



ELSEVIER

Available online at [www.sciencedirect.com](http://www.sciencedirect.com)
**Current Opinion in  
Neurobiology**

# Electrophysiological recordings from behaving animals—going beyond spikes

Edith Chorev, Jérôme Epsztein, Arthur R Houweling, Albert K Lee and Michael Brecht

Most of our current knowledge about the neural control of behavior is based on electrophysiology. Here we review advances and limitations of current electrophysiological recording techniques applied in behaving animals. Extracellular recording methods have improved with respect to sampling density and miniaturization, and our understanding of the nature of the recorded signals has advanced. Juxtacellular recordings have become increasingly popular as they allow identification of the recorded neurons. Juxtacellular recordings are relatively easy to apply in behaving animals and can be used to stimulate individual neurons. Methods for intracellular recordings in awake behaving animals also advanced, and it has become clear that long-duration intracellular recordings are possible even in freely moving animals. We conclude that the electrophysiological methods repertoire has greatly diversified in recent years and that the field has moved beyond what used to be a mere spike counting business.

## Address

Bernstein Center for Computational Neuroscience Berlin, Humboldt University, 10115 Berlin, Philippstr. 13 Haus 6, Germany

Corresponding author: Brecht, Michael ([michael.brecht@bccn-berlin.de](mailto:michael.brecht@bccn-berlin.de))

**Current Opinion in Neurobiology** 2009, **19**:1–7

This review comes from a themed issue on  
New technologies  
Edited by Ehud Isacoff and Stephen Smith

0959-4388/\$ – see front matter  
Published by Elsevier Ltd.

DOI [10.1016/j.conb.2009.08.005](https://doi.org/10.1016/j.conb.2009.08.005)

Neural control of behavior is achieved through computations, in which neurons integrate electrical signals and generate an output of electrical pulses. Electrophysiology allows one to register such signals and thus is uniquely suited to capture the brain's natural language. Electrophysiological techniques combine high spatiotemporal resolution with ease of application making them particularly attractive tools for awake behaving preparations.

## Improved technology for extracellular recording

Classically, work done in behaving animals was limited to extracellular recordings of single units, multiple units and

field potentials. There is a growing awareness for the need to sample larger portions of the network and as a consequence technologies for dense recordings from multiple sites were developed. In recent years advances in such technologies continue, making the recordings more dense, the recording gear lighter and more robust.

Many variants of extracellular recording techniques are available. Largely these methods can be clustered into two groups: single sited electrodes (can be an array of such electrodes) [1] and multi sited electrodes (i.e. stereotrodes) [2]. The advantages of the latter are that the signals can be triangulated between several recording points and thus the signals can be separated more reliably into units. Using silicon probes over self-manufactured probes has the advantage that they are smaller in size, thus implicating less damage to the tissue recorded. Nevertheless, the ease and cost effectiveness of tetrodes make it the most popular approach for extracellular neuronal recordings.

Extracellular recording have been and will continue to dominate the field of system neuroscience. These techniques led to major findings, one example is the field of spatial learning and the hippocampus, using these tools place cells were discovered [3] and their firing in relation to theta cycle [4]. The use of multiple electrodes led to the discovery of offline replay of spatial trajectories firing patterns [5,6].

## Limitations

The immense success of extracellular recordings should not blind one to the limitations inherent to this approach. The key problem is that the cellular elements that generate the recorded signals are not identified. To date spike signals are often classified according to spike width to putative excitatory neurons (with broader spikes) and putative inhibitory neurons (with narrower spikes). What remains problematic is that these methods are rarely verified *in vivo*; furthermore it remains unclear, why some authors observe and publish bimodal spike width distributions (suggesting the existence of two separable cell classes) while other investigators do not observe bimodal spike width distributions. Another disadvantage is that only the output signals of neurons, in the form of spikes, can be recorded, leaving the synaptic inputs inaccessible. It has become clear that extracellular recordings might be subjected to considerable sampling biases such as tendency to record from more active neurons and from

## 2 New technologies

larger neurons [7–10]. The application of novel optical recording methods in awake behaving animals may resolve such problems and the first results suggest that cortical activity in awake behaving animals is much more sparse than previously assumed [11]. Finally extracellular methods are restricted to neuronal recording (as opposed to controlled stimulation of the recorded neurons) and thus the analysis is limited, almost exclusively, to a correlative framework.

### Advances

Increasing the number of recording electrodes allows for better sampling of the neuronal population. Increasing the density of recording sites allows for better separation of the signal sources. Recently, the density of recording sites was further increased by making the probes dual sided. Employing a 3D architecture of the recording device further improves the separation capabilities [12•].

Lighter drives enable animals to behave more naturally. The lighter machinery can also be applied to smaller animals such as mice and zebra finch [13•,14]. The ability to record from mice during behavioral studies has the advantage that neural recordings can be combined with genetic manipulations.

Methodologies for online denoising of the signals from non-neuronal noise arising from animal's movement are also being developed. These use the fact that such signals tend to occur on all electrodes simultaneously and thus by correlating signals over multiple electrodes one can get rid of such noise [15].

Telemetry is yet another step in making the recording gear less bulky, enabling animals to socially interact with other animals [16] and explore 3D environments [13•,17•].

### Advances in the understanding and analysis of extracellular signals

Many of the recent advances relate to the analysis of extracellular signals. Given that synchronicity of neural activity is of great interest one would like to be able to detect events that occur simultaneously. Improved solutions for this problem have recently been developed [18], which also enable the online detection and sorting of events under changing circumstances. Another challenge is being able to verify that the recordings are stable and that the same units are being recorded over long periods of time. This is particularly important for following changes in populations of neurons during learning. Previously, recording stability across days was claimed on the basis of similarity between action potential waveforms [19,20] or waveform features [21]. Recently statistical frameworks were employed to calculate a confidence measure for the signals being from the same neuron [22,23••].

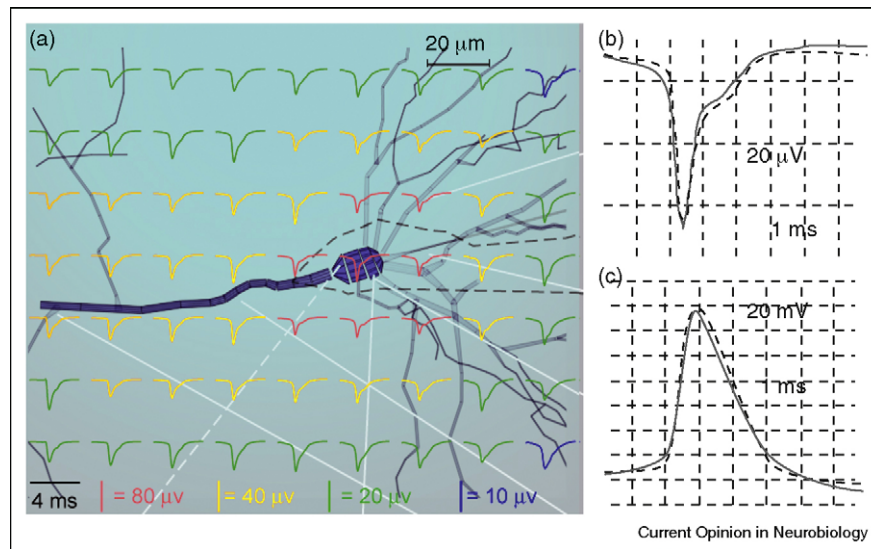
The availability of high dimensional data also requires analysis tools that enable extraction of high order interaction between the recorded units (for review see [24•] and [25]).

Another direction is trying to extrapolate information on intrinsic properties of the units from extracellular waveforms. To this end dual intracellular and extracellular recordings were performed linking features of the extracellular waveform to intrinsic properties of action potentials [26]. From this study it was concluded that several intracellular parameters can be deduced from extracellular spike waveforms. The width and amplitude of the intracellular spike are reflected by distinct properties of the extracellular waveform. Modeling studies try to better understand the source of variability of the extracellular signals. To that end, dual intracellular and extracellular recordings were performed [27••]. Using the line source approximation method developed by Holt and Koch [28] the extracellular waveforms at different locations were calculated (Figure 1a) and compared to the recorded extracellular waveforms (Figure 1b solid and dotted line respectively). The extracellular and intracellular action potential waveforms (Figure 1b and c respectively dotted lines) were then used in order to tune the densities and the kinetics of the modeled neuron such that the recorded and simulated intracellular spikes were similar (Figure 1c solid and dotted line respectively). In Figure 1a are the simulated extracellular waveforms for one pyramidal neuron. From fitting such models to experimental data it was observed that a large variability in the intrinsic properties of the modeled neurons was required. This indicates that variability in the intrinsic properties of neurons is a key source for the variability of the recorded waveforms [29]. As expected a major source of variability is the location of the recording electrode relative to the cell.

### Juxtacellular recording and stimulation

Juxtacellular recording techniques have the significant advantage over extracellular recordings in that the recorded units can be stimulated and labeled [30]. Both stimulation and labeling of the cells is achieved by injecting currents through the pipette. Such currents electroporate the membrane of the cell creating small holes. Ions can then cross the membrane polarizing the cell. If biocytin is included in the recording pipette then these molecules will also enter the cell and label it. Similar to conventional extracellular recording, this technique can be used in behaving animals [31•,32••,33]. Juxtacellular recordings present a great advantage over intracellular and whole-cell recording techniques in chronic preparations because juxtacellular recordings are easy to apply and they do not require dura removal. *In vivo* whole-cell recordings are typically limited to relatively few recording sessions for a given cortical area due to the deterioration of the exposure after dura

Figure 1



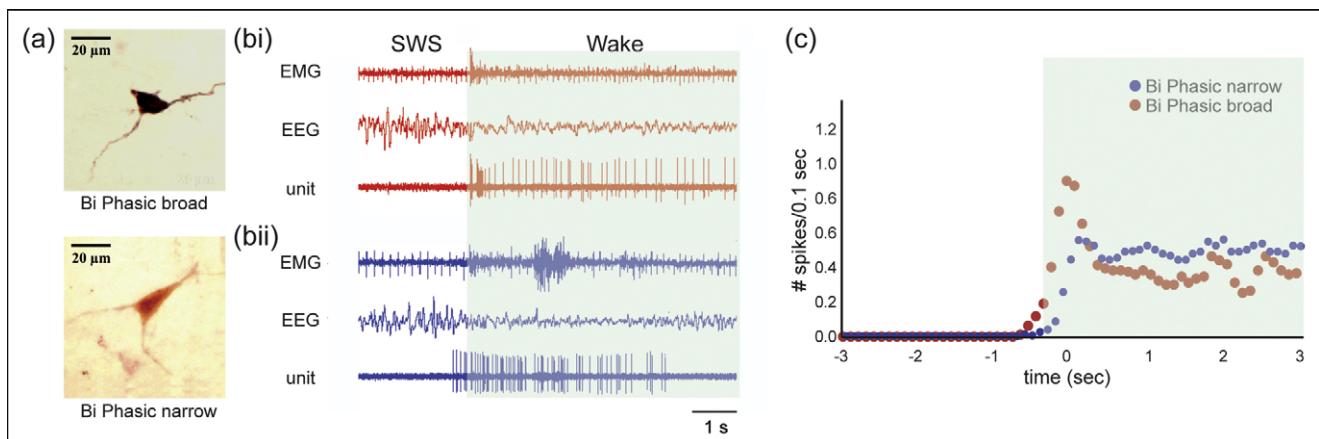
Line source approximation method captures the waveform of extracellular spike. Dual intra and extra cellular recordings (**b and c dotted lines, respectively**) were used for tuning the intracellular channel distributions and kinetics. The line source approximation method was used to calculate the extracellular spike waveforms at different locations. The extracellular electrode is marked by a dashed black line the intracellular electrode is marked by white lines (**a**). This method managed to capture both the intra (c) and extra cellular (b) properties of the action potential (dotted line averaged recorded signal, solid line simulated waveform). Modified from [27\*\*].

removal. The identification of neurons allows to correlate the activity together with morphology connectivity and other molecular markers that can be tested. Figure 2 shows an example of one such study [32\*\*], which used juxtacellular recording technique to correlate the firing patterns of thalamic waking-active neurons (Figure 2bi and 2bii bottom traces and Figure 2c), their morphology (Figure 2a), expression of orexin (Figure 2a), and state of

the animal (i.e. animal awake or asleep and state of sleep) (Figure 2bi and 2bii top two traces).

Using the stimulation advantage of juxtacellular methodology it was shown that the initiation of just 15 spikes in single cells can affect behavior [31\*]. These results argue for coding scheme in somatosensory cortex, in which few neurons and a small number of spikes can lead to a

Figure 2



Juxtacellular recording, staining and posthoc immunohistochemistry identification of neurons related to the sleep-wake transitions. Neurobiotin labeled biphasic broad and biphasic narrow thalamic waking-active neurons (**a top and bottom panels respectively**). The broad biphasic neuron shows also anti-orexin antibodies labeling. (**b**) EMG, EEG and unit recording from biphasic broad (bi) and biphasic narrow waking-active neurons (bii). The unit results are summarized in (**c**). Modified from [32\*\*]. SWS - slow wave sleep.

#### 4 New technologies

behavioral outcome. Similar conclusions were reached using light stimulation of channelrhodopsin expressing layer 2/3 somatosensory cells [34<sup>•</sup>].

##### Limitations

To date the main drawback of this technique compared to other extracellular techniques is that it requires a precise positioning of the electrode relative to the recorded neuron, thus limiting the application of this technique to very few cells. Especially in awake animals, the necessity for the recording pipette to be in close proximity to the recorded cell might result in perturbation of the cell and in many cases limit the recording duration. This problem also prevents chronic recordings from single neurons. To date this technique was used in awake head fixed animals but efforts are underway possible to adapt this method for freely moving animals [35].

##### Advances

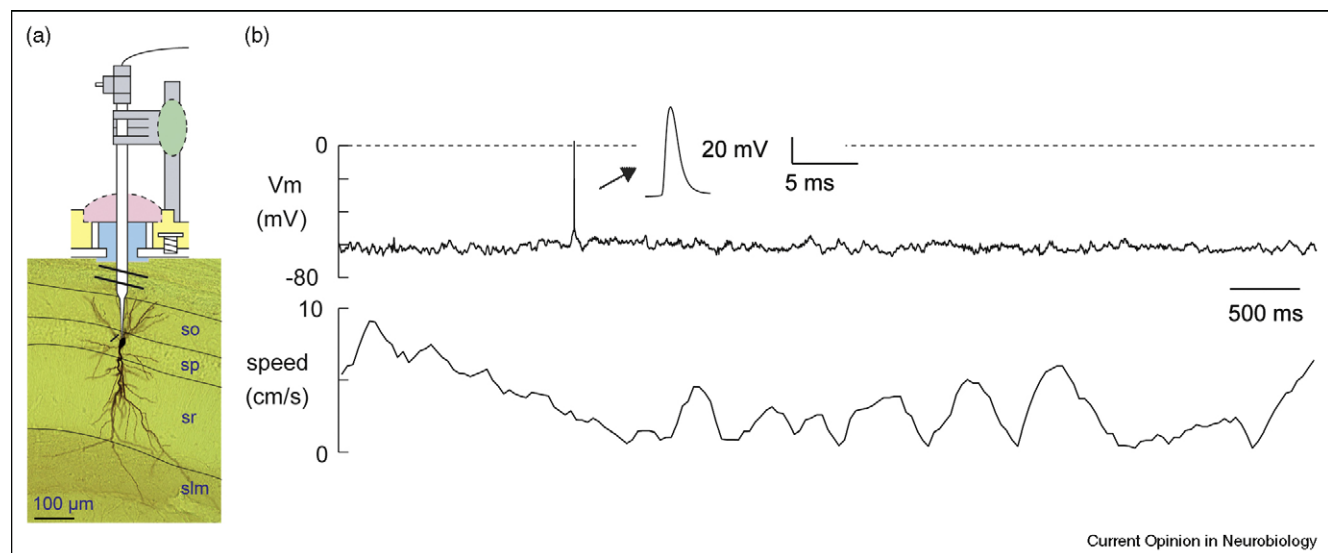
Identification and stimulation of neurons can be also achieved by other means such as genetically targeting specific cell types with activity inducing markers such as channelrhodopsin [36]. This is of course limited to cells that can be targeted and to locations where light can be delivered. A major advantage of this method is the ability to activate/inactivate specific cell groups and observe the effect it exerts on behavior and activity of cells, thus giving functional information on top of correlative information. The juxtacellular method, on the contrary, allows for controlled single cell stimulation, thus verifying a functional relation of the recorded neuron activity to

the task [31<sup>•</sup>,33]. Recently it was demonstrated that using this technique one can also deliver plasmid DNA into the recorded neuron. This allows to genetically manipulate single neurons that are shown to effect behavior, enabling to further dissect the mechanisms underlying single neuron computations [37<sup>••</sup>].

##### Intracellular recording

Neuronal input–output relations cannot be deciphered with extracellular recording techniques. Changes in firing patterns are usually attributed to changes in the network but it is clear that such changes can also occur due to changes within neurons. The only method to date that can record inputs and outputs of the cell is intracellular recording. This method is being used in awake behaving experiments either in restrained [38] or freely moving animals [39<sup>•</sup>,40,41]. This method has all the advantages of the juxtacellular method: labeling of the cell (Figure 3a) and ability to stimulate single cells. But the information gained is much richer, including sub-threshold events (Figure 3b top panel) as well as spiking information (Figure 3a inset). These events include synaptic potentials, plateau-potentials, calcium spikes and spikelets, all of which can be document during locomotion (Figure 3b bottom panel). Using this method one can monitor changes in intrinsic properties of neurons during different global states and in the course of learning. This sort of data will be able to link the knowledge on firing patterns of cells in behaving animals to cellular mechanisms that usually are studied in *in vitro* preparations.

**Figure 3**



Whole-cell recording of a hippocampal neuron in a freely moving animal. (top) A schematic of the recording configuration, in which the recording pipette is 'head-anchored' cementing to post and to an acrylic implant. Having biocytin in the recording pipette enabled to recover the morphology of the recorded CA1 pyramidal neurons (bottom). (b) For the cell in (a), membrane potential (top) during a period when the animal is awake and moving around in a behavioral arena. AP shown at expanded timescale to the right. Corresponding velocity of animal's head (bottom). Modified from [39<sup>•</sup>].

### Limitations

The main limitation of the freely behaving intracellular recording method is the low success rates. To reach such a recording one must start with an anesthetized animal, once a stable recording is achieved the electrode is anchored to the skull, only then the animal can be removed from the stereotax and given an antidote for the anesthesia [39,40]. The recordings are often lost in the process of stabilization and during waking up of the animals [39,40]. The success rates can be higher using a head restrained variation of the methodology. The duration of recording is yet another limitation. The recordings from freely moving animals are limited to about 1 h of recording; usually the durations are much shorter. This is both due to stability problems and to washout of intracellular modulators and membranous conductances, known to occur in whole-cell recordings. This limits the scope of questions that can be studied with this technique. The fact that this method is limited to few cells is another drawback, especially since the patching is blinded thus making it hard to select for the desired cells. In principle, however, methods for targeted patching [42–44] can be combined with this method.

### Advances

The advantages of intracellular recordings are quite obvious, having the record of subthreshold activity of neurons during behavior. This allows one to follow ongoing changes in input patterns as well as changes in intrinsic properties of neurons. For example, one can understand what underlies the attenuation of responses during awake active whisking as compared to non-whisking periods. According to Crochet and Peterson [41] this is due to a combined effect of the neurons being in a depolarized state during active whisking and to the thalamic inputs being depressed. Advances are being introduced to this relatively new method. Creative means for using this method in restrained animals are also being developed [45]. The use of a floating ball allows for walking without mobility [46,47], and combining this with virtual reality [48–50] enables to simulate mobility for the animal without really mobilizing it. The latest development in this technique is the head anchoring technique, which allows for higher success rates [39] and enable to get information on subthreshold activity in freely moving animals during natural behaviour [51,52].

### Conclusions

The brain generates behavior instantaneously and can store experiences of single episodes in distributed networks. Most of what we know about the brain and its plasticity, however, relates to repetitive stimuli and plasticity in single synapses. Although we are virtually ignorant of how the brain solves real life problems and forms episodic memories, the methodological advances reviewed here will help confront these problems. Moving

from single unit recording to multiple unit recordings allows one to extract more information about the stimuli and about the outcome. Documenting and analyzing neuronal responses of identified neurons will frame our thinking in terms of activity of specific circuits rather than stating our results in mere action potential counts. Recording postsynaptic potentials in conscious animals during tasks such as navigation will help to bridge the gap between synaptic plasticity, learning and memory formation.

### Acknowledgments

We would like to thank Dr John Tukker and Dr Jason Wolfe for their constructive review of the manuscript. This work was supported by the BCCN Berlin (the BMBF), the EU FP7 BIOTACT grant, the Neurobehavior ERC grant to MB, and Neurocure.

### References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- of special interest
  - of outstanding interest
1. Csicsvari J, Henze DA, Jamieson B, Harris KD, Sirota A, Bartho P, Wise KD, Buzsaki G: **Massively parallel recording of unit and local field potentials with silicon-based electrodes.** *J Neurophysiol* 2003, **90**:1314-1323.
  2. McNaughton BL, O'Keefe J, Barnes CA: **The stereotrode: a new technique for simultaneous isolation of several single units in the central nervous system from multiple unit records.** *J Neurosci Methods* 1983, **8**:391-397.
  3. O'Keefe J, Dostrowsky J: **The hippocampus as a spatial map. Preliminary evidence from unit activity in the freely-moving rat.** *Brain Res* 1971, **34**:171-175.
  4. O'Keefe J, ML R: **Phase relationship between hippocampal place units and the EEG theta rhythm.** *Hippocampus* 1993, **3**:317-330.
  5. Skaggs W, McNaughton BL: **Replay of neuronal firing sequences in rat hippocampus during sleep following spatial experience.** *Science* 1996, **271**:1870-1873.
  6. Nadasdy Z, Hirase H, Czurko A, Csicsvari J, Buzsaki G: **Replay and time compression of recurring spike sequences in the hippocampus.** *J Neurosci* 1999, **19**:9497-9507.
  7. Towe AL, Harding GW: **Extracellular microelectrode sampling bias.** *Exp Neurol* 1970, **29**:366-381.
  8. Stone J: **Sampling properties of microelectrodes assessed in the cat's retina.** *J Neurophysiol* 1973, **36**:1071-1079.
  9. Olshausen BA, Field DJ: **Sparse coding of sensory inputs.** *Curr Opin Neurobiol* 2004, **14**:481-487.
  10. Brecht M, Schneider M, Manns ID: In *The Plasticity Of The Sensory-Motor Cortices*. Edited by Ebner F. CRC Press; 2005:2005.
  11. Greenberg DS, Houweling AR, Kerr JN: **Population imaging of ongoing activity in visual cortex of awake rats.** *Nat Neurosci* 2008, **11**:749-751.
  12. Du J, Riedel-Kruse IH, Nawroth JC, Roukes ML, Laurent G, Masmanidis SC: **High-resolution three-dimensional extracellular recording of neuronal activity with microfabricated electrode arrays.** *J Neurophysiol* 2009, **101**:1671-1678.
- This paper described double-sided recording probes that enable very high density recordings.
13. Schregardus DS, Pieneman AW, Ter Maat A, Jansen RF, Brouwer TJF, Gahr ML: **A lightweight telemetry system for recording neuronal activity in freely behaving small animals.** *J Neurosci Methods* 2006, **155**:62-71.

## 6 New technologies

A light weight telemetry system for recording from mice and zebra finch. This enables freely behaving recording from animals in their natural environments.

14. Battaglia FP, Kalenscher T, Cabral H, Winkel J, Bos J, Manuputy R, van Lieshout T, Pinkse F, Beukers H, Pennartz C: **The Lantern: An ultra-light micro-drive for multi-tetrode recordings in mice and other small animals.** *J Neurosci Methods* 2009, **178**:291-300.
  15. Paralikar K, Rao C, Clement RS: **Automated reduction of non-neuronal signals from intra-cortical microwire array recordings by use of correlation technique.** *Conf Proc IEEE Eng Med Biol Soc* 2008:46-49.
  16. Jürgens U, Hage SR: **Telemetric recording of neuronal activity.** *Methods* 2006, **38**:195-201.
  17. Ye X, Wang P, Liu J, Zhang S, Jiang J, Wang Q, Chen W, Zheng X: **A portable telemetry system for brain stimulation and neuronal activity recording in freely behaving small animals.** *J Neurosci Methods* 2008, **174**:186-193.
- A light weight telemetry system for recording from mice and zebra finch. This enables freely behaving recording from animals in their natural environments.
18. Franke F, Natora M, Boucsein C, Munk M, Obermayer K: **An online spike detection and spike classification algorithm capable of instantaneous resolution of overlapping spikes.** *J Comput Neurosci* 2009.
  19. Rousche PJ, Normann RA: **Chronic recording capability of the Utah intracortical electrode array in cat sensory cortex.** *J Neurosci Methods* 1998, **82**:1-15.
  20. Schmitzer-Torbert N, Redish AD: **Neuronal activity in the rodent dorsal striatum in sequential navigation: separation of spatial and reward responses on the multiple T task.** *J Neurophysiol* 2004, **91**:2259-2272.
  21. Nicolelis MAL, Dimitrov D, Carmena JM, Crist R, Lehew G, Kralik JD, Wise SP: **Chronic, multisite, multielectrode recordings in macaque monkeys.** *Proc Natl Acad Sci U S A* 2003, **100**:11041-11046.
  22. Liu X, McCreery D, Bullara L, Agnew W: **Evaluation of the stability of intracortical microelectrode arrays.** *IEEE Trans Neural Syst Rehabil Eng* 2006, **14**:91-100.
  23. Tolia AS, Ecker AS, Siapas AG, Hoenselaar A, Keliris GA, Logothetis NK: **Recording chronically from the same neurons in awake behaving primates.** *J Neurophysiol* 2007, **98**:3780-3790.
- A statistical quantitative measure for determining the likelihood that a signal is from the same unit over consecutive days.
24. Quiñero Quiroga R, Panzeri S: **Extracting information from neuronal populations: information theory and decoding approaches.** *Nat Rev Neurosci* 2009, **10**:173-185.
- An excellent review on methodologies applied for analyzing high dimensional population data using decoding and information theory.
25. Paninski L, Pillow J, Lewi J: **Statistical models for neural encoding, decoding and optimal stimulus design.** *Prog Brain Res* 2007, **165**:493-507.
  26. Henze DA, Borhegyi Z, Csicsvari J, Mamiya A, Harris KD, Buzsáki G: **Intracellular features predicted by extracellular recordings in the hippocampus in vivo.** *J Neurophysiol* 2000, **84**:390-400.
  27. Gold C, Henze DA, Koch C, Buzsáki G: **On the origin of the extracellular action potential waveform: a modeling study.** *J Neurophysiol* 2006, **95**:3113-3128.
- Building on data from combined intracellular and extracellular recordings from the same neuron this modeling study explores the distribution, variability and origin of extracellular signals. Addressing these issues will be crucial to the interpretation of extracellular recordings.
28. Holt G, Koch C: **Electrical interactions via the extracellular potential near cell bodies.** *J Comput Neurosci* 1999, **6**:169-184.
  29. Gold C, Henze D, Koch C: **Using extracellular action potential recordings to constrain compartmental models.** *J Comput Neurosci* 2007, **23**:39-58.
  30. Pinault D: **A novel single-cell staining procedure performed in vivo under electrophysiological control: morpho-functional features of juxtacellularly labeled thalamic cells and other central neurons with biocytin or neurobiotin.** *J Neurosci Methods* 1996, **65**:113-136.
  31. Houweling AR, Brecht M: **Behavioural report of single neuron stimulation in somatosensory cortex.** *Nature* 2008, **451**:65-68.
- Rats were trained to detect micro-stimulation to the barrel cortex. After training low stimulation of a single neuron, using juxtacellular recording, could be detected.
32. Takahashi K, Lin JS, Sakai K: **Neuronal activity of orexin and non-orexin waking-active neurons during wake-sleep states in the mouse.** *Neuroscience* 2008, **153**:860-870.
- This paper shows that different cell types in the posterior hypothalamus show different responses when the animal moves from awake states to slow wave sleep and vice versa.
33. Voigt BC, Brecht M, Houweling AR: **Behavioral detectability of single-cell stimulation in the ventral posterior medial nucleus of the thalamus.** *J Neurosci* 2008, **28**:12362-12367.
  34. Huber D, Petreanu L, Ghitani N, Ranade S, Hromádka T, Mainen Z, Svoboda K: **Sparse optical microstimulation in barrel cortex drives learned behaviour in freely moving mice.** *Nature* 2008, **451**:61-64.
- Mice were trained to detect light activated layer 2/3 pyramidal neurons in barrel cortex. Post training low stimulation of hundreds of neurons could be detected or using stronger stimulation activating tens of neurons sufficed.
35. D. Sullivan, S. Ozen, G. Buzsáki: **Juxtacellular recording and labeling in the hippocampal dentate gyrus of freely moving rats.** In SFN abstract 435.2/H7, 2008.
  36. Kuhlman SJ, Huang ZJ: **High-resolution labeling and functional manipulation of specific neuron types in mouse brain by cre-activated viral gene expression.** *PLoS ONE* 2008, **3**:e2005.
  37. Judkewitz B, Rizzi M, Kitamura K, Hausser M: **Targeted single-cell electroporation of mammalian neurons in vivo.** *Nat Protocols* 2009, **4**:862-869.
- Using single cell electroporation (i.e juxtacellular stimulation) plasmid DNA could be introduced into neurons. Stable transgene expression was reliably induced.
38. Margrie T, Brecht M, Sakmann B: **In vivo, low-resistance, whole-cell recordings from neurons in the anaesthetized and awake mammalian brain.** *Pflügers Archiv Eur J Physiol* 2002, **444**:491-498.
  39. Lee AK, Epsztein J, Brecht M: **Head-anchored whole-cell recordings in freely moving rats.** *Nat Protocols* 2009, **4**:385-392.
- This paper describes an improved method for whole-cell recordings in freely moving animals.
40. Lee AK, Manns ID, Sakmann B, Brecht M: **Whole-cell recordings in freely moving rats.** *Neuron* 2006, **51**:399-407.
  41. Crochet S, Petersen CCH: **Correlating whisker behavior with membrane potential in barrel cortex of awake mice.** *Nat Neurosci* 2006, **9**:608-610.
  42. Komai S, Denk W, Osten P, Brecht M, Margrie TW: **Two-photon targeted patching (TPTP) in vivo.** *Nat Protocol* 2006, **1**:647-652.
  43. Kitamura K, Judkewitz B, Kano M, Denk W, Hausser M: **Targeted patch-clamp recordings and single-cell electroporation of unlabeled neurons in vivo.** *Nat Methods* 2008, **5**:61-67.
  44. Margrie TW, Meyer AH, Caputi A, Monyer H, Hasan MT, Schaefer AT, Denk W, Brecht M: **Targeted whole-cell recordings in the mammalian brain in vivo.** *Neuron* 2003, **39**:911-918.
  45. Dombeck DA, Khabbazi AN, Collman F, Adelman TL, Tank DW: **Imaging large-scale neural activity with cellular resolution in awake, Mobile Mice.** *Neuron* 2007, **56**:43-57.
- In this paper population of cells are imaged while the animal is behaving. Although the animal is head anchored it can still mobilize on a floating ball.

46. Dahmen H: **A simple apparatus to investigate the orientation of walking insects.** *Experientia* 1980, **36**:685-687.
47. Mason A, Oshinsky M, Hoy R: **Hyperacute directional hearing in a microscale auditory system.** *Nature* 2001, **410**:686-690.
48. Hassabis D, Chu C, Rees G, Weiskopf N, Molyneux PD, Maguire EA: **Decoding neuronal ensembles in the human hippocampus.** *Curr Biol* 2009, **19**:546-554.
49. Ye N, Tonntiva A, He J: **A cluster analysis of neuronal activity in the dorsal premotor cortical area for neuroprosthetic control.** *Conf Proc IEEE Eng Med Biol Soc* 2008:2638-2641.
50. Jarosiewicz B, Chase SM, Fraser GW, Velliste M, Kass RE, Schwartz AB: **Functional network reorganization during learning in a brain-computer interface paradigm.** *Proc Natl Acad Sci U S A* 2008, **105**:19486-19491.
51. J. Epszstein, A.K. Lee, M. Brecht: **Fast prepotentials in CA1 pyramidal cells from freely moving rats.** In SFN abstract 690.21/UU2, 2008.
52. A.K. Lee, J. Epszstein, M. Brecht: **Whole-cell recordings of hippocampal CA1 place cell activity in freely moving rats.** In SFN abstract 690.22/UU3, 2008.