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Using multi-neuron population recordings for neural prosthetics

John K Chapin

Classical single-neuron recording methods led to 'neuron-centric' concepts of neural coding, whereas more recent multi-neuron population recordings have inspired 'population-centric' concepts of distributed processing in neural systems. Because most neocortical neurons code information coarsely, sensory or motor processing tends to be widely distributed across neuronal populations. Dynamic fluctuations in neural population functions thus involve subtle changes in the overall pattern of neural activity. Mathematical analysis of neural population codes allows extraction of 'motor signals' from neuronal population recordings in the motor cortices, which can then be used in real-time to directly control movement of a robot arm. This technique holds promise for the development of neurally controlled prosthetic devices and provides insights into how information is distributed across several brain regions.

Just as the advent of fine electrode recordings in the 1940s shifted our neurophysiological focus from the whole brain to the single neuron, the advent of multi-neuron recordings has shifted our focus to the study of the neuronal population as a whole. Single-neuron recordings can define receptive fields[1,2], but these receptive fields are problematic in that they do not specify a neuron's actual response to a stimulus, but merely its potential responses, summed across the range of conditions in which it is tested. In the somatosensory cortex, receptive fields can be so large that they cannot (by themselves) accurately specify stimulus information[3]. Another drawback to single-neuron recordings is that there can be a marked variability in the neurons' responses, even to controlled, discrete stimuli. In awake animals, much of this 'noise' is also related to spontaneously fluctuating brain states, such as attention or intention[4,5].

Although this coarse coding and volatility diminishes the usefulness of single-neuron recordings for extracting sensory or motor information from the brain, it increases the usefulness of multi-neuron recordings. A central tenet of parallel distributed processing theory[6] is that neural information is spread across populations of neurons, and that each neuron contributes to the processing of many different informational factors. If so, one should be able to extract more information from the brain by recording simultaneously from large numbers of neurons. Over time, this basic hypothesis has sparked the development of a variety of electrode arrays and electronic devices for this purpose. Several laboratories use chronically implanted electrode arrays because they allow stable recordings of discriminated single neurons and/or field potentials from up to hundreds of electrodes over long time periods[7–16].

The development of such methods allowed neural recordings to be analyzed at the level of neuronal populations, as well as the single-neuron level. Because the same variables (*e.g.*, neurons) are recorded simultaneously, one can directly measure the evanescent patterns of synchronous activity that typically occur in neuronal populations during spontaneous fluctuations in brain and/or behavioral state. This ability to statistically account for covariance within neuronal ensembles provides a major advantage over the alternative approach of recording the same single neurons in serial order. Whereas multi-neuron recordings can use neuronal covariance patterns to detect spontaneous changes in brain state, in serial single-neuron recordings, such variance is normally unexplained and thus must be considered as noise. One can utilize this approach to measure complex and heterogeneous changes in neuronal population activity recorded over many time frames, ranging from fractions of seconds, as in brain oscillations, to several hours or days, as in drug or hormone effects[17–22].

How then does one usefully extract the information contained within neuronal populations? Statistical approaches, such as linear or nonlinear multivariate regression and discriminant and principal components analysis (PCA), provide a more accurate estimation of neural information than the direct summation of neuronal receptive (or motor) fields, unless their unique features are laboriously measured in isolation (see ref. 23, p. 456–461 this issue). Linear regression, for example, can use neuronal populations in the motor cortex to predict arm movement and control external devices[13,14]. Time-binned neural and arm position data from several training trials are used to 'fit' a regression equation that specifies a weighting for each neuron's contribution to the arm movement. Sequential arm positions can then be predicted in real time by weight-summing the neuronal population activity for each new time bin. The accuracy of this prediction (*i.e.*, its correlation with real arm movement) monotonically increases with the number of recorded neurons[11].

A major advantage of generating predictions of neural population coded outputs is that they can be directly compared to real external events (*e.g.*, movements). Thus one can easily test the usefulness of different mathematical approaches to extract the neuronal information.

Though conventional statistics include many approaches and provide clear measures of significance[24], other approaches may often be

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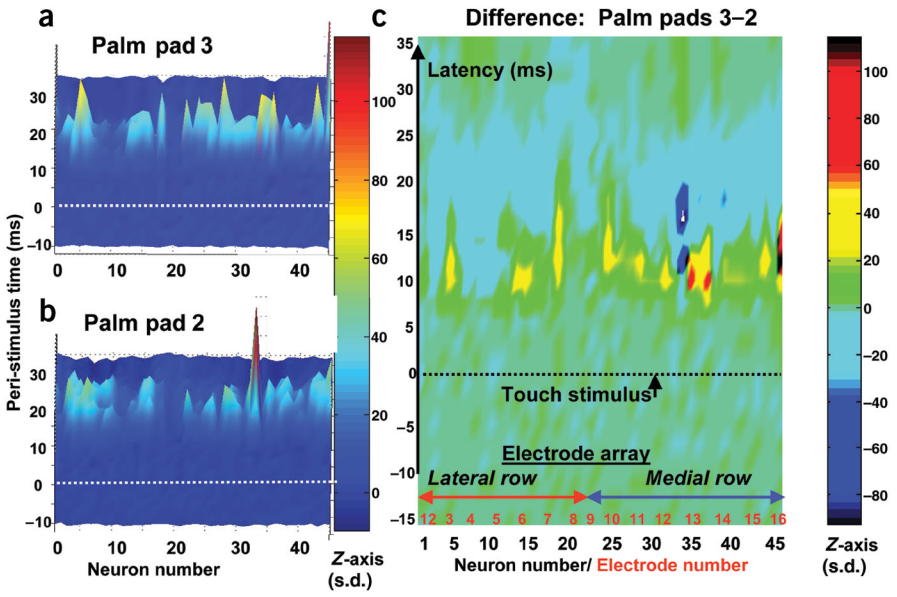

Figure 1 Neuronal population response maps. Normalized 3D surfaces depict post-stimulus responses of the same 45 simultaneously recorded neurons (in rat S1 cortex) to vibromechanical touch of (**a**) palm pad 3, (**b**) palm pad 2 and (**c**) their difference. Each neuron's peristimulus responses were standardized into *Z* scores. (Mean and standard deviation (s.d.) of responses measured in the 15-ms period before the stimulus were used to standardize all peristimulus bins.) For each plot, the *x* axis shows neuron number (1–45), the *y* axis is response latency (–15 ms to 35 ms around stimulus), and the *z* axis (in s.d.) depicts standardized response level in relief and color codes (calibrated in bars at right of **a**–**c**). Panel **c** is also a 3D surface, but viewed from above to show the precise spatiotemporal difference pattern between palm pad 3 (positive in yellow/red) and palm pad 2 (negative in green/blue). It also shows (in red) the spatial arrangement of the 16 recording electrodes in the array, which consisted of two rows of 8 electrodes apiece (0.28 mm tip separation; 0.5 mm row separation). The whole array was chronically implanted across the forepaw representation (electrode 1 most caudolateral; electrode 16 most rostromedial). A week later, 1–4 single neurons were discriminated from each electrode, and recordings began. All stimuli used a vibromechanical stimulator with a 1-mm diameter shaft tip held just above the skin between stimuli (0.5 mm displacement, 500 μs duration, 2 Hz, 340 stimuli). Figure from J.K.C. and S. Xu, unpublished data.

preferable because of particularities of data distribution or the underlying hypothesis. Thus, neuronal population recordings have been analyzed using Bayesian statistics, artificial neural networks and kernel analysis.

Analysis of spatiotemporally distributed information

It is becoming clear that information in the brain is coded not only in space (across neuronal populations) but also in time (temporal patterning of neuronal responses). For example, vibromechanical touch stimuli to the palm pads of rats produce discrete responses in the primary and secondary afferents, but as these signals ascend through the thalamus and cortex, they become increasingly distributed across larger portions of the somatosensory representation; they also show an increasing range of response latencies[10]. A different view of neural coding thus emerges from multi-neuron recordings in the thalamus and cortex (**Fig. 1**). When the responses to fine punctate tactile stimulation of palm pad 3 and palm pad 2 were obtained from 45 neurons recorded from a 16-electrode array covering the whole somatosensory cortical forepaw area in a rat (**Fig. 1a**,**b**) and plotted as normalized three-dimensional (3D) surface maps, both showed spatiotemporally complex patterns of neural responses that were distributed across the whole forepaw representation, even though the two stimulus sites were on closely adjacent palm pads. Any mathematical procedure used to discriminate between these two stimuli must incorporate both spatial and temporal criteria, because the significant information is spread out over many neurons and also over post-stimulus time[3].

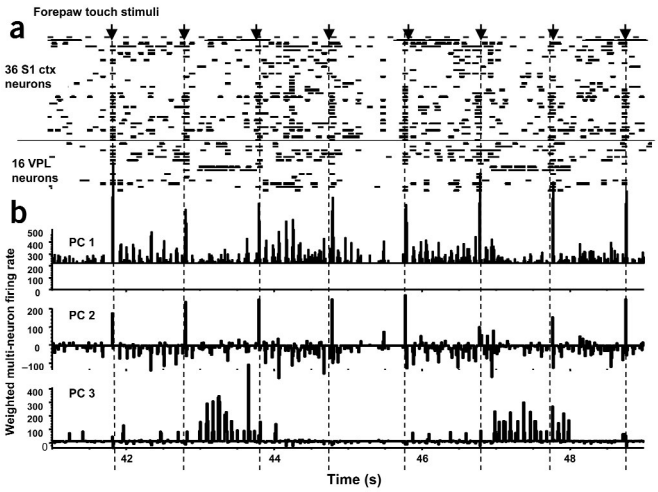

Figure 2 Interactions between sensory stimuli and brain dynamics in neural populations. (**a**) Spike rasters of 36 simultaneously recorded neurons in S1 cortex and 16 in VPL thalamus during 8 vibromechanical stimuli of palm pad 3 (0.5 mm displacement, 500 μs duration, 1 Hz). Stimulation times at arrows. (**b**) Population functions encoded using weights derived from a principal components analysis (PCA) using neural data from the whole experiment. PCA involved eigenvalue decomposition of the 52×52 correlation matrix between all neurons. Population functions for PCs 1–3 were constructed by binning the spiking data (10 ms), multiplying each neuron's firing by its weighting in PCs 1–3, and summing over all neurons. Population functions are displayed as rate meters. Bin heights scaled as weighted total firing rate (vertical axis). Figure from J.K.C. and S. Xu, unpublished data.

Encoding multi-functional and dynamical phenomena

Distributed processing theory posits that neurons are multi-functional—that is, under different conditions they can manifest different information. As a simple example, **Figure 2** shows recordings from neuronal populations in the somatosensory cortex and thalamus that are rapidly shifting between two distinct functional states: sensory response processing and spontaneous oscillations. Here we show that one population coding method (PCA) can be used to cleanly distinguish between these two functions, allowing their interactions to be studied[25]. These functional states cannot be differenti-

ated in single neurons because they are distinguished by the different levels of correlation among neurons. Our PCA method involves cross-correlating the binned spiking activity of all recorded neurons over some time period and then performing successive eigenvalue rotations of this correlation matrix to yield a set of uncorrelated principal components, each representing a uniquely weighted average of the original neurons. Neuronal populations were recorded in the cortex and thalamus during rhythmic oscillations and also during 1-Hz stimulation of the forepaw (**Fig. 2a**). We used three neural population functions, weighted to depict principal components 1–3 (PC1–3) of the whole neuronal population (**Fig. 2b**). Whereas PC1 resembles an unweighted population average, PC2 segregates the paw stimuli (positive) from the main thalamocortical oscillatory regime (negative), and PC3 isolates a secondary oscillatory regime emanating from the thalamus. In statistical terms, each neuron contributes weighted portions of its variance to each of these three components, which here discriminate between different functional activities of the overall population. Although the correctness of various methods for deriving and applying the weights will be investigated for years, this general concept has proved to be quite useful for understanding population coding in neuronal populations, especially those discussed below.

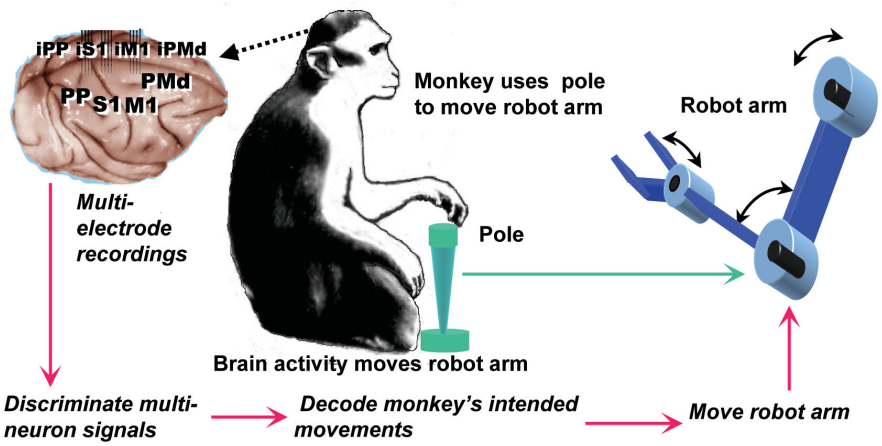

Figure 3 Brain-controlled neural prosthesis. (**a**) Monkey is initially trained to sit in a chair and manipulate a pole to move a cursor toward a target depicted on a computer screen (not depicted here). This pole movement is also translated into equivalent movement of a robot arm. Three tasks are trained in serial order: (1) move pole to a particular target position, (2) squeeze force transducer on pole to reach a force target, and (3) do 1 (move) and then 2 (squeeze) in sequence. The first experiments involve 'pole control' (depicted in green) in which the pole output goes to the robot controller, which moves the robot and/or its gripper. Feedback from the robot then moves the cursor on the screen. Once this task is learned, the control of the robot is changed to 'brain control' (depicted in red), utilizing multi-neuron recordings obtained from microwire electrode arrays implanted in several contralateral and ipsilateral sensorimotor cortices, including primary motor (M1), dorsal premotor (PMd), primary somatosensory (S1) and posterior parietal (PP) cotices. Multi-neuron recordings are amplified, filtered and discriminated by an acquisition system box (Plexon Inc.), as controlled by a graphics interface on a host computer that also functions as a data server. A client computer receives spike times and field potential data from the server in real time, and uses adaptive linear or nonlinear fitting algorithms to 'predict' the pole movement, transforming the neural data into neuronal population functions suitable for controlling the robot and/or its gripper. The resulting feedback from sensors on the robot, including arm position, velocity and/or force is then represented with a cursor on the monkey's computer display. The monkey ultimately learns to use the decoded neural population prediction functions to directly control the cursor movement toward the target, often without moving the arm at all. Figure adapted from ref. 31.

Extraction of neuronal population information: neural prostheses

The most visible success of multi-neuron recording to date has been in extracting information from the brain in real time and using this information to control external devices[26]. We originally developed such technology for online population encoding of multi-neurons in the motor cortex (M1) and thalamus (ventral lateral) in rats trained to press a lever to move a robot arm that retrieved water from a dropper[27]. Population encodings of the brain's 'motor signal' were electronically implemented in real time, allowing the robot arm to be moved in direct proportion to the population function amplitude. The rat thereafter obtained its daily water by using this neural signal alone to control the robot's movement to the water dropper. Over time, the rat was able to obtain its water without actually pressing the lever, suggesting that the M1 cortex neurons had learned a direct representation of the robot arm, independent of the real arm.

Similar results have now been obtained in monkeys[12,28–31], derived from simultaneous recording from hundreds of neurons across the primary motor, premotor, somatosensory and parietal cortices (**Fig. 3**). An offline computer was used to calculate the neuronal weightings for multivariate linear regression predictive filters (as described above). An on-line computer then used these filters to convert real-time neuronal activity into neural population codes that simultaneously specified three dimensions of hand position, velocity and/or force. These population-coded outputs were then used to control a robot arm and/or a cursor on a computer screen with good accuracy (R^2 = 0.5–0.8) compared with the monkey's arm itself. Though the quality and quantity of useful coding information obtained in these recordings varied across the bilaterally recorded sensorimotor cortical areas, all of these areas contributed at least some useful information to the control. This is consistent with previous findings that cortical neurons tend to be widely tuned[1–3,29,30] and thus can be active in a wide variety of experimental conditions. Much of the success of multiple-electrode recording is attributable to this wide tuning, because the investigator can depend on obtaining useful signals from the majority of recorded neurons.

Future of neural population recording

Thanks to these early successes, this field may soon have commercial implications. The Nicolelis laboratory has already demonstrated the ability of simultaneously recorded neurons in the brains of awake human patients to predict arm and hand movements[32]. Further successes will necessitate further research in a number of areas, including development of biocompatible ultra-miniaturized multi-electrode designs, implantable electronics to amplify and process these recordings, and embedded computer systems to control the output functions, such as computer screens, robots and wheelchairs. Moreover, this neuroprosthetic technology will be joined with others, such as 'functional neuromuscular stimulation', which uses stimulating electrodes to activate a paralyzed patient's muscles. As another example, our current focus is to convert the open-loop brain-controlled robotic systems into a closed-loop neural interface by using multi-electrode arrays for both recording and stimulation in the brain[33].

Finally, non-invasive techniques, such as EEG, MEG, fMRI and infrared (IR) methods may also be important in many of these technologies. Overall, this explosion of information will also require a major neuroinformatic effort to design database methods capable of efficiently storing the necessary data so that they can be quickly mobilized for use in controlling a robot arm or a real arm in real time.

At the same time, basic scientists will find increased impetus to work on the problem of population coding in the brain. This will require more cooperation between experimentalists, theoreticians and neuroinformaticists, particularly in the sharing of datasets. Though the current academic and funding culture tends to discourage such interactions, focused government efforts can in theory overcome these difficulties.

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COMPETING INTERESTS STATEMENT

The authors declare that they have no competing financial interests.

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1. Chapin, J.K. & Lin, C-S. Mapping the body representation in the SI cortex of anesthetized and awake rats. *J. Comp. Neurol.* **229**, 199–213 (1984).
2. Chapin, J.K. Laminar differences in sizes, shapes and response profiles of cutaneous receptive fields in the rat SI cortex. *Exp. Brain Res.* **262**, 549–559 (1986).
3. Nicolelis, A.L. *et al.* Simultaneous representation of tactile information by three primate cortical areas. *Nat. Neurosci.* **1**, 621–630 (1998).
4. Chapin, J.K. & Woodward, D.J. Modulation of sensory responsiveness of single somatosensory cortical cells during movement and arousal behaviors. *Exp. Neurol.* **72**, 164–178 (1981).
5. Chapin, J.K. & Woodward, D.J. Somatic sensory transmission to the cortex during movement: II. Phasic modulation over the locomotor step cycle. *Exp. Neurol.* **78**, 670–684 (1982).
6. Rumelhart, D.E., Hinton, G.E. & McClelland, J.L. A general framework for parallel distributed processing. in *Parallel Distributed Processing: Explorations in the Microstructure of Cognition. Vol. 1: Foundations* (eds. Rumelhart, D.E., McClelland, J.L. and the PDP Research Group) (MIT Press, Cambridge, Massachusettes, 1986).
7. Lilly, J.C. Correlations between neurophysiological activity in the cortex and short-term behavior in the monkey. in *Biological and Biochemical Bases of Behavior* (ed. Woolsey, H.H.C.) (Univ. Wisconsin Press, Madison, Wisconsin, 1958).
8. Kruger, J. Simultaneous individual recordings from many cerebral neurons: techniques and results. *Rev. Physiol. Biochem. Pharmacol.* **98**, 177–233 (1983).
9. McNaughton, B.L., O'Keefe, J. & Barnes, C.A. The stereotrode: a new technique for simultaneous isolation of several single units in the central nervous system from multiple unit records. *J. Neurosci. Methods* **8**, 391–397 (1983).
10. Nicolelis, M.A.L., Baccala, L.A., Lin, C-S. & Chapin, J.K. Synchronous neuronal ensemble activity at multiple levels of the rat somatosensory system anticipates onset and frequency of tactile exploratory movements. *Science* **268**, 1353–1358 (1995).
11. Deadwyler, S.A. & Hampson, R.E. Ensemble activity and behavior – what's the code. *Science* **270**, 1316–1318 (1995).
12. Laubach, M., Wessberg, J. & Nicolelis, M.A. Cortical ensemble activity increasingly predicts behaviour outcomes during learning of a motor task. *Nature* **405**, 567–571 (2000).
13. Wessberg, J. *et al.* Real-time prediction of hand trajectory by ensembles of cortical neurons in primates. *Nature* **408**, 361–365 (2000).
14. Taylor, D.M., Tillery, S.I. & Schwartz, A.B. Direct cortical control of 3D neuroprosthetic devices. *Science* **296**, 1829–1832 (2002).
15. Moxon, K.A., Leiser, S.L., Gerhardt, G.A. & Chapin, J.K. Ceramic-based multisite electrode arrays for chronic single-neuron recording. *IEEE Trans. Biomed. Eng.* **51**, 647–656 (2004).
16. Chapin, J.K. Population-level analysis of multi-single neuron recording data: multivariate statistical methods. in *Many-Neuron Recording* (ed. Nicolelis, M.) (CRC Press, 1998)
17. Chapin, J.K. & Woodward, D.J. Ethanol withdrawal increases sensory responsiveness of single somatosensory cortical neurons in the awake, behaving rat. *Alcoholism* **13**, 8–14 (1989).
18. Patel, I.M. & Chapin, J.K. Ketamine effects on somatosensory cortical single neurons in behaving rats. *Anesth. Analg.* **70**, 635–644 (1990).
19. Shin, H-C., Park, H.J., Oh, Y.S. & Chapin, J.K. Cocaine-induced changes in functional connectivities between simultaneously recorded single neurons in the SI cortex and the VPL thalamus of conscious rats. *Kor. J. Physiol.* **27**, 79–91 (1993).
20. Smith, S.S. & Chapin, J.K. The estrous cycle and the olivo-cerebellar circuit: I. Contrast enhancement of sensorimotor-correlated Purkinje cell discharge. *Exp. Brain Res.* **111**, 371–384 (1996).
21. Smith, S.S. & Chapin, J.K. The estrous cycle and the olivo-cerebellar circuit: II. Enhanced selective sensory gating of responses from the rostral dorsal accessory olive. *Exp. Brain Res.* **111**, 385–392 (1996).
22. Nicolelis, M.A.L., Lin, C-S., Woodward, D.J. & Chapin, J.K. Peripheral block of ascending cutaneous information induces immediate spatio-temporal changes in thalamic networks. *Nature* **361**, 533–536 (1993).
23. Brown, E.N., Kass, R.E. & Mitra, P.P. Multiple neural spike train data analysis: state-of-the-art and future challenges. *Nat. Neurosci.* **7**, 456–461 (2004).
24. Chapin, J.K. & Nicolelis, M.A.L. Beyond single unit recording: characterizing neural information in networks of simultaneously recorded neurons. in *Scale in Conscious Experience: Is the Brain Too Important to Be Left to Specialists to Study?* (eds. King, J. & Pribram, K.) (Laurence Erlbaum Assoc., Mahwah, NJ, 1995).
25. Chapin, J.K & Nicolelis, M.A.L. Population coding in simultaneously recorded neuronal ensembles in ventral posteromedial (VPM) thalamus: multidimensional sensory representations and population vectors. *J. Neurosci. Methods* **94**, 121–140 (1999).
26. Nicolelis, M.A.L. & Chapin, J.K. Building brain-machine interfaces to restore and augment human motor performance. *Sci. Am.* **4**, 45–52 (2002).
27. Chapin, J.K., Markowitz, R.A., Moxon, K.A. & Nicolelis, M.A.L. Direct real-time control of a robot arm using signals derived from neuronal population recordings in motor cortex. *Nat. Neurosci.* **2**, 664–670 (1999).
28. Isaacs, R.E., Weber, D.J. & Schwartz, A.B. Work toward real-time control of a cortical neural prosthesis. *IEEE Trans. Rehabil. Eng.* **8**, 196–198 (2000).
29. Donoghue, J.P. Connecting cortex to machines: recent advances in brain interfaces. *Nat. Neurosci.* **5**, 1085–1088 (2002).
30. Nicolelis, M.A.L. *et al.* Chronic, multisite, multielectrode recordings in macaque monkeys. *Proc. Natl. Acad. Sci. USA* **100**, 11041–11046 (2003).
31. Carmena, J.M. *et al.* Learning to control a brain-machine interface for reaching and grasping by primates. *PLoS. Biol.* **1**, E42 (2003).
32. Patil, P.G., Carmena, J.M., Nicolelis, M.A.L. & Turner, D.A. Ensembles of subcortical neurons as a source of motor control signals for a brain-machine interface in humans. *Neurosurgery* (in press).
33. Talwar, S.K. *et al.* "Virtual" operant conditioning using brain microstimulation facilitates training of complex behaviors in freely roaming animals. *Nature* **417**, 37–38 (2002).