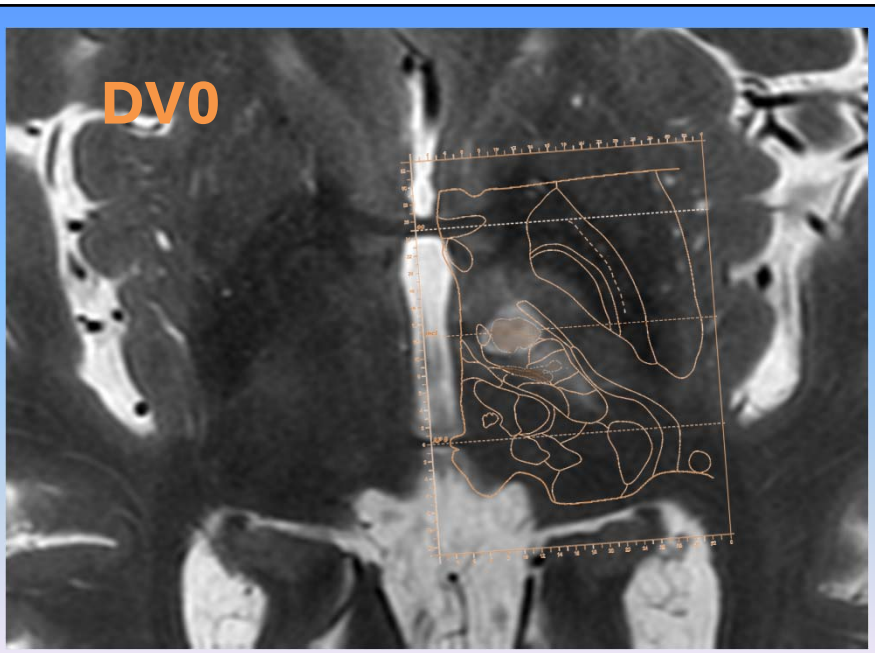
  Tony Coray, Rodiag Diagnostics Centers, Solothurn
  Jörg Vogel, Rodiag Diagnostics Centers, Solothurn
  Oskar Blosser, Rodiag Diagnostics Centers, Solothurn


eyes closed
Healthy controls
Patient 3 month post-surgery
pain patients
Patient pre-surgery
Power 10*log10 (μV²/Hz)
Frequency (Hz)


55 Controls, 1 Patient(s), Band Edges = 2 5 9 12 18 30 80
Controls
pre-op
post-op 3 months
Power Spectrum Amplitude [dB]
Frequency [Hz]


49 Controls, 1 Patient(s)
Controls
Pre-op
Post-op 1 year
Post-op 2 years
Magnitude [dB]
Frequency [Hz]
δ
θ
α
β1
β2
γ





Pallido-thalamic Tractotomy