Uncovering the Mysterious Origins of Local Field Potentials

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In this issue of *Neuron*, Katzner et al. use a combination of multielectrode recordings and optical imaging to determine the spatial extent of local field potential (LFP) activity in primary visual cortex. By estimating the orientation selectivity of stimulus-evoked LFP activity from the map of orientation preference obtained using optical imaging, they find that LFP selectivity is best fit using signals within 250 μm of the recording electrode.

In Conan Doyle's *The Adventure of the Noble Bachelor*, Mr. Lestrade of Scotland Yard holds the key to the case—a card from the pocket of the missing Bride's dress. Unfortunately for Lestrade, the crucial piece of information is found not on the front of the card where he expected it to be. The clue is on the back and is contained in the numbers of a fragmented hotel bill. Lestrade dismisses the numbers, saying "There's nothing in it. I looked at it before." Sherlock Holmes, however, deduces their significance and cracks the case in his inimitable style. "Ah, Watson. Draw your chair up and hand me my violin, for the only problem we have still to solve is how to while away these bleak autumnal evenings." says Holmes, smiling.

Solving the mystery of how the brain works is doubtless more challenging than uncovering the misdeeds of the wealthy, but like any mystery, the solution depends not just on our powers of deduction, but also on knowing how to interpret the clues we have in hand. Clues can come from unlikely sources, and the local field potential (LFP) is a case in point. Operationally, LFPs are low-frequency (<~300 Hz) electrical events that can be recorded with an extracellular recording electrode placed within or on the surface of the brain. Although there is evidence that extracellular potentials can influence spike timing (Radman et al., 2007), whether LFPs have a clear causal role in neural function remains to be established. Since LFP activity is difficult to interpret, spiking activity has historically received far more attention.

Times are changing, however, and there is fast-growing interest in LFP activity. This excitement is based, in part, on reports that LFP activity is a remarkably precise measure of the neural processes that guide our behavior such as perception, attention, memory, and action (Frien et al., 2000; Henrie and Shapley, 2005; Scherberger et al., 2005; Womelsdorf et al., 2006). In some cases, LFP activity is as, or even more, precise than the activity of individual neurons (Pesaran et al., 2002; Mehring et al., 2003). These strides make interpreting LFP signals even more pressing.

We know that LFP activity mainly reflects synaptic potentials and is a measure that averages activity across a region of tissue. Yet complications abound. Synaptic potentials can either have local origins due to recurrent collaterals or reflect inputs from other brain regions. This can have advantages if, for example, the signatures of LFP activity differ across neural circuits (Pesaran et al., 2008).

The spatial extent of LFP activity is also complex and rests on the biophysics of LFP measurements. Neural activity generates patterns of current flow in the extracellular space (Mitzdorf, 1985), and the recording electrode carries out a spatially weighted sum of the voltage elements due to these microscopic current flows (Malmivuo and Plonsey, 1995). The spatial weights depend on the geometry of the recording electrode. The voltage elements depend on the geometry of the neural currents. Their combination determines the spatial extent of any given LFP measurement. The hardest part of the problem is determining the geometry of the neural currents because it depends on solving an ill-posed inverse problem. Against this, the apparent precision of LFP activity presents a mysterious paradox. Why is an average measure, which seems to indiscriminately blur different neural signals, so precise?

In this issue of *Neuron*, Katzner et al. (2009) neatly tackle this problem and measure the local origins of LFP activity. They do this by avoiding thorny issues related to electromagnetism and taking a functional approach, directly measuring the degree to which a spatial average of neural selectivity across cortex can predict LFP selectivity. They begin by optically imaging the exquisite orientation selectivity maps in primary visual cortex of the anesthetized cat using voltage-sensitive dyes. This measurement provides them with a map of stimulus selectivity across cortex. They then insert microelectrodes into locations on this map and carefully register the recording locations using recordings of multiunit activity. Multiunit activity is known to be aligned with the optical maps within ~30 μm. Once they have aligned the two measurements, they compare LFP activity with the orientation maps.

LFP activity in primary visual cortex features ongoing oscillations that contain power in specific frequency bands as well as transient responses that can be evoked by the presentation of visual stimuli. Katzner et al. (2009) reason that the LFP responses will be greatest for transient visual stimuli because these stimuli will evoke synchronous neural firing. Therefore, they record LFP responses while flashing gratings with a different orientation and spatial phase every 32 ms in a pseudorandom sequence. The LFP responds briskly and at most recording sites selectively encodes a preferred orientation of the stimulus.

With the LFP orientation selectivity curve at a location in the map in one hand and the spatial distribution of orientation selectivity from the optical imaging in the other, they can obtain a measure of the spatial extent of the LFP activity. They do this through a reconstruction of the LFP tuning curve using a spatial average of the orientation selectivity from the optical maps centered on the LFP recording location. Tuning curves generated from the optical maps were a surprisingly good fit to the LFP responses. Varying the width of the spatial average, the standard deviation of the Gaussian smoothing kernel applied to the orientation map, revealed that LFP activity was best fit ($r^2 = 0.73$) by a kernel with standard deviation 100 μm, corresponding to a kernel width of ~250 μm. Most importantly, increasing the kernel width dramatically reduced the quality of the fit, giving confidence in their procedure. A kernel width of 1 mm (σ = 400 μm) gave poor reconstruction with $r^2 = \sim 0.2$.

Katzner and colleagues (2009) convincingly demonstrate that the selectivity of LFP activity is in fact quite spatially localized. Cortical pyramidal neurons have dendritic arborizations that extend several hundred microns. The result that LFP activity shows similar spatial selectivity is impressive. The implication—that the spatial extent of LFP activity is derived from the extent of cellular dendritic fields—is attractive and deserves a closer look.

Various confounding influences, such as tissue filtering, volume conduction and current spread, have been floated to explain why LFP activity has limited spatial resolution. These ideas jibe with the presence of extensive correlations between LFP recordings at widely separated cortical sites (Leopold et al., 2003). If LFP activity is as local as Katzner et al. (2009) report, these LFP correlations are not simply measurement confounds. They could reflect correlations in the underlying neural currents which must, in turn, depend on anatomical constraints such as cellular morphologies and connections. If this is true, LFP coherence, a normalized measure of correlation, may be an especially useful measure for tracking processing across neural circuits (Buschman and Miller, 2007).

A range of questions can now be answered using Katzner's approach. The properties of the recording electrode can be varied and the spatial extent of the resulting LFP measured. The location of the recording electrode can also be changed. How much broader is the selectivity in the LFP at the pia or in the white matter? Katzner et al. (2009) speculate that their results are specific to microelectrode recordings within the cortical layers. This will need to be tested as there are reports of strong selectivity even at the pia. Complementary ways to measure the spatial extent of LFP activity and comparisons between them are also needed. The retinotopy of V1 offers one approach. Varying the retinal location of visual stimuli will activate different parts of the retinotopic map and the transformation between retinal space and cortical space can be measured.

This finding brings us forward, nevertheless, loose ends remain. Eschewing biophysical modeling means that we cannot predict how changing the electrode geometry or location will influence the measured LFP response. An experiment is needed each time. If we knew the geometry of the underlying neural currents, we could plug in electrode properties and design electrodes that were tailor made for specific applications. Electrode design is especially important for developing biomedical applications, such as prostheses (Andersen et al., 2004). Future work will, inevitably, need to tackle this issue more directly. One approach may be to marry optical and electrophysiological tools and infer the current distributions.

We are clearly a long way from knowing how to deduce the workings of the brain from electrical potentials, but the clues we have seem promising and not entirely mysterious.

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