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Commentary

Thalamocortical dysrhythmia and chronic pain

The paper by Walton et al. [13] in this issue of Pain brings a new perspective to the problem of central pain, in this case complex regional pain syndrome without peripheral nerve injury (CRPSI). It is a perspective that may have escaped the notice of many pain scientists and sensory physiologists. Walton et al. [13] using magnetoencephalography (MEG) compared brain activity in sufferers from type I complex regional pain syndrome and healthy controls, found peaks of low frequency activity in the delta and theta bands concentrated over the somatosensory representation of the region in which pain was localized, as well as in orbito-fronto-temporal cortex. The latter may be associated with the affective element in the perception of the pain. To those for whom the pathway to perception proceeds along a hierarchy of thalamocortical and corticocortical connections, these may seem unremarkable findings. But when cast in the light of modern views of the large-scale synchrony of thalamic and cortical neuronal activity that underlies states of vigilance, the new results assume a high degree of relevance. The findings can be seen as another demonstration of an emerging series of disorders characterized as Thalamocortical Dysrhythmias (TCD) [6,8].

Rhythmic entrainment of activity in the interconnected thalamo-cortico-thalamic network occurs during all states of consciousness and is reflected in the presence of wave forms at different frequencies in the MEG and EEG. These state-dependent rhythms are reflections of the remarkable capacity of thalamocortical relay neurons (TCRs) to discharge trains of action potentials in different patterns that are dependent upon the membrane potential of the neurons [5]. When relatively depolarized (positive to about −65 mV), largely under the influence of the cholinergic systems of the brainstem, TCRs discharge tonically in response to inputs coming from the periphery or cortex. The corticothalamic input entrains the population of TCRs in a high-frequency (~40 Hz) oscillation [11] that spreads to the zone of cortex to which they project, and throughout the network that interconnects them Spread of this oscillation across cortex and thalamus is thought to facilitate the "binding" of all aspects of a sensory event into a unified percept.

By contrast, when TCRs drift towards hyperpolarization, because of a potassium leak current [10], a low threshold calcium conductance dependent on T type (Cav 3.1) calcium channels, which is inactivated at normal resting membrane potentials, is activated ("de-inactivated"). This results in a low threshold calcium spike and a short, high-frequency burst of action potentials. This burst is succeeded by a return to hyperpolarization and a repetition of the burst. The TCR cell is then said to be in "burst mode". Entrainment of the bursts by re-entrant inhibition from the thalamic reticular nucleus serves to entrain both the populations of bursting neurons and the network as a whole in a low frequency (4–10 Hz) oscillation. The oscillation is reflected in the MEG as activity in the delta and theta ranges, [9] which is seen in the results of Walton et al. Under these conditions, activity in the corticothalamic system has its greatest effect upon the reticular nucleus [1] and serves to maintain the oscillation. The lengthy intervals of hyperpolarization that intervene between bursts effectively disconnect the thalamus and thus the cortex from the periphery, although this is not a viewpoint shared by all sensory physiologists.

The idea behind the concept of TCD is that abnormal, internally generated low frequency oscillations in the thalamo-cortico-thalamic network will disrupt the normal state-dependent flow of information between thalamus and cortex. This in turn would lead to disturbances of sensation, motor performance and cognition. The basis for this belief lies in the demonstration of abnormal low frequency oscillations in thalamic neurons and altered rhythms in the network as a whole in a number of human conditions, including tinnitus, migraine, Parkinson's disease, as well as neuropathic pain and even psychosis [2,8,12].

Walton et al. [13] argue that the increased spontaneous activity at frequencies below 5 Hz in their patients, while awake and at rest, provides a pathophysiological explanation for the presence of chronic pain in the absence of nerve damage but still localized to a particular part of the periphery. In this view, it is not the abnormally bursting neurons themselves or the low frequency oscillations in the part of the network in which they lie, but rather the heightened activity of neurons in *adjacent* parts of the somatosensory representation that are released from the inhibition normally imposed upon them by the focus of enhanced slow wave activity [7], This would cause the unaffected cortical neurons to discharge in spontaneous, continuous, high-frequency oscillations, which could lead to a persistent painful sensation localized to a part of the periphery represented in the region of heightened activity. A similar effect operating in the limbic regions would maintain the persistence of the unpleasantness associated with the pain.

To support their conclusions, Walton et al. point to studies in which MEG or EEG recordings show that the signal evoked by stimulation of an affected limb in CRPSI is greater than that ensuing from stimulation of the unaffected limb. Alterations in somatosensory representations in other forms of chronic pain of central origin may be explicable in terms similar to those used to account for CRPSI. It is in these other conditions that some clues as to how peripheral events may set up aberrant thalamic neuronal activity characterized by low frequency oscillations of TCRs. Other studies, in fact, show that the thalamus can be profoundly affected by peripheral perturbations that lead to altered somatosensory input. At worst, the thalamus can show chronic, progressive neuronal atrophy and death in response to peripheral nerve injuries, amputations or spinal damage. The reorganization of the thalamus that occurs under these conditions can be massive [3] and it is not with-

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out significance that when such conditions are associated with chronic pain, neurons in the somatosensory thalamus show enhanced bursting activity [4]. The effectiveness of deep brain stimulation for alleviating certain cases of phantom limb pain may involve depolarization of TCRs, which would interrupt bursting and low frequency oscillations [12]. Similarly, application of drugs that interfere with T type calcium channel function and prevent low frequency bursting may provide a new strategy for reversing TCD and alleviating not only CRPSI but also the numerous other conditions that are coming to be recognized as having their basis in TCD.

Conflict of interest

The author declares no conflict of interest.

References

[1] Golshani P, Liu XB, Jones EG. Differences in quantal amplitude reflect GluR4-subunit number at corticothalamic synapses on two populations of thalamic neurons. Proc Natl Acad Sci USA 2001;98:4172–7.
[2] Jeanmonod D, Magnin M, Morel A. Low-threshold calcium spike bursts in the human thalamus. Common physiopathology for sensory, motor and limbic positive symptoms. Brain 1996;119:363–75.
[3] Jones EG. Cortical and subcortical contributions to activity-dependent plasticity in primate somatosensory cortex. Annu Rev Neurosci 2000;23:1–37.
[4] Lenz FA, Kwan HC, Dostrovsky JO, Tasker RR. Characteristics of the bursting pattern of action potentials that occurs in the thalamus of patients with central pain. Brain Res 1989;496:357–60.
[5] Llinás R, Jahnsen H. Electrophysiology of mammalian thalamic neurones in vitro. Nature 1982;297:406–8.
[6] Llinás R, Ribary U, Jeanmonod D, Cancro R, Kronberg E, Schulman J, Zonenshayn M, Magnin M, Morel A, Siegmund M. Thalamocortical dysrhythmia I. Functional and imaging aspects. Thal Rel Sys 2001;1:237–44.
[7] Llinás R, Urbano F, Leznik E, Ramizeriz R, Van Marle H. Rhythmic and dysrhythmic thalamocortical dynamics: GABA systems and the edge effect. Trends Neurosci 2005;28:325–33.
[8] Llinás 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.
[9] Llinás RR, Steriade M. Bursting of thalamic neurons and states of vigilance. J Neurophysiol 2006;95:3297–308.
[10] McCormick DA, Bal T. Sleep and arousal: thalamocortical mechanisms. Annu Rev Neurosci 1997;20:185–215.
[11] Pedroarena C, Llinás R. Dendritic calcium conductances generate high-frequency oscillation in thalamocortical neurons. Proc Natl Acad Sci USA 1997;94:724–8.
[12] Ray N, Jenkinson N, Kringelbach M, Hansen P, Pereira E, Brittain J, Holland P, Holliday I, Owen S, Stein J, Aziz T. Abnormal thalamocortical dynamics may be altered by deep brain stimulation: using magnetoencephalography to study phantom limb pain. J Clin Neurosci 2009;16:32–6.
[13] Walton KD, Dubois M, Ljinás R. Abnormal thalamocortical activity in patients with complex regional pain syndrome (CRPS) type I. Pain 2010. doi:10.1016/j.pain.2010.02.023.

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