



## Editorial

## The shadows of pain

A major roadblock in understanding pain mechanisms is, arguably, the current limitation regarding the precise dynamics exhibited by the cortex during perception of a painful experience. Certainly, researchers will welcome Ohara and colleagues' (2006) report (on page 244 of this issue) on the fascinating possibility that pain can be traced to the emergence of large-scale synchrony, occurring at two distinctive frequency bands; a synchrony that can be enhanced or destroyed by attention and distraction. These results seem to suggest that what matters most, in the case of cortical dynamics during pain, is not the oscillations by themselves but the synchrony. In previous work, the authors have already shown how various cortical regions engage in long-range oscillations. Here, Ohara and colleagues used a laser as a nociceptive skin stimulus while recording from the surface of primary somatosensory (SI), parasyllian (PS) and medial frontal (MF) cortices through dozens of subdural electrodes, implanted for the purposes of epilepsy treatment. Their results show two fundamental aspects of the cortical response to acute pain: (1) preceding the stimulus there is a beta range (16–24 Hz) synchrony between SI and PS that is seen only if the subject pays attention to the stimulus, but is absent if the subject is distracted. (2) The stimulus arrival destroys any beta range coherent pattern and is replaced by a low frequency (6–14 Hz) oscillation with strong synchrony between MF and SI when the subject is paying attention to the stimulus. This lower frequency synchrony is much weaker when the subject is distracted (Fig. 1).

Pain-induced cortical oscillations are known at least since Krauthamer and Whitaker (1974) recorded oscillations between 3 and 10 Hz after intra-arterial injection of bradykinin, seen mostly in SI and more variably in other cortical areas. Now, Ohara et al.'s linkage between the electrophysiological dynamics and relevant cognitive states suggests a number of intriguing connections: attention, arousal, object recognition, and top-down modulation of sensory processes seem to correspond

to relatively fast synchronous oscillations (Singer, 1999). In the context of the present experiment, anticipating the pain corresponded to fast beta oscillations. On the other hand, pain seems to imply, in agreement with numerous earlier reports (for example Chen and Herrmann, 2001), a “slowing down” of the cortical dynamics. One wonders whether the switch observed in Ohara et al. from fast to slow synchrony is the dynamical signature underlying pain perception (the electrophysiological shadow of pain; borrowing from Varela's “perception's shadow” (Rodriguez et al., 1999)). This dynamical aspect of the oscillations is consistent with Llinas's view of chronic pain as a thalamocortical dysrhythmia (Llinas et al., 1999), where the slow rhythm is produced by a disruption of thalamocortical feedback. The Ohara et al. observations are also consistent with recent results indicating that in severe cases of chronic pain the EEG power is shifted towards low frequencies, which seems to be reversed by successful therapy consisting of medial thalamic lesions (Sarnthein et al., 2006). Furthermore, the empirical observation that distraction destroys the coherent substrate seemingly sustaining the perception of pain may be more significant than appears at first. The effect of distraction over the oscillations may be the electrophysiological mechanism concerning the recent demonstration that pain can be efficiently manipulated by a neurofeedback paradigm (deCharms et al., 2005), where subjects used their own MF magnetic resonance imaging activity as information to learn to distract away from the pain. In addition the present results provide a dynamical signature for the numerous fMRI and behavioral findings showing attentional modulation of pain, for example (Wiech et al., 2005).

Theoreticians should also welcome Ohara et al.'s observations, since there are few data amenable to modeling in the field of pain. As discussed above, little is known about the detailed spatiotemporal dynamics and such interactions during an instance of pain. What theoreticians would like to know is the “language” that

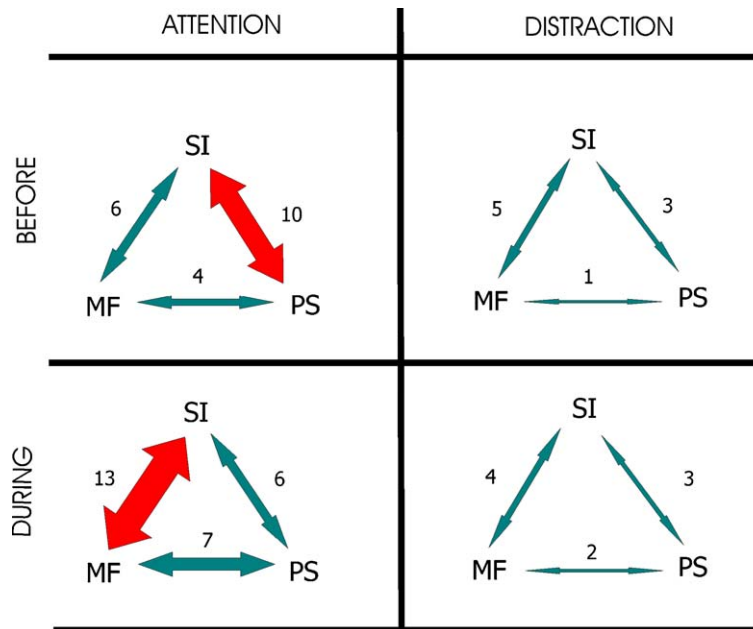


Fig. 1. Summary of the mutual synchronization of the three cortical regions investigated by Ohara et al. (2006), before and after a painful stimulus, during attention and distraction. Numbers and relative arrow widths indicate the number of electrode pairs with significant synchrony at high frequency (before) and low frequency (during), respectively.

these regions use to talk to each other during the painful experience. The data by Ohara et al. help to shorten the “word list” to a few dynamical possibilities: either the regions receiving nociceptive inputs cooperate to form ensembles oscillating at a common frequency, or they interact in a synchronous but transient collective pattern. This distinction is important regarding neuronal plasticity, which is undoubtedly a culprit of chronic pain: oscillations as a cooperative phenomena, emerges always out of synchrony but synchrony could exist alone without oscillations, and each impact differently over Hebbian synapses. Knowing the language of pain might also permit the design of manipulations directed to alleviate the painful experience if one can disrupt (as in the case of neurofeedback above) the oscillation, or the synchrony, or a particular pattern of collective behavior determined by connectivity.

The main suggestion of Ohara et al.’s results is that pain perception may correspond to the emergence of slow large-scale synchrony in a few cortical structures. Distraction from pain could mean destroying or preventing the formation of such coherent structures, and both suggestions have obvious implications for understanding and controlling pain.

## References

Chen ACN, Herrmann CS. Perception of pain coincides with the spatial expansion of electroencephalographic dynamics in human subjects. *Neurosci Lett* 2001;297:183–6.

- deCharms R, Maeda CF, Glover GH, Ludlow D, Pauly JM, Soneji D, et al. Control over brain activation and pain learned by using real-time functional MRI. *Proc Natl Acad Sci USA* 2005;102(51):18626–31.
- Krauthamer GM, Whitaker AH. Cortical synchronization evoked by noxious bradykinin stimulation under barbiturate anesthesia. *Brain Res.* 1974;80141–5.
- Llinas RR, Ribary U, Jeanmonod D, Kronberg E, Mitra PP. Thalamocortical dysrhythmia: a neurological and neuropsychiatric syndrome characterized by magnetoencephalography. *Proc Natl Acad Sci USA* 1999;96:15222–7.
- Ohara S, Crone NE, Nirit W, Lenz FA. Analysis of synchrony demonstrates “pain networks” defined by rapidly-switching, task-specific, functional connectivity between pain-related cortical structures. *Pain* 2006;123:244–53.
- Rodriguez E, George N, Lachaux JP, Martinerie J, Renault B, Varela F. Perception’s shadow: long-distance synchronization in the human brain. *Nature* 1999;397:340–3.
- Sarnthein J, Stern J, Aufenberg C, Rousson V, Jeanmonod D. Increased EEG power and slowed dominant frequency in patients with neurogenic pain. *Brain* 2006;129(1):55–64.
- Singer W. Neuronal synchrony: a versatile code for the definition of relations? *Neuron* 1999;24:49–65. 111–125.
- Wiech K, Seymour B, Kalisch R, Stephan KE, Koltzenburg M, Driver J, et al. Modulation of pain processing in hyperalgesia by cognitive demand. *Neuroimage* 2005;27(1):59–69.

A. Vania Apkarian \*

Dante R. Chialvo

Department of Physiology, Northwestern University,  
Chicago, IL 60611, USA

E-mail address: a-apkarian@northwestern.edu

(A.V. Apkarian)

\* Corresponding author. Tel.: +1 312 5030404; fax: +1 312 5035101.