Chasing Map Plasticity in Neuropathic Pain

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Key words
- Eye
- fMRI
- Implant
- Perception
- PET
- Phantom
- Somatosensory reorganization

Abbreviations and Acronyms
AD: Anesthesia dolorosa
BOLD: Blood-oxygen-level dependence
fMRI: Functional magnetic resonance imaging
IPG: Internal pulse generator
PET: Positron emission tomography
SI: Primary somatosensory cortex
SII: Secondary somatosensory cortex
TMS: Transcranial magnetic stimulation

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Citation: World Neurosurg. (2013) 80, 6:901.e1-901.e5. http://dx.doi.org/10.1016/j.wneu.2012.12.009

Journal homepage: www.WORLDNEUROSURGERY.org

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OBJECTIVE: **Recently, somatosensory cortex stimulation has been proposed as a possible treatment for neuropathic deafferentation pain, based on a simple 4-step concept: (1) pain is associated with increased activity in the somatosensory cortex, (2) allodynia-evoked blood-oxygen-level dependence functional magnetic resonance imaging (fMRI) activation depicts the area involved in the pain, (3) if fMRI-guided, neuronavigation-based transcranial magnetic stimulation can transiently suppress the pain, then (4) an extradural electrode can be implanted targeting the same area.**

CASE DESCRIPTION: **A patient who was successfully treated with this approach for over 6 years for trigeminal anesthesia dolorosa associated with a subjectively malpositioned eye after multiple recurrent facial skin tumor removals developed new pain after more extensive surgery. Reprogramming the implanted electrode was unsuccessful. The presence of the electrode yielded too many artifacts on a renewed fMRI, and therefore a positron emission tomography (PET) scan was performed under evoked allodynia. Fusing the previous fMRI with the new PET images depicted 2 novel targets for stimulation, 1 anterior and 1 posterior of the previous target and beyond the spatial configuration of the implant. After the addition of 2 new electrodes, the pain could again be controlled in a placebo-controlled way, but only when the 2 electrodes were activated.**

CONCLUSIONS: **Combining fMRI and PET scanning can potentially demonstrate continuing map plasticity under progressive somatosensory deafferentation. The functional imaging data can be used as target for pathophysiology-based somatosensory cortex stimulation.**

INTRODUCTION

Anesthesia dolorosa (AD) is a form of deafferentation pain belonging to the group of neuropathic pain syndromes. It is most commonly iatrogenic in nature, following surgically induced lesions of the trigeminal nerve. It can occur after glycerol injection, partial nerve sections, radiofrequency rhizotomy, gamma knife surgery, balloon compressions, and microvascular decompression. AD is characterized by a painful anesthesia often associated with numbness. The neuropathic pain is associated with allodynia (feeling of pain on touch) and hyperalgesia (exaggerated reaction to painful stimuli). It can be continuous with superimposed lancinating paroxysms. AD typically presents as a burning feeling associated with or without numbness, itching, and a feeling of coldness.

It is typically very treatment resistant, and therefore is often treated by neuromodulatory approaches such as motor cortex stimulation (22), somatosensory cortex stimulation (8), or deep brain stimulation (18).

We present a case of AD in the ophthalmic division of the trigeminal nerve that developed after multiple resections of a basal cell carcinoma of the forehead. It was initially successfully treated by functional magnetic resonance imaging (fMRI)—guided stereotactic somatosensory cortex stimulation (7), but after more surgery for tumor recurrences, became intractable. A successful approach using positron emission tomography (PET)-guided implantation of 2 extra electrodes with successful stimulation is described.

CASE REPORT

A 53-year-old woman presented at the BRAI²N clinic with a 10-year history of persistent lancinating pain in the right supraorbital region. The pain arose a few weeks after a surgical excision of basal cell carcinoma on the right side of the forehead. Initially she suffered a normal postoperative pain progressively evolving to a constant, sharp lancinating pain. Multiple surgical procedures that followed caused aggravation of the symptoms (Figure 1). The pain was initially treated with medication consisting of paracetamol 500 mg/codeine 10 mg, up to 8 tablets per day. The patient subsequently also took

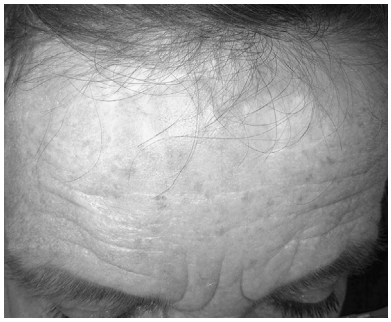

Figure 1. Multiple old scars can be detected on the right forehead, as well as a skin transplant (*light color*) crossing the midline.

tramadol 4 × 50 mg, amitriptyline 50 mg, zolmitriptan 2.5 mg, valproic acid chrono 2 × 500 mg, carbamazepine 3 × 200 mg, and gabapentin 3 × 300 mg, all to no avail. Transcutaneous electrical nerve stimulation was applied without success, and a stellate block brought no pain relief. Finally the right supraoptic nerve was cut, inducing AD.

Aside from the pain, she also developed a sensation of her right eye being located on her right maxillary arc. Despite a normal vision as demonstrated by an extensive neuro-ophthalmological workup, the subjective eye misplacement often induced a misperception of the position of surrounding objects, causing her to run into obstacles ipsilateral to the phantom sensation.

Clinical Examination

The presence of hyperalgesia and a loss of sensation of temperature and vibration in the right V1 dermatoma were noted. Tactile stimulation of the medial cornea and upper eyelashes of the right eye were sensed at the subjectively malpositioned eye at the right maxillary arc (Figure 2B). Tactile stimulation of the medial cornea and medial upper and lower eyelashes of the misplaced eye were referred to the corresponding areas at the ipsilateral eye. A corneal reflex could not be elicited by striking at the subjectively malpositioned eye. Further clinical examinations were normal.

fMRI

fMRI was performed on a 3-T magnetic resonance system using the blood-oxygen-level dependence (BOLD) method and consisted of acquisition of whole-brain fast field echo-echo planar imaging (resolution of 3 × 3 × 4 mm, TE/TR = 33/3000 ms) as well as high-resolution T1-weighted anatomical images. The stimulation paradigm was a blocked fMRI design alternating 30-second epochs of sensory stimulation (the patient rubbed the painful right V1 skin area using her left hand) with 30-second epochs of non-stimulation (rest). Statistical comparison

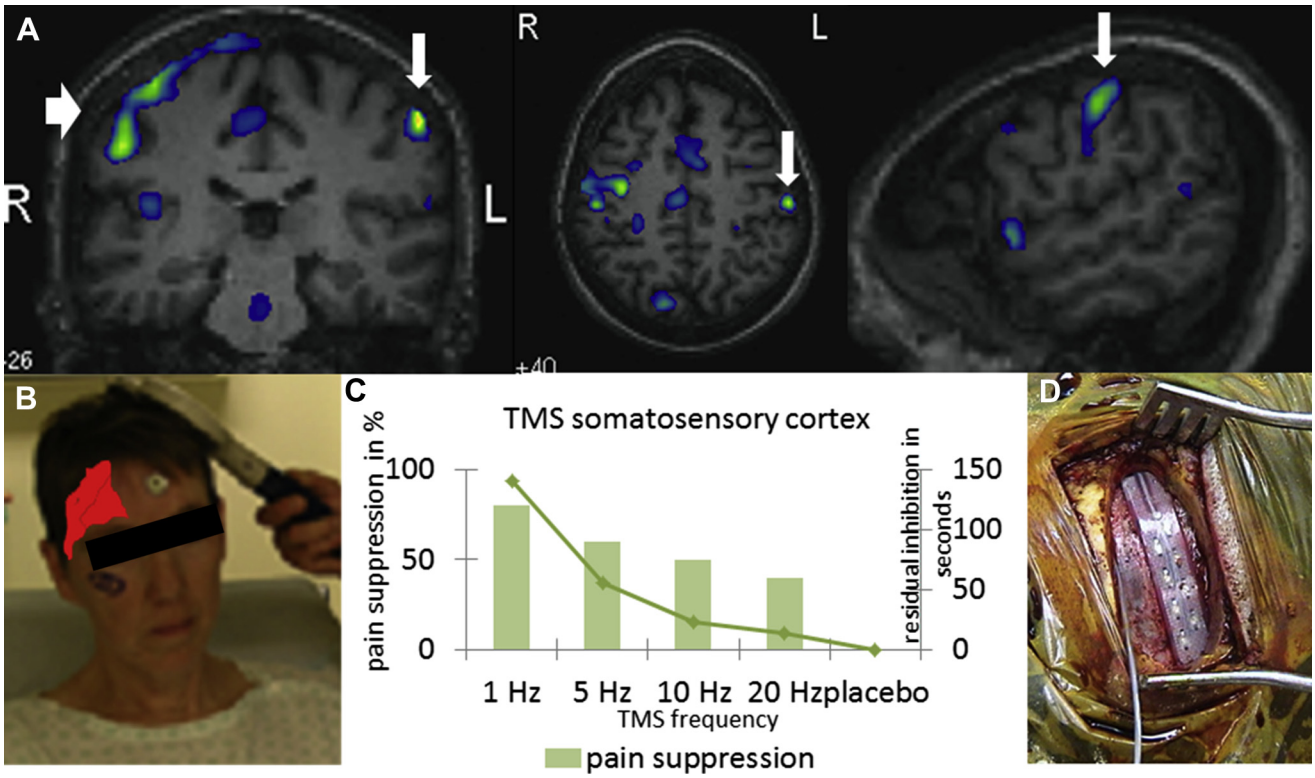

Figure 2. (**A**) Functional magnetic resonance imaging activation elicited by allodynia of the V1 dermatoma (*downward arrow*). The motor cortex activation is the result of using her left hand in the MRI machine to rub her right forehead (*horizontal thick arrow*). (**B**) The area of anesthesia dolorosa with allodynia is represented by *red coloring* in the area on her forehead. The phantom eye is drawn on her right cheek. (**C**) The amount of transcranial magnetic stimulation (TMS)–related pain suppression for each frequency is depicted by the *boxplot*, the residual inhibition for each TMS stimulation frequency by the *green dots connected by a line*. (**D**) Extradural implant. This corresponds to the middle electrode on Figure 4. Figure adapted from De Ridder et al. (7).

of brain activity during skin stimulation to rest resulted in a significant area of activity in the left postcentral gyrus corresponding to the area of perception of pain located within the left primary sensory cortex (Figure 3). Other areas of activity were found in the left primary sensorimotor cortex, supplementary motor area, and left cerebellum, and are related to the motor activity of the left hand and arm rubbing the right V1 skin area (Figure 2).

Transcranial magnetic stimulation (TMS) was performed with a Super Rapid magnetic stimulator (Magstim Inc., Wales, UK), allowing stimulation in a range of 1 to 50 Hz. Magnetic stimulation is performed after neuronavigation-guided localization (Stealth, Sofamor Danek, Broomfield, Colorado, USA) of the area of cortical reorganization based on the predefined area on the fMRI. Several series of stimulation are applied with different frequencies and intensities on target and adjacent areas. The TMS caused a maximum reduction of 80% of the supraorbital pain and a complete disappearance of the subjective eye malpositioning. The suppression of the pain was obtained immediately after starting the TMS and had a residual effect, whereas the subjectively malpostioned eye shifted back to its normal position after a longer period of stimulation.

TMS on target (Figure 2) using a rate of 1 pulse per second (pps) during 60 seconds at an intensity of 90% motor threshold (MT) caused an immediate pain reduction of 80% and complete disappearance of the subjective eye malpositioning after 25 seconds of stimulation. The same pain relief was obtained with TMS at a rate of 5 pps and 90% MT, but the misplaced eye shifted back in 10 seconds. TMS with 10 consecutive 500-ms bursts at 20 pps at 90% MT had no beneficial effect on the pain or the subjective eye malpositioning. Lowering the output to 80% MT at a rate of 1 pps still induced an 80% pain reduction, but the phantom progressively disappeared after 35 seconds of stimulation. Sham stimulation had no effect. TMS at 110% MT did not elicit any motor activity.

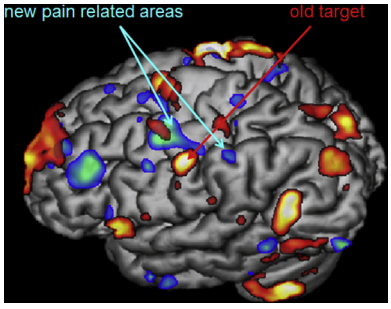

Figure 3. Fused functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) image. In *yellow/red* is the preoperative fMRI, evoked by allodynic touching of the skin. In *blue/green* is the PET scan performed after recurrence of the pain in a more extended area.

Consecutively an epidural octopolar electrode (Lamitrode 44, St. Jude Medical, Plano, Texas, USA) was implanted for electrical stimulation of the area of BOLD activation on the primary somatosensory cortex elicited by worsening the pain using tactile stimulation (allodynia) (Figure 2). The electrode was located at the predefined target using fMRI-based frameless stereotactic guidance. The leads of the electrodes were tunneled subcutaneously to the abdominal wall and connected to the internal pulse generator (IPG) (Genesis, St. Jude Medical) and implanted in a subcutaneous pocket. The postoperative course was uneventful.

After recovery from surgery, the patient felt the same pain and subjective eye malpositioning as preoperatively. On the first postoperative day, the IPG was activated and a complete suppression of pain and a complete disappearance of the subjective eye malpositioning was obtained. Stimulation parameters were set in an alternating 30 seconds on mode and 60 seconds off mode with 52-μs pulse width, 4 pps at 1.0 mA. Stimulating with these parameters induced paresthesias in the right supraorbital region. Lowering the intensity to 0.3 mA had a similar effect on the pain and subjective eye malpositioning but without any paresthesias. Furthermore, the patient had no problem in determining the exact position of surrounding objects after stimulation parameters were set.

The patient was discharged 4 days after surgery completely free of pain and with the feeling of the eye in its normal position, and remained as such after 70 months follow-up. Postoperative images revealed a correct position of the lead on the primary somatosensory cortex and not on the motor cortex.

After being pain free for more than 6 years, another skin surgery removing recurrences of the basal cell carcinoma was performed, this time with a skin transposition taken from the inside of the left upper arm (Figure 1). The patient again developed neuropathic pain with allodynia and hyperpathia, but more extensively than before, and it could not be controlled by reprogramming the electrode. Strangely enough she felt paresthesias when the electrode was on at high amplitudes, a feature normally not encountered in sensory cortex stimulation, except with very long stimuli. However, these high amplitudes were not necessary for pain suppression, permitting placebo-controlled stimulation.

A new allodynia-evoked fMRI was performed in the same way as the first fMRI performed before the extradural cortical implant. This was done after disconnecting the IPG from the extension wire. The fMRI yielded too many implant-material-related artifacts and could therefore not be interpreted. Therefore, an $H_2{}^{15}O$ water PET scan was performed and fused with the preoperative fMRI to further investigate reorganizational plasticity. Indeed, adjacent to the first fMRI BOLD spot, 2 allodynia-induced PET activations were noted, 1 anteriorly and 1 posteriorly (Figure 4).

Subsequently 2 extra electrodes were implanted, 1 anteriorly to the previously implanted electrode, 1 posteriorly (Figure 4). Recordings were performed on all electrodes looking for signs of thalamocortical dysrhythmia, i.e., a clear theta peak (*green arrow* in Figure 4) instead of or associated with the normal alpha peak on a power-to-frequency analysis. The areas that demonstrate abnormal recordings (*green colored areas* on Figure 4) overlap anatomically with the allodynia-evoked PET activation (Figure 4).

When programming the anterior electrode at these PET/thalamocortical dysrhythmia areas, pain could be suppressed from 9 of 10 to 4 of 10; when programming the posterior electrodes at the PET/thalamocortical dysrhythmia areas, the pain was suppressed to 5 of 10. Only when stimulating at both PET-activated areas was the pain suppressed almost

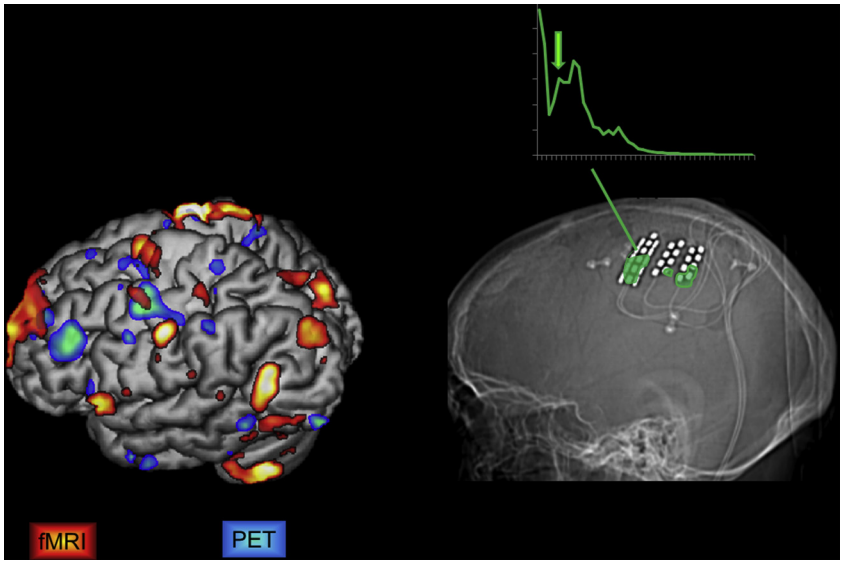

Figure 4. The 2 new electrodes can be seen anteriorly and posteriorly to the old electrode. The theta peak, as a signature of thalamocortical dysrhythmia, is represented on green power to frequency plot (*green arrow*). The second peak is the normal alpha peak characteristic for sensory cortices.

completely (1 to 2 of 10). Placebo stimulation did not modulate pain perception.

DISCUSSION

Recently, somatosensory cortex stimulation has been developed as a treatment for deafferentation pain. The concept was adapted from earlier experience with auditory cortex stimulation (10) for auditory deafferentation resulting in tinnitus, considering that the pathophysiology, clinical presentation, and treatment is analogous between these 2 sensory symptoms (9).

Somatosensory cortex stimulation is based on the concept of thalamocortical dysrhythmia, which has been proposed as a pathophysiological model for the development of gamma band activity related to the pain and tinnitus perception (17, 24). According to this model, pain is caused by an abnormal, spontaneous, and constant high-frequency (beta and gamma) band activity generated as a consequence of hyperpolarization of specific thalamic nuclei. In normal circumstances, somatosensory stimuli increase thalamocortical alpha oscillations to gamma band activity (6, 14). In the deafferented pain state, however, oscillatory alpha activity decreases to theta band activity (4 to 7 Hz) (20). As a result, lateral inhibition is reduced, inducing a surrounding beta and gamma band activity known as the edge effect (19, 21). Synchronized gamma band activity in the sensory cortex is proposed to represent the perception of pain (2, 6, 14). Thus, decreased lateral inhibition in the somatosensory cortex results in increased gamma band activity, a prerequisite for somatosensory consciousness, and therefore possibly contributing to the perception of pain. Recently it has also been proposed that the theta component of the thalamocortical dysrhythmia reflects the stable pain state, whereas the gamma reflects modulation of the pain (25).

Sensory deafferentation, as in phantom limb pain, is also associated with map plasticity of the somatosensory cortex (11, 12), and the more severe the pain the larger the cortical reorganization (11). This reorganization develops rapidly after amputation (27) and reverses mirroring decreased pain perception (3).

After 6 years, the patient required new surgery of the forehead skin, enlarging the previous AD area. We hypothesized that this could induce further map plasticity, and that the reorganization extended beyond the reach of the implanted electrode. After extensive but unsuccessful reprogramming, an $H_2{}^{15}O$ PET scan was performed in view of a failed fMRI scan. The activation on the PET scan was evoked by allodynic pain, and indeed showed 2 areas adjacent to the previous BOLD spot, 1 on the primary and 1 on the secondary somatosensory cortex. The recordings on the electrodes demonstrated theta peaks at the areas of PET activation, elicited by worsening of pain, suggesting indeed that these areas are related to the pain perception. Stimulating electrically at these areas suppresses the pain, demonstrating that these areas are causally related to the pain perception. Why both areas must be stimulated simultaneously to get full pain suppression is unclear. fMRI studies have demonstrated that experimentally induced and complex regional pain syndrome–related allodynia evokes activation in both contralateral SI and bilateral SII (21).

The involvement of SI has been linked to localization and discrimination of induced pain intensity (4, 26), with S1 responding in an exponential way, truly reflecting intensity, but S2 in a S-curve, rather reflecting a thresholding behavior, as in recognition of pain (26). SI has also been linked to anticipation of pain (29), and might serve as a location for storing pain memory traces (1). Structural brain changes in SI (decreased gray matter) have been demonstrated in humans with neuropathic trigeminal pain (15), and this might relate to the decreased functional connectivity of SI in (diabetic) neuropathic pain with multiple thalamic and cortical areas (5). This can potentially also explain why allodynia does not generate detectable PET activation in SI (28), which is in contrast with an fMRI study of experimental allodynia and complex regional pain syndrome–related allodynia (21). One reason for this contradiction might be related to the duration of the neuropathic pain. In chronic neuropathic pain there is no PET activation in SI and SII, in contrast to experimentally induced acute pain (16). SII, on the other hand, has been more consistently linked to neuropathic pain (13) and allodynia (23). Because both SI and SII seem to be involved differentially in chronic neuropathic pain, targeting both areas might result in better pain suppression in a chronic pain state, as experienced by this woman.

CONCLUSIONS

This case report demonstrates the feasibility of advanced functional imaging to chase changing map plasticity as a target for neuromodulation.

ACKNOWLEDGEMENTS

The authors thank Mr. Kwinten Porters and the radiopharmacy team of the Leuven PET Center for their skilled help.

REFERENCES

1. Albanese MC, Duerden EG, Rainville P, Duncan GH: Memory traces of pain in human cortex. J Neurosci 27:4612-4620, 2007.
2. Babiloni C, Babiloni F, Carducci F, Cincotti F, Rosciarelli F, Arendt-Nielsen L, Chen AC, Rossini PM: Human brain oscillatory activity phase-locked to painful electrical stimulations: a multi-channel EEG study. Hum Brain Mapp 15: 112-123, 2002.
3. Birbaumer N, Lutzenberger W, Montoya P, Larbig W, Unertl K, Topfner S, Grodd W, Taub E, Flor H: Effects of regional anesthesia on phantom limb pain are mirrored in changes in cortical reorganization. J Neurosci 17:5503-5508, 1997.
4. Bushnell MC, Duncan GH, Hofbauer RK, Ha B, Chen JI, Carrier B: Pain perception: is there a role for primary somatosensory cortex? Proc Natl Acad Sci U.S.A 96:7705-7709, 1999.
5. Cauda F, D'Agata F, Sacco K, Duca S, Cocito D, Paolasso I, Isoardo G, Geminiani G: Altered resting state attentional networks in diabetic neuropathic pain. *J Neurol Neurosurg Psychiatry* 81: 806-811, 2010.
6. De Pascalis V, Cacace I: Pain perception, obstructive imagery and phase-ordered gamma oscillations. Int J Psychophysiol 56:157-169, 2005.
7. De Ridder D, De Mulder G, Menovsky T, Sunaert S, Kovacs S: Electrical stimulation of auditory and somatosensory cortices for treatment of tinnitus and pain. Prog Brain Res 166:377-388, 2007.
8. De Ridder D, De Mulder G, Verstraeten E, Sunaert S, Moller A: Somatosensory cortex stimulation for deafferentation pain. Acta Neurochir Suppl 97:67-74, 2007.
9. De Ridder D, Elgoyhen AB, Romo R, Langguth B: Phantom percepts: tinnitus and pain as persisting aversive memory networks. *Proc Natl Acad Sci U S A* 108:8075-8080, 2011.
10. De Ridder D, Menovsky T, van de Heyning P: Auditory cortex stimulation for tinnitus suppression. Otol Neurotol 29:574-575, 2008 [author reply 575].
11. Flor H, Elbert T, Knecht S, Wienbruch C, Pantev C, Birbaumer N, Larbig W, Taub E: Phantom-limb pain as a perceptual correlate of cortical reorganization following arm amputation. Nature 375:482-484, 1995.
12. Flor H, Nikolajsen L, Staehelin Jensen T: Phantom limb pain: a case of maladaptive CNS plasticity? Nat Rev Neurosci 7:873-881, 2006.
13. Friebel U, Eickhoff SB, Lotze M: Coordinate-based meta-analysis of experimentally induced and chronic persistent neuropathic pain. *Neuroimage* 58:1070-1080, 2011.
14. Gross J, Schnitzler A, Timmermann L, Ploner M: Gamma oscillations in human primary somatosensory cortex reflect pain perception. PLoS Biol 5:e133, 2007.
15. Gustin SM, Peck CC, Wilcox SL, Nash PG, Murray GM, Henderson LA: Different pain, different brain: thalamic anatomy in neuropathic and non-neuropathic chronic pain syndromes. J Neurosci 31:5956-5964, 2011.
16. Hsieh JC, Belfrage M, Stone-Elander S, Hansson P, Ingvar M: Central representation of chronic ongoing neuropathic pain studied by positron emission tomography. Pain 63:225-236, 1995.
17. Jeanmonod D, Schulman J, Ramirez R, Cancro R, Lanz M, Morel A, Magnin M, Siegemund M, Kronberg E, Ribary U, Llinas R: Neuropsychiatric thalamocortical dysrhythmia: surgical implications. Neurosurg Clin N Am 14:251-265, 2003.
18. Kumar K, Toth C, Nath RK: Deep brain stimulation for intractable pain: a 15-year experience. Neurosurgery 40:736-746, 1997 [discussion 746-737].
19. Llinás R, Urbano FJ, Leznik E, Ramirez RR, van Marle HJ: Rhythmic and dysrhythmic thalamocortical dynamics: GABA systems and the edge effect. Trends Neurosci 28:325-333, 2005.
20. Llinas RR, Ribary U, Jeanmonod D, Kronberg E, Mitra PP: Thalamocortical dysrhythmia: a neurological and neuropsychiatric syndrome characterized by magnetoencephalography. Proc Natl Acad Sci U S A 96:15222-15227, 1999.
21. Maihofner C, Handwerker HO, Birklein F: Functional imaging of allodynia in complex regional pain syndrome. Neurology 66:711-717, 2006.
22. Nguyen JP, Keravel Y, Feve A, Uchiyama T, Cesaro P, Le Guerinel C, Pollin B: Treatment of deafferentation pain by chronic stimulation of the motor cortex: report of a series of 20 cases. Acta Neurochir Suppl 68:54-60, 1997.
23. Peyron R, Laurent B, Garcia-Larrea L: Functional imaging of brain responses to pain. A review and meta-analysis. Neurophysiol Clin 30:263-288, 2000.
24. Sarnthein J, Jeanmonod D: High thalamocortical theta coherence in patients with neurogenic pain. Neuroimage 39:1910-1917, 2008.
25. Schulz E, Tiemann L, Schuster T, Gross J, Ploner M: Neurophysiological coding of traits and states in the perception of pain. *Cereb Cortex* 21: 2408-2414, 2011.
26. Timmermann L, Ploner M, Haucke K, Schmitz F, Baltissen R, Schnitzler A: Differential coding of pain intensity in the human primary and secondary somatosensory cortex. J Neurophysiol 86:1499-1503, 2001.
27. Weiss T, Miltner WH, Huonker R, Friedel R, Schmidt I, Taub E: Rapid functional plasticity of the somatosensory cortex after finger amputation. Exp Brain Res 134:199-203, 2000.
28. Witting N, Kupers RC, Svensson P, Jensen TS: A PET activation study of brush-evoked allodynia in patients with nerve injury pain. Pain 120: 145-154, 2006.
29. Worthen SF, Hobson AR, Hall SD, Aziz Q, Furlong PL: Primary and secondary somatosensory cortex responses to anticipation and pain: a magnetoencephalography study. *Eur J Neurosci* 33:946-959, 2011.

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Received 14 March 2012; accepted 7 December 2012; published online 12 December 2012

Citation: World Neurosurg. (2013) 80, 6:901.e1-901.e5. http://dx.doi.org/10.1016/j.wneu.2012.12.009

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