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SCIENTIFIC COMMENTARIES

Spatiotemporal aspects of slow-waves and seizures in humans

This commentary addresses two articles published in the current issue of *Brain*. The papers have in common the recording and analysis of neuronal activity in human cerebral cortex using a combination of microscopic and macroscopic recording techniques, revealing the spatiotemporal structure of this activity. The first article by Csercsa *et al*. (Occasional paper, page 2814) implements laminar electrodes in different subjects suffering from intractable focal epilepsy in terms of discharge focus mapping and surgical treatment. The authors investigate the laminar distribution of activity in slow-wave sleep, using both local field potentials—measuring the extracellular potential within grey matter—and neuronal (unit) firing activity. This type of combined measurement has been studied extensively in animal experiments during slow-wave oscillations occurring in both anesthetized and natural sleep conditions (reviewed in Steriade, 2003; Buzsaki, 2006), but only recently in humans (Cash *et al*., 2009). Similar to animal experiments, the present study demonstrates that slow-waves occur as periods of activity separated by silences, termed 'Up' and 'Down' states, respectively. The Up-states are characterized by sustained unit activity, sometimes of rhythmic nature with oscillations in various frequency bands (gamma, beta, spindles, etc.), as found in anesthetized animals (Steriade *et al.*, 1993). The Down states are characterized by a synchronized silence in all cells, in parallel with a depth-positive slow-wave in the local field potentials. This Up/Down state activity is remarkably synchronized across all cortical layers. These characteristics are identical to those found in multisite local field potentials and unit recordings in cat parietal cortex during natural sleep (Destexhe *et al.*, 1999).

Contrary to animal experiments, however, the human current-source density profiles calculated from the local field potentials showed activity mostly in superficial layers, while deep layers did not display the prominent current sinks and sources found in cats (Steriade and Amzica, 1996) and rats (Sirota *et al.*, 2003). Another difference was that the mean firing rate of the recorded cells is in general lower compared with cats or rats, even in superficial layers. In addition, there is no preferential layer where the Up-state activity starts; and, in particular, no particular leading activity in Layer IV, suggesting that the potential thalamic generators of slow-waves (Crunelli and Hughes, 2010) do not play a leading role here. Similarly, there is no apparent precedence of Layer V to start the Up state, contrary to *in vitro* measurements in ferrets (Sanchez-Vives and McCormick, 2000).

These findings challenge the current view of the genesis of Up and Down state activity by cortical networks, which was thought to involve generators in deep layers, as suggested by the leading role of Layer V *in vitro* (Sanchez-Vives and McCormick, 2000) and the strong current sinks and sources in deep layers *in vivo* (Steriade and Amzica, 1996; Sirota *et al*., 2003). This pattern was not found in human recordings, which rather suggests that the Up-state activity can start anywhere in the network. Another possible interpretation is that the Up state is generated in another cortical area, which recruits the recorded area via long-range cortico-cortical fibres (mostly terminating in Layer 1), consistent with the sink and sources found here exclusively in superficial layers. Computational models of slow-wave oscillations (Timofeev *et al*., 2000; Compte *et al*., 2003; Destexhe, 2009) should examine these possibilities in the future and determine more quantitatively which provides the most plausible explanation.

In the second article, Stead *et al*. (page 2789) use multi-electrode recording techniques to characterize the activity of epileptic cortex in patients with focal epilepsy, as above, and in subjects suffering from intractable facial pain (providing 'control' non-epileptic recordings). The recordings are based on low-impedance 'macroelectrodes', similar to those used in common subdural recordings, combined with high-impedance 'microelectrodes'. The latter sample a much more localized portion of the target tissue. This recording configuration revealed the occurrence of 'microseizures' and associated interictal events, which were not visible on macroelectrodes. This important finding has a number of consequences not only for the mechanisms of focal epilepsy, but also for focus identification and localization.

This increased spatial resolution reveals that the activity in epileptic cortex is much less homogeneous than previously thought to be the case. It contains a myriad of microseizures, probably involving very small portions of tissue (a few hundred microns, similar to the 'columns' of other cortical areas). Most of the time, these microseizures occur with no generalization to larger portions of the tissue, and thus are invisible from macroelectrode recordings. These events are clearly pathological but missed by current recording techniques. In some instances, microseizures can lead to a full-blown seizure, perhaps due to the synchronization of several such microfoci. This contrasts with the usually accepted

mechanism of seizure initiation, which is assumed to start at a single, well-defined location. In contrast, the present recordings show that the seizure activity can involve the interaction between different local populations of neurons, but most of the time this does not generalize to larger cortical territories. Another interesting finding is that microseizures always precede the occurrence of full-blown seizures. Consequently, as these events are invisible from macroelectrode recordings, the localization of the epileptic focus, both in space and time, may be biased by this invisibility. However, whether the localization of such microseizure activity is critical to the localization of the focus at scales relevant to surgery remains to be demonstrated.

Together, these results call for a re-examination of the mechanisms of seizure generation and implicate interacting 'microdomains' rather than a unique focus. The current computational models of focal seizures (Traub *et al*., 2005; Ullah and Schiff, 2009), as well as generalized spike-and-wave seizures (Destexhe, 2007; Sitnikova, 2010), will need to take these findings into account.

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Polymorphisms in ion channel genes: emerging roles in pain

Why does one soldier, after sustaining a missile wound in the radial nerve on the battlefield, experience incapacitating neuropathic pain, while another, with a similar injury, complains of motor and sensory deficits in the absence of pain? Why is one patient with diabetic neuropathy disabled with neuropathic pain, while another patient with diabetic neuropathy of apparently similar severity experiences numbness or paraesthesias that are not painful? Pain is a complex phenomenon, mediated by transductive processes in the periphery, conduction to the spinal cord via first-order spinal sensory (dorsal root ganglion) neurons and processing at multiple higher levels that include the dorsal horn, thalamus and cortex. Multiple processes and molecules undoubtedly shape the perception of pain. Exciting progress, however, has recently been made in linking common variants of genes encoding two different ion channels within first-order sensory neurons along the pain pathway to inter-individual differences in pain. Discovery and characterization of these genetic variants, and of additional variants that will likely be identified in the future, open up the