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## Is There a Common Origin to Surround-Inhibition as Seen Through Electrical Activity Versus Hemodynamic Changes? Focus on “Duration-Dependent Response in S1 to Vibrotactile Stimulation in Squirrel Monkey”

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A common aspect of neocortical electrophysiology is that even a brief and spatially localized stimulus leads to activation that both outlives the stimulus and spreads well beyond the patch of cortex that receives direct afferent input. In this issue of the *Journal of Neurophysiology*, Simons et al. (p. 2121–2129) present new evidence for the spatial sharpening of cortical sensory representation in primary somatosensory (S1) cortex. The investigators make use of optical imaging of hemodynamic-related signals in conjunction with a vibrotactile peripheral stimulus in an anesthetized squirrel monkey preparation. A critical finding is that the evolution of spatial sharpening of the response in cortex was accompanied by a gradually decreasing hemodynamic signal in the surround region. The evolution of the hemodynamic signal must involve the intricate but incompletely understood balance of excitatory and inhibitory signaling in underlying circuitry (Brecht and Sakmann 2002; Brecht et al. 2003; Manns et al. 2004; Trevelyan and Watkinson 2005). Although the details of this process are contentious, the present work lends credence to the notion that a drop in blood oxygenation, commonly referred to as “negative BOLD”, can reflect a concomitant increase in neuronal inhibition.

Negative BOLD strictly refers to a decrease in the blood oxygen level dependent contrast functional magnetic resonance imaging (BOLD-contrast fMRI) signal (Belliveau et al. 1991; Ogawa et al. 1990, 1992) that is interpreted as a net decrease in the ratio of oxy- to deoxyhemoglobin (Ernst and Hennig 1994; Menon et al. 1995). The same term is used in the intrinsic optical imaging community to refer to a decrease in the ratio of oxy- to deoxyhemoglobin as inferred from changes in the optical rather than magnetic properties of hemoglobin that accompany a change in ligand binding. The two uses are in principle synonymous, but of course the analysis of magnetic resonance versus optical data involves different assumptions and approximations. With these caveats in mind, we note that a number of recent studies suggest that negative BOLD can reflect functional neuronal inhibition. Shmuel et al. (2006) simultaneously measured BOLD-contrast fMRI and multiple-unit electrical activity in monkey and found evidence for a decrease in neuronal spiking concomitant with a negative BOLD-contrast fMRI signal. Two optical-based imaging studies support the occurrence of surround inhibition in cortex (Derdikman et al. 2003; Takashima et al. 2001). In particular,

Derdikman et al. (2003) recorded voltage-sensitive dye signals from vibrissa S1 cortex in rat in response to either deflections of the vibrissae or cutaneous stimulations of the vibrissa pad. This signal reports the spatially averaged level of depolarization versus hyperpolarization of the underlying tissue (Grinvald et al. 1982). The data demonstrated hyperpolarization of the region that surrounds the epicenter of the response. In complementary work, Devor et al. (2003) measured the intrinsic optical signal in vibrissa S1 cortex of rat, with a stimulus paradigm similar to that in Derdikman et al. (2003), simultaneously with multiple-unit electrical activity. Although the optical signal indicated negative BOLD contrast in the surround, this decrease in oxygenation was not accompanied by a concomitant decrease in multiunit activity. These data cannot be easily reconciled with the fMRI studies of Shmuel et al. (2006).

The preceding synopsis is suggestive of a complex relation between multiunit spiking and the aggregate level of polarization of the underlying neuronal tissue. Yet it is likely that electrical activity per se is not the fundamental issue. Rather the milieu of signaling molecules, e.g., neurotransmitter and neuropeptide release during synaptic transmission, is the predominant factor in the initiation of the hemodynamic response (Cauli et al. 2004; Gurden et al. 2006; Hamel 2004, 2006; Iadecola 2004). Thus activation of specific types of neurons as opposed to the dynamics of multiunit spiking is likely to determine the hemodynamic response. Under the assumption that such a correlation exists, the spatial sharpening of cortical sensory representation found by Simons et al. as a consequence of increased stimulus duration (Simons et al. 2007) or increased stimulus amplitude (Simons et al. 2005) provides a neurological basis for improved human tactile localization with stronger vibrating stimuli (Tannan et al. 2006). Further, the new observations by Simons et al. (2007) for S1 cortex in squirrel monkeys complement the results on spatial sharpening in vibrissa S1 cortex in rat. Spatial diminution of the center response for the duration of a somatosensory stimulus has been observed by imaging either the voltage-sensitive dye response (Kleinfeld and Delaney 1996) or by imaging the intrinsic optical signal under increased frequency of single-vibrissa stimulation (Sheth et al. 2005). Thus prolonged stimulation results in enhanced spatial localization of the cortical response. Interestingly, sharpening of the sensory response in the vibrissa area of S1 cortex is further observed when animals are introduced to novel (Polley et al. 1999) and naturalistic environments (Polley et al. 2004).

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Insight into the recruitment of surround-inhibition may be gleaned from studies on focal neocortical epilepsy in vivo. During interictal activity, the field potential (Gummit and Takahashi 1965), the intracellular potential (Prince and Wilder 1967), and the intrinsic optical signal (Schwartz and Bonhoeffer 2001) show a tight focus of activity that is surrounded by an annulus of inhibition. This pattern is similar to the pattern of stimulus-evoked activation in the normal state. The transition to a propagating ictal event is associated with reduced inhibition in the annulus (Prince and Wilder 1967). Yet surround inhibition is evident when the ictal activity breaks away from its original focus, in that newly recruited pyramidal cells receive GABAergic synaptic volleys ahead of excitatory volleys (Schwartz and Bonhoeffer 2001; Timofeev et al. 2002; Timofeev and Steriade 2004). This is consistent with feed-forward inhibition that propagates ahead of the front of ictal activity.

Further insight into the nature of the inhibitory surround comes from a second "pathological" preparation, the in vitro neocortical slice. Neurons in slice preparations are generally quiescent, owing to the lack of external inputs and the absence of neuronal modulators (Whittington et al. 1995). Yet extracellular stimulation of slices in conventional bathing media excites a narrow column of tissue (MacLean et al. 2005; Petersen and Sakmann 2001). Bath application of low levels of antagonist to fast inhibitory GABA<sub>A</sub> synaptic transmission is observed to first increase the horizontal spread of stimulus-induced excitation (Chagnac-Amitai and Connors 1989) until, above a threshold concentration of GABA<sub>A</sub> blockade, stimulation provokes a rapidly propagating ictal front (Chagnac-Amitai and Connors 1989; Golomb and Amitai 1997; Pinto et al. 2005). As in the in vivo case, these in vitro experiments illustrate the role of inhibition in maintaining topography of the excitatory response.

A complementary in vitro model of epilepsy involves the depletion of extracellular Mg<sup>2+</sup>, which triggers ictal activity while largely preserving inhibition. One critical feature of this model is a remarkably powerful feed-forward inhibition ahead of the ictal event, which effectively vetoes the excitatory drive to pyramidal cells. Propagation of the ictal event appears to lurch (Trevelyan et al. 2006) with an average speed that is two orders of magnitude slower than propagation in the disinhibited slice (Trevelyan et al. 2006; Wong and Prince 1990) as the front of depolarization continually encounters barricades formed by inhibitory connections. A second feature of the model is a defined choreography of inhibitory input from different subpopulations of interneurons onto the pyramidal neurons as an ictal event invades a new region of cortex (Kawaguchi 2001; Ziburkus et al. 2006). It is not unreasonable to conjecture that the same choreography underlies surround inhibition in the normal state in vivo.

We close by noting progress in the development of new approaches to delineate the balance of activity among subtypes of excitatory and inhibitory neurons in the awake behaving animal (Brecht et al. 2004; Kleinfeld and Griesbeck 2005). These include the use of specific labeling of identified neuronal phenotypes through genetic methods (Heintz 2000; Meyer et al. 2002), the advent of endogenous indicators of neuronal activity (Miyawaki 2005; Tsien 2003), and neurotransmitter release (Okumoto et al. 2005). These new approaches should allow the relation between local signaling among neurons to be

directly related to neurovascular coupling and changes in hemodynamics as reported in this issue by Simons et al. (2007).

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