

## Representations based on neuronal interactions in motor cortex

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### Introduction

The brain is remarkably adept at constructing complex sensory and motor representations to perceive and act upon the outside world. The neural basis of such representations has been both elusive and highly debated. The concept that representations of complex objects are formed by a single most sensitive neuron (i.e. the lower envelope principle) (Barlow, 1972) or by a so-called 'grandmother cell' which, by itself, mediates an entire representation has become less tenable, although there remain strong proponents of the idea (Parker and Newsome, 1998). One serious problem with such representational schemes is that there are nearly an infinite variety of complex representations that can be learned and, therefore, there are simply not enough neurons for them to act as unique encoders.

Neural representations undoubtedly recruit groups of neurons but this observation alone does not clarify how neuron populations form representations. In visual cortex, experimental evidence accumulated over the past thirty years suggests that separate clusters of neurons represent specific features of a complex visual scene such as color, form, texture, and motion.

Thus, the neural representation of a complex scene would be composed of the activations of multiple groups of neurons, each of which would represent a simple visual feature. This would solve the problem of representing a nearly infinite number of possible objects that might occur in the world because, according to this scenario, each cluster of neurons represents a visual primitive which is used and reused in different combinations with other clusters to represent any complex object (Bienenstock and Geman, 1995).

While less clear than in sensory systems, complex movements appear to be composed of elementary components whose neural representations are assembled together in some manner to form a global representation of a desired action. In the motor cortex, cells coding for basic motor components, such as direction, amplitude or force are readily encountered. Within motor cortex even the simplest of motor behaviors such as repetitive movements of a single finger involves a distributed group of cells (Schieber and Hibbard, 1993; Sanes et al., 1995; Kakei et al., 1999). The existence of a global motor representation can be demonstrated by writing one's signature using the fingers, the wrist, the whole arm, the head or the foot. In each case the general form of the signature is the same (though the quality varies), despite formidable differences in the effector used to create that signature. For such a movement to be made, some general plan of action must be processed into the muscle language that each of these mechanically

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quite different body parts speaks. The plan of action we term a motor representation.

Although the idea that complex representations are built up from simpler representations is very appealing, von der Malsburg was one of the first to point out a fundamental problem with such a scheme (von der Malsburg, 1981). If multiple objects needed to be represented at the same time, there would be no way to unambiguously associate the feature representations comprising one object from those belonging to the other object. Consider the condition where multiple color-selective cells are active when looking at several different colored objects. How does the system know how to ascribe the correct color to the correct object?

The 'superposition catastrophe', as it is called, could be solved, according to von der Malsburg, if there was some mechanism by which neurons representing features belonging to an object were linked (von der Malsburg, 1981). He suggested that the correlated firing of these neurons would be a way to establish such links. Detection of fine temporal synchrony in visual cortex has been a major driving force for continued investigations of this hypothesis (Singer and Gray, 1995). Spikes from different neurons occurring at the same time, or in some regular temporal relationship, could signal that cells belong to the same grouping (Abeles et al., 1993). Despite recent interests in the phenomenon of synchrony, correlated activity amongst cortical neurons has been known for many years. However, these patterns were often dismissed as being a result of shared input from a common anatomical connection (Fetz et al., 1991), and not the reflection of a dynamic process that might signal linking of elementary neural representations. The hypothesis is currently hotly debated (see e.g. recent issue of the journal, *Neuron*, vol. 24, 1, dedicated to binding), and no generally convincing resolution of this argument has been presented. The technical difficulty in simultaneously recording from multiple neurons, the problem of manipulating synchrony and firing rate independently, and the theoretical need for appropriate statistical methods have limited the resolution of the issue. The recent emergence of several multiple neuron recording methods has removed the first barrier and advances in statistical tools have helped with the last of these challenges. Directly manipulating timing in isolation

has been achieved only in invertebrate preparations (Stopfer et al., 1997) and remains a formidable experimental challenge.

In this chapter, we briefly review recent evidence concerning the nature of representations formed from groups of neurons in motor cortex and also draw upon examples from vision and from other systems to illustrate how representations might be coded through higher-order interactions among neuronal groups. We also present some of our recent analytical results which demonstrate that groups of motor cortical neurons carry substantial amounts of information related to motor behavior. As suggested from the discussion above, we will make a formal distinction between population codes which assume that representations involve the collective activity of independently firing neurons and ensemble (or relational) codes which depend on statistical dependencies (such as correlations) among neurons to form a represented variable.

### Population code

From a statistical point of view, a population code is a first-order code because it assumes that information resides in the mean activities of the engaged neurons. The work of Georgopoulos and his colleagues in the motor cortex has clearly demonstrated the power of population codes based on vector averages. This work established that firing rates of primary motor cortex (MI) neurons vary with direction of arm reaching. A cosine describes well the directional tuning of these neurons; the peak of this function defines the preferred direction (PD; i.e. the direction of maximal firing) of the cell (Georgopoulos et al., 1982). However, individual cell firing rates vary considerably from trial to trial (i.e. the variance is larger than the mean) which contributes 'noise' to this form of directional coding (Lee et al., 1998; Maynard et al., 1999). Georgopoulos presented a simple and elegant scheme that relieved this noise problem: averaging the firing rate of individual cells across a population. The decoding algorithm is based upon the population vector average, in which each contributing neuron defines a vector whose direction corresponds to its PD and whose length is proportional to its firing rate on a particular trial. Such a population vector algorithm returns a reli-

able estimate of the actual direction performed. This approach has great appeal because it helps to deal with the apparent noisiness of neurons and averaging is a mechanism that is biologically plausible. Vector averaging has been applied to a variety of systems including the visual system to estimate the orientation of faces (Oram et al., 1998), and in the auditory system to localize a sound source based on intraural time differences (Fitzpatrick et al., 1997).

There are, however, several strong assumptions made by vector-averaged population coding. These include the requirement that each cell has a single-peaked tuning curve and the necessity that the population of neurons have PDs that cover the space of possible directions (or values of any other vector quantity that is represented) uniformly. However, a more fundamental assumption of this method is most relevant to the central thesis of this paper. Namely, the firing rates of the population are assumed to be statistically independent. That is, conditional on a particular movement direction knowing the firing rate of one neuron provides no information about the firing rate of any other neuron in the population. It is this assumption, in fact, which provides this coding scheme with its ability to reduce noise so effectively. Mathematically the variability of the population estimate of direction or any parameter decreases as one over the square root of the number of neurons in the population, if the neurons fire independently. On the other extreme, if the neurons are perfectly correlated, the variability of the population estimate remains constant with the number of neurons (Rieke et al., 1997). That is, nothing is gained by adding more neurons into the decoder because each neuron is providing a redundant estimate of the parameter.

Cells in motor cortex are embedded in a rich matrix of modifiable intrinsic connections (Hess and Donoghue, 1994) and, therefore, on anatomical grounds, it would be unlikely that motor cortical neurons fire independently. Numerous cross-correlation studies in motor cortex show that MI neurons are not statistically independent (Allum et al., 1982; Murphy et al., 1985a,b; Fetz et al., 1991; Hatsopoulos et al., 1998b). If we extend the theoretical arguments made by von der Malsburg to motor cortex, statistical interactions among motor cortical neurons could exist to combine elementary motor representations to generate a coordinated motor action.

## Ensemble codes

Instead of assuming that information resides only in the first-order statistics of neurons (i.e. their mean firing rate), ensemble codes incorporate higher-order interactions among neurons, such as pair-wise correlations. It is immediately apparent that these kinds of codes could provide richer representations and, therefore, additional information unavailable from neurons treated independently. Our decimal system of numeric representation is one simple example of an ensemble code (i.e. given 1 and 2, four numbers are possible, 1, 2, 12, 21; meaning is determined by the relationship of one number to the next as well as by the numbers themselves). Given the seemingly immense representational capacity of the cortex, some form of ensemble code seems likely to overcome the coding limitations of populations of independent neurons.

Our recent work has revealed that pairs of motor cortical neurons engage in correlated discharge on several different time scales (Hatsopoulos et al., 1998a,b; Maynard et al., 1999). Moreover, we have shown that more accurate prediction of movement direction is possible when these correlations are incorporated into a decoding algorithm. Until recently, it has been difficult to investigate the existence of ensemble coding because it required recording simultaneously from large sets of cortical neurons. However, new methods have emerged to allow such recording. These methods include the use of chronically implanted microwires, multiple moveable microelectrodes, and fixed arrays of many electrodes. We have been using a fixed silicon-based array with 100 microelectrodes (Nordhausen et al., 1994) to chronically record extracellular action potentials in behaving primates. Currently, this method makes it possible to monitor up to 50 single sites from a  $10 \times 10$  grid of silicon electrodes each separated by 400  $\mu\text{m}$ . One or more single units can be detected on many of these electrodes. Using this method we have recorded from up to 14 well-isolated units in macaque monkey MI cortex during arm reaching movements in the horizontal plane (Fig. 1). The monkeys have been trained to hold a manipulandum, which controls a position-feedback cursor on a computer monitor, and are instructed to move the cursor from a center target to one of eight peripherally positioned targets (the so-called 'center-out'

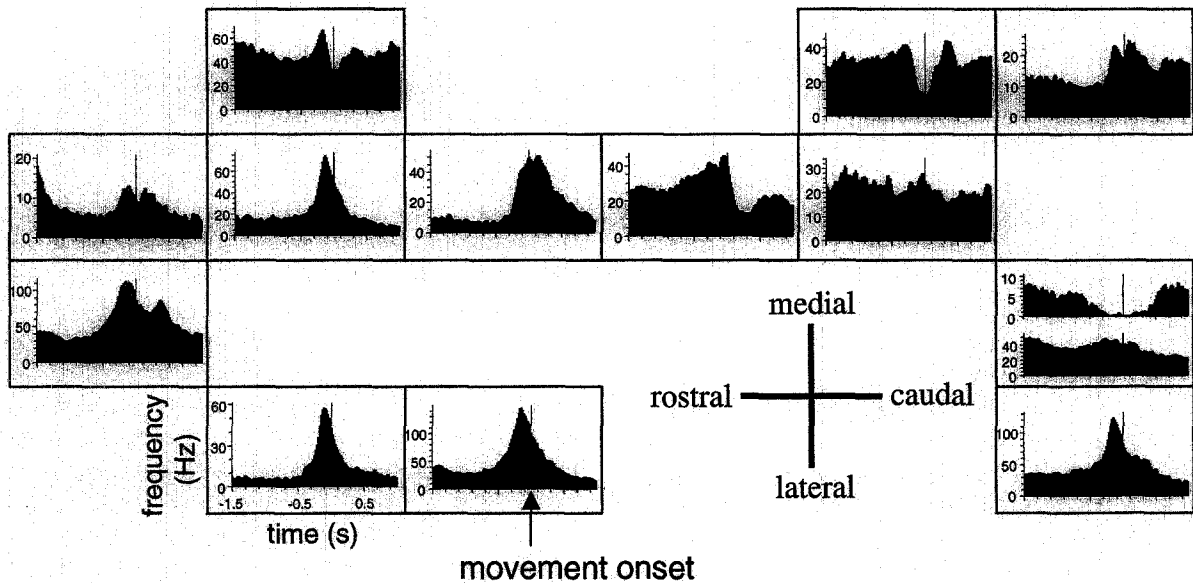


Fig. 1. Diversity of firing patterns across MI during movement. The peri-event time histograms show data from 14 primary motor cortical (MI) neurons recorded simultaneously while a monkey performed leftward reaching movements. The histograms (20 ms bin-width) are based on 150 trials of data aligned on movement onset and have been smoothed. The spatial configuration of the histograms corresponds to the spatial layout of the array cortex; adjacent histograms are separated by 400  $\mu\text{m}$ . Two units have been isolated from one electrode located to the far right.

task used by a number of researchers to examine directional tuning; see Hatsopoulos et al. (1998a) for more details on the behavioral task. Briefly, each trial was composed of three periods: a 500 ms hold period during which time the monkey had to keep the cursor over the center target, a variable (1–1.5 s) instruction period during which one of the eight peripherally positioned targets appeared, and a go period at which time the peripheral target began blinking which signaled to the animal to execute the instructed action. Unless specified otherwise, we will present results using a task with only two possible movement directions: left and right. This simplified version of the center-out task offers the advantage that we were able to collect sufficiently large numbers of trials necessary to use methods that incorporate higher-order statistical interactions within neuronal ensembles.

### Fine temporal synchrony

As others have shown previously, motor cortical neurons often engage in synchronous activity. Using standard cross-correlation techniques, we found that

up to 30% of cell pairs fired synchronously (Hatsopoulos et al., 1998b), meaning that they had a peak in their cross-correlogram centered at 0 ( $\pm 1$  ms). Among those cell pairs, the temporal precision of synchrony defined as the width of the cross-correlation histogram (CCH) peak at half-height was usually between 10–15 ms for the majority of pairs. However, we occasionally observed CCH with very narrow peaks ranging from 1 to 3 ms wide especially when these histograms were built using data from a narrow time window (Fig. 2A). This high temporal precision was particularly remarkable given the large inter-electrode distance that could occur between these neurons (over 1 mm).

Although cross-correlation techniques have been traditionally used to infer anatomical relationships between neurons, our main interest was to investigate the role that synchrony might play in motor representation. Towards this end, we examined the temporal dynamics of the observed synchrony and found that it was not a static property of neuronal pairs but tended to occur around movement onset (Fig. 2B) (Hatsopoulos et al., 1998b). Moreover, the strength of synchronous discharge varied not only with time

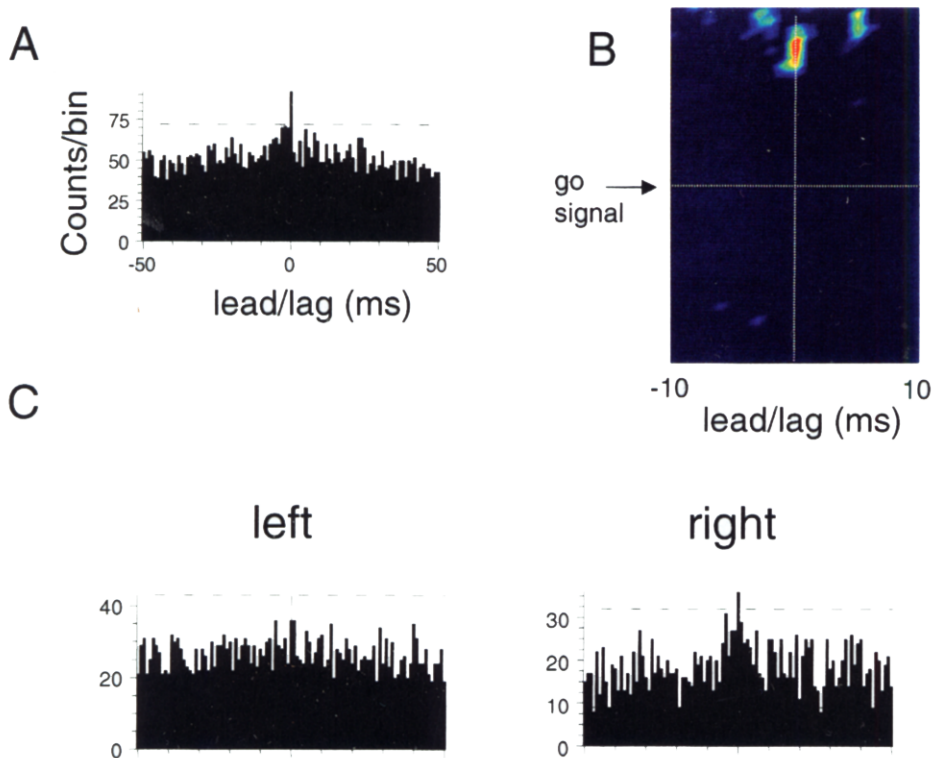


Fig. 2. Synchronous discharge between MI neurons during arm movements. (A) Significant synchrony between two MI neurons can occur on a millisecond time scale. This figure shows the cross-correlation histogram (1 ms bin-width) between two neurons; the correlogram plots the number of spikes occurring in one neuron (the target neuron) relative to all spikes in another neuron (the reference neuron) and using data from a 400 ms period straddled around movement onset. (B) Synchrony is a dynamic property of neuron pairs. This plots the cross-correlogram (1 ms bin-width) between two neurons which measures the magnitude of coincident spikes at different leads and lags and as a function of time across the trial. The color code ranges from dark blue which represents non-significant coincidence rates to bright red which reflects significant coincident rates ( $P < 0.01$ ; see Abeles (1982) for significance test). (C) Synchrony varies with movement direction. Note the presence of a correlation peak only for the rightward direction. The cross-correlogram is from one pair of MI neurons for left and right movements based on 400 ms period around the signal instructing the animal to initiate the movement.

but also with movement direction (Fig. 2C). This strongly suggested that synchrony might actually carry information about the direction of the arm movement. Using an information-theoretic analysis, we found that directional information was available in the synchronous spikes between simultaneously recorded neurons and that the amount of information increased near movement onset. However, as is true of most MI neurons, firing rates modulate either up or down around movement onset. The number of synchronous spikes will likewise modulate up or down around movement onset, simply as a consequence of these rate changes, even if the two cells are conditionally independent. To account for this confounding factor, we estimated the information

available from synchronous spikes after shuffling the trial order of one of the neurons relative to the other. This shuffling technique removed the trial-specific synchrony but preserved the synchrony that was due to common rate modulation. By shuffling multiple times we could estimate the distribution of information available from synchrony, assuming that the two neurons fired independently. These data allowed a statistical test of the amount of synchrony. We found that 45% of cell pairs carried directional information in their synchronous discharge (defined on 1 ms time scale) around movement onset beyond that available from chance coincidences. This does not imply, however, that synchronous spikes provide additional directional information *beyond* that available

from the firing rates of the two constituent neurons. In fact, preliminary results suggest the information available from synchrony is redundant with that of the rates of the two neurons (Oram et al., 2001). Of course, these results cannot resolve whether firing rate modulation of single cells or synchronous discharge between neurons is a code that is actually being used by the cortex to represent or drive motor behavior. These results do imply, however, that synchrony is an independent information channel distinct from that based on coincident spikes of independently firing neurons of single neurons.

### Spike count covariance

In addition to synchrony measured on a relatively fine time scale, correlated activity occurs on the tens

and hundreds of millisecond time scale. That is, the number of spikes counted in a large time window from one neuron covaries with that from another neuron if measured repeatedly over different trials (Fig. 3A). This broad spike covariance has been observed in many different cortical areas besides motor cortex including visual cortex (van Kan et al., 1985; van der Togt et al., 1998), infero-temporal cortex (Gochin et al., 1991; Gawne and Richmond, 1993), and medial temporal cortex (Zohary et al., 1994). It has been considered to be a nuisance variable for population coding schemes because they require that spike count variability or 'noise' across the neuronal population is independent in order to wash away its effects on parameter estimation. Although this form of correlation is observed by many researchers, it has largely been dismissed as being insignificant espe-

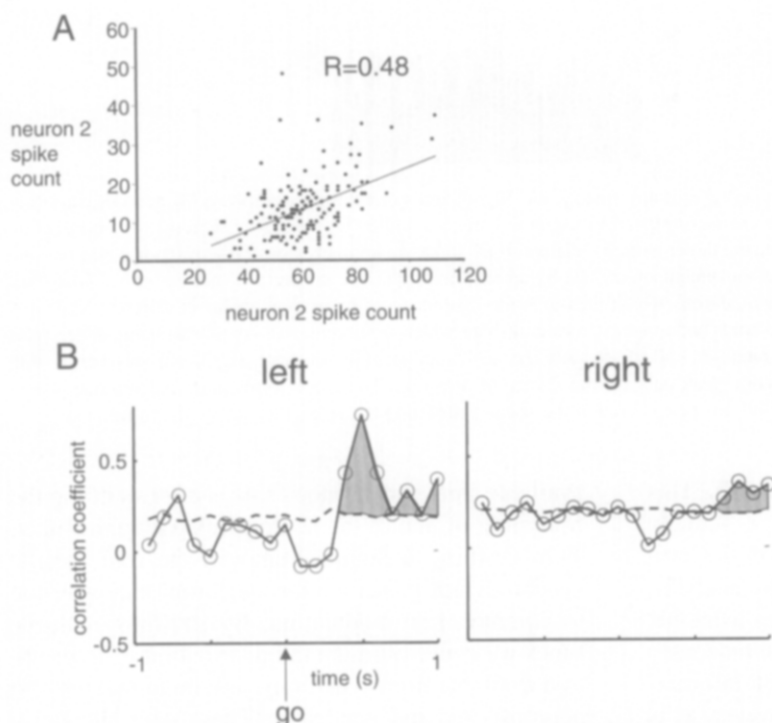


Fig. 3. Pairs of MI neurons engage in correlated activity on a broad time scale. (A) Scatter plot of the number of spikes generated by one neuron relative to another neuron measured in a 500 ms period after movement onset. Each point in the scatter plot represents a different trial. The plot demonstrates that the spike counts between the two neurons are significantly correlated ( $P < 0.01$ ). (B) Correlations vary dynamically over time. These plots show that the Fisher  $z$ -transform of the correlation coefficient between the spike counts of two neurons computed for 100 ms intervals is plotted as a function of time relative to the go signal for movement to the left and to the right. The dashed line corresponds to 2.33 standard deviations above the mean of 50 correlation coefficients ( $z$ -transformed), computed by randomly shuffling the trial order of one of the neurons relative to the other. Therefore, the dashed line approximates the 99% significance level. That is, correlation coefficients above the dashed line are significantly different from zero at the 1% level.

cially at large inter-electrode distances (Lee et al., 1998). Lee and colleagues showed that this broad correlation is more strongly related to the similarity of the preferred directions of the cells at small inter-electrode distances but did not directly demonstrate that the correlation strength decreases with distance. Our results suggest that the strength of covariation in motor cortex remains relatively constant with inter-electrode distance (Maynard et al., 1999).

Recent theoretical studies have shown that broad correlations can improve neural discrimination of different stimuli or behaviors (Oram et al., 1998). Using more sophisticated statistical models incorporating the observed covariance between neurons in a population, we were the first to demonstrate using simultaneously recorded unit data that estimation of movement direction can be improved (Maynard et al., 1999). While others have computed single estimates of spike count correlation across all experimental conditions (Gawne and Richmond, 1993; Zohary et al., 1994; Lee et al., 1998), we measured the spike count correlation between neurons separately for each movement direction. We found that the correlation strength varies in time and with movement direction (Fig. 3B) and contributes to the improved directional estimation.

To demonstrate the contribution that correlated activity makes in direction estimation, we tried to predict movement direction from single trials of multi-neuron data. We used a simple maximum-likelihood classifier to assign individual trials of data into different directional classes. We used a Gaussian model to fit the observed number of spikes measured in a time window anchored to one of several stimulus or behavioral events: the instruction signal, the go signal, movement onset, and end of movement. The window anchoring time represented the end of the window and not the middle. This convention was adopted because neural activity in motor cortex generally precedes movement onset and, therefore, is assumed to predict motor behavior in the future. For single neurons, two parameters had to be estimated: the mean and the variance of the number of spikes. For a population of  $N$  neurons, we had to estimate a mean vector of length  $N$  and a covariance matrix of size  $N \times N$ . By creating a separate model for each movement direction, we could estimate the likelihood of observing a particular number

of spike counts on a single trial given each model, and assigning that trial to the class with the largest likelihood. To avoid overfitting, we cross-validated the classification by leaving one trial of data out for testing and estimating the model parameters on the remaining set of data.

The results of this classification procedure demonstrate a number of important points with regard to neural representations in motor cortex, specifically, and to cortical coding in cortex, in general. First, the performance of classifier using an 8 neuron ensemble (thick solid line, Fig. 4) is better than the single best neuron (thin solid line, Fig. 4). Note that at every time point the performance of the best of the 8 neurons is plotted even if different neurons are best at different times. The ensemble classifies nearly perfectly (i.e. 100% correct classification) near the end of the reaction time period which corresponds to about 300–400 ms after the go signal. Although the single best neuron can perform quite well and considerably better than many other neurons in the population, the neural ensemble almost always provides more predictive power. Thus, the performance of the neural ensemble cannot be accounted for by the most sensitive neuron in the recorded population, which suggests that Barlow's 'lower envelope' principle may not hold in this case (Barlow, 1972). In Fig. 5A, the mean performance over all possible subsets of  $N$  neurons is plotted as  $N$  increases. The performance of the classifier increases monotonically as the number of cells in the ensemble increases. This monotonic function is shown more clearly in Fig. 5B where the classifier's performance based on a 300 ms period after the onset of the go signal is plotted versus the number of cells.

Second, the ability to reliably predict the movement direction can occur quite early during the trial (see Fig. 4, left most panel). As early as 300 ms (i.e. 100 ms to 300 ms given a 200 ms integration window) after the onset of the instruction signal, one can predict the movement direction with 70% accuracy compared to chance performance of 50%. This period of time is over 1000 ms before the movement is executed. Thus, MI neurons are not simply 'upper motor neurons' that execute a command that is planned somewhere else in the brain. It is also noteworthy that the classifier's performance increases



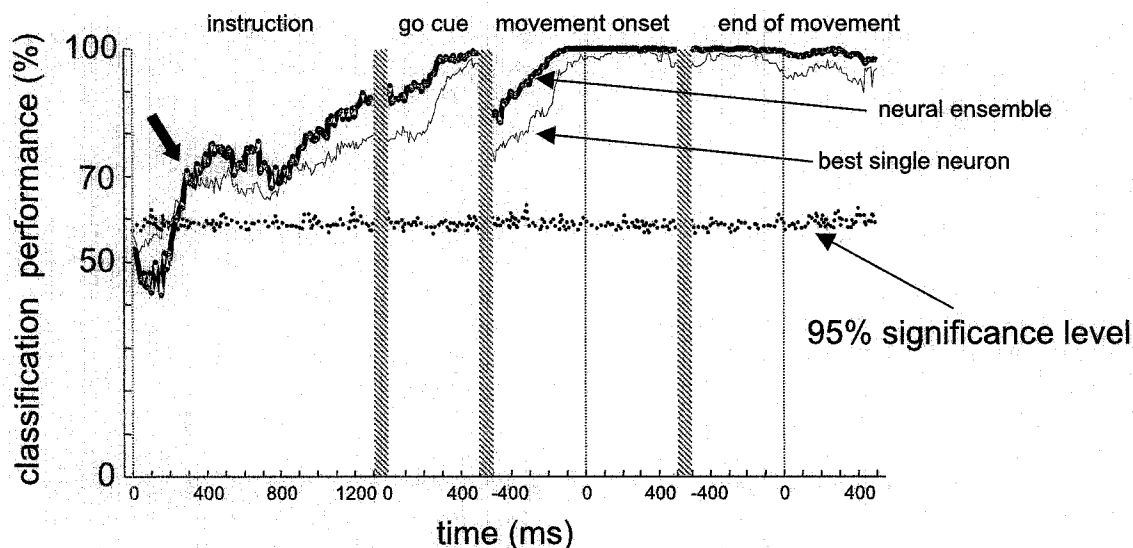


Fig. 4. Performance of the maximum-likelihood classifier on single-trial data from a two-direction (left/right) movement task. The thick solid line plots the performance of the classifier based on cross-validated data aligned on different stimulus or behavioral events: instruction signal, go cue, movement onset, and end of movement. At each time point, the classifier's performance is based on the number of spikes in each neuron in a 200 ms period ending at that time point. By comparison, the thin solid line plots the performance of the single neuron that classifies direction best at each time point. Note that each point on the solid line does not necessarily represent the same neuron. The dotted line is the 95% significance level based on the classifier's maximum performance from 59 shuffles in which each trial's direction label is randomly assigned to another trial. Thus, values exceeding this level are significantly different from chance at the 5% level. The arrow indicates that both the ensemble and the single best neuron can predict the movement direction with about 70% accuracy as early as 300 ms after the instruction signal.

sharply from 200 to 300 ms after the onset of the instruction signal. It then almost levels off until 800 ms after the instruction onset at which time it begins to increase steadily again.

Third, the fact that prediction can be quite good even using very small integration time windows calls into question the sharp distinction between rate coding versus temporal coding that is often posited in the literature (Fig. 6). Even at a peak rate of 150 Hz around movement onset, an integration window of only 10 ms will contain only about 1 to 2 spikes. Although direction prediction reaches a peak of about 85% for 8 cells, it is important to note that many more neurons are active during such a task, and, therefore, it may not be unreasonable to assume that direction estimation could be nearly perfect using only the presence or absence of a single spike across a population.

Fourth, the ability to predict movement direction on a single-trial basis is improved if the spike count correlations between neurons are incorporated into the statistical models used to decode the neural data.

We have shown that classification in an 8-direction task improves by 3% to 19% (average of 11% over all data sets) when the pair-wise correlations are taken into account (Maynard et al., 1999). In that study, we did not use a maximum-likelihood classifier when considering the complete neuronal ensemble but rather implemented a Monte Carlo technique to simulate data with the pair-wise correlations observed in the real data and used a nearest-neighbor classifier. In the two-direction task (left or 180°/right or 0°) that we examine here, we found no statistical difference in classification performance between the maximum-likelihood classifier that incorporated the correlations versus the same classifier that ignored these correlations. This is not surprising given the fact that the individual spike rates of the population differ so markedly between opposite movement direction. In fact, the performance of the classifier becomes perfect (i.e. 100%) after movement onset when all 8 neurons are included (see Fig. 4). This ceiling effect prevents other statistical parameters such as correlation to improve performance: no fur-



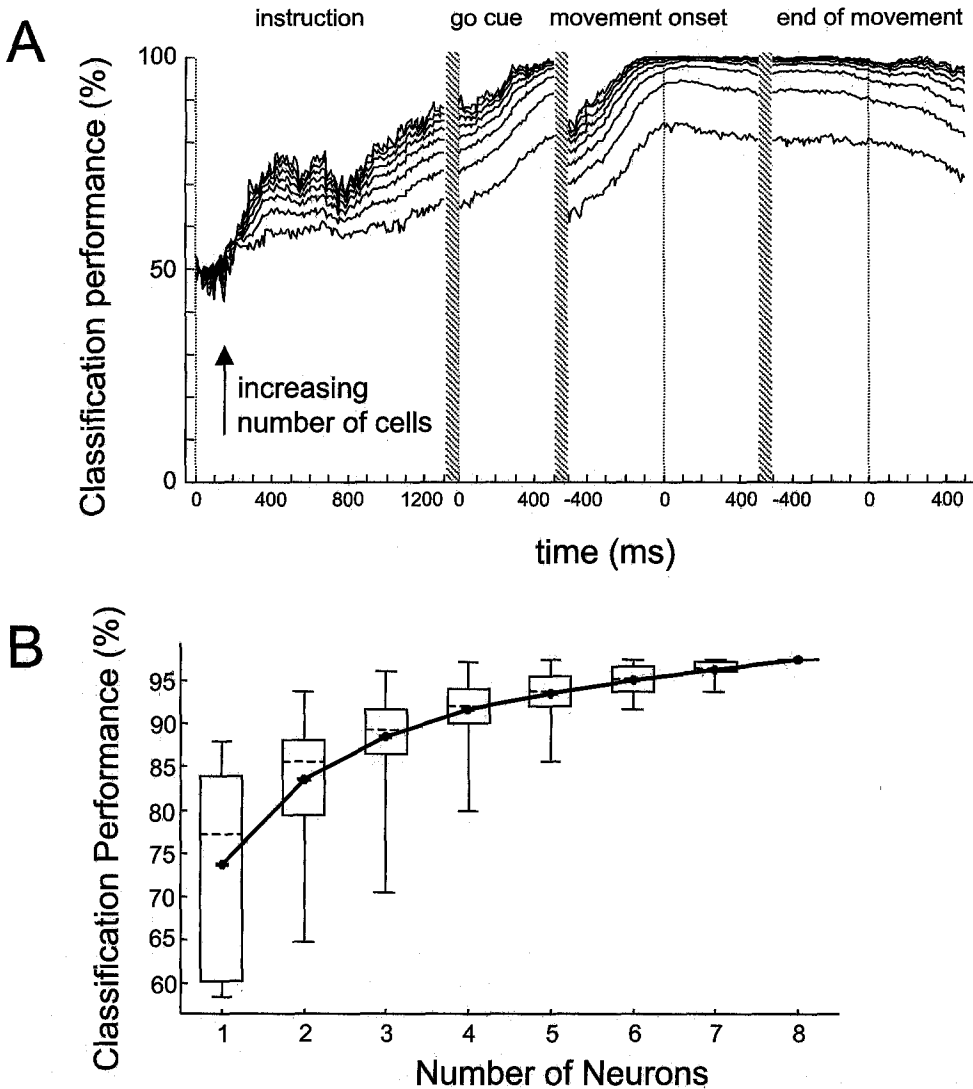


Fig. 5. The maximum-likelihood classifier's performance improves as more neurons are added into the ensemble. (A) The classifier's performance is plotted in time (based on the number of spikes in a 200 ms period) averaged over all subsets of  $N$  neurons from 1 to 8. (B) The classifier's performance based on a 300 ms period after the go signal as a function of the number of neurons. The black line connects the mean performance averaged over all subsets of neurons as the number of neurons in the subset increases. The dashed horizontal lines represent the median performance, and the boxes span the range from the 1st to the 3rd quartile. The 'error-bars' represent the full range of performance values.

ther information can be added by a new measure if it is fully specified by the original one. However, by examining data that were collected using two directions that differ by only  $45^\circ$ , we were able to observe improved classification when the pairwise correlations were included. Fig. 7 compares the performance of the 2-neuron classifier using a

600 ms integration window when the correlations are included (solid line) versus when the correlations are ignored (dashed line). Notice how the classifier performs better (gray region) when the spike count covariations are included from 200 ms after movement onset (i.e.  $-400$  ms to  $+200$  ms) to 500 ms (i.e.  $-100$  ms to  $+500$  ms).

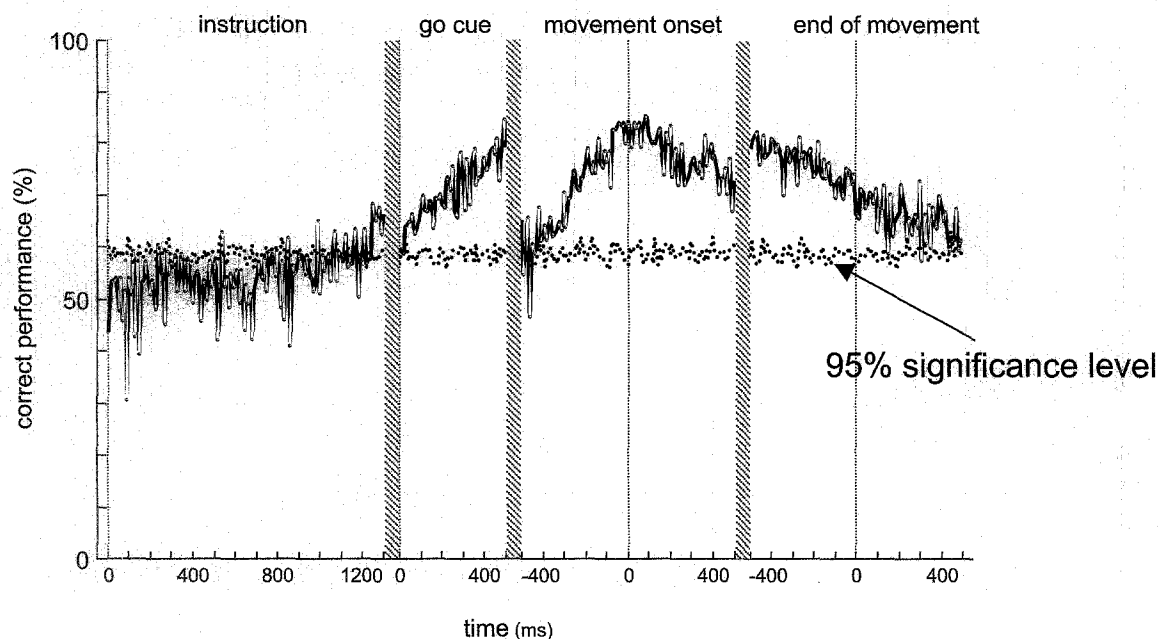


Fig. 6. Classification success for small numbers of spikes. The plot shows the performance of a maximum-likelihood classifier on single-trial data from a two-direction (left/right) movement task. The analysis is the same as in Fig. 4, using all 8 neurons, but here the integration window is only 10 ms instead of 200 ms wide. Performance reaches a maximum of  $\sim 85\%$  at around movement onset. In such a narrow integration window, motor cortical neurons may fire only one or two spikes. A decoding scheme based on the presence or absence of a single spike across a population of neurons can predict movement direction quite well, and, therefore, the assumption that rate codes require large integration windows may not be well founded.

## Conclusion

Large groups of cortical neurons are simultaneously active when a stimulus is perceived or a motor act is planned and executed. The fact that nearly all units from which we recorded, using an immovable, chronically implanted array in motor cortex, modulated their activity during execution of a simple reaching movement attests to the idea that a very large number of neurons participate in even the simplest of behaviors. What is less clear is whether the statistical interactions among these neurons participate in perceptual and motor representations that are used by the nervous system to drive perception or guide behavior. Population decoding strategies such as the population vector algorithm assume that neurons are noisy but independent encoders. These types of decoding algorithms have demonstrated that pooling the noisy signals from many neurons can reduce the detrimental effects of noise and can predict the direction of movement quite reliably. However, what has been termed 'noise' is actually correlated

and carries information. We have tried to extend the idea of a first-order population code by taking into account higher-order relationships between neurons as well as their mean firing rates. By recording from multiple neurons simultaneously, we have found that neurons are not independent encoders of movement direction. They exhibit statistical dependencies on both a fine time scale (i.e. synchrony) and a broad time scale (i.e. spike count covariations). By incorporating these correlations into our statistical coding and decoding schemes, we have shown that they are not necessarily detrimental to decoding movement direction but can improve our predictive power.

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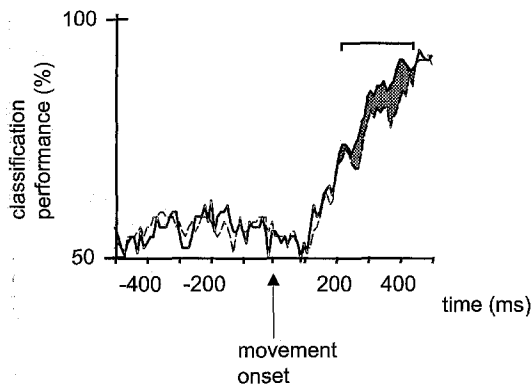


Fig. 7. Higher-order codes may optimize separation of similar activity patterns. This figure plots the classification rate for two movements that are close to the same directions ( $45^\circ$  apart). The performance of the classifier is stronger after movement onset when the 2nd-order interactions among the neurons are explicitly included in the classifier's statistical models (see bracket; gray shading). The solid line is generated by the maximum-likelihood classifier described in the paper. The dashed line is generated in the same manner except that the covariances are forced to zero, i.e. the neurons are assumed to be conditionally independent given the movement direction. A 600 ms integration window was used.

## References

- Abeles, M. (1982) Quantification, smoothing, and confidence limits for single-units' histograms. *J. Neurosci. Methods*, 5: 317–325.
- Abeles, M., Bergman, H., Margalit, E. and Vaadia, E. (1993) Spatiotemporal firing patterns in the frontal cortex of behaving monkeys. *J. Neurophysiol.*, 70: 1629–1638.
- Allum, J.H.J., Hepp-Reymond, M.C. and Gysin, R. (1982) Cross-correlation analysis of interneuronal connectivity in the motor cortex of the monkey. *Brain Res.*, 231: 325–334.
- Barlow, H.B. (1972) Single units and sensation: A neuron doctrine for perceptual psychology. *Perception*, 1: 371–394.
- Bienenstock, E. and Geman, S. (1995) Compositionality in neural systems. In: M. Arbib (Ed.), *The Handbook of Brain Theory and Neural Networks*. Bradford Books/MIT Press, Cambridge, MA, pp. 223–226.
- Fetz, E.E., Toyama, K. and Smith, W. (1991) Synaptic interactions between cortical neurons. In: A. Peters and E.G. Jones (Eds.), *Cerebral Cortex*. Plenum, New York, pp. 1–80.
- Fitzpatrick, D.C., Batra, R., Stanford, T.R. and Kuwada, S. (1997) A neuronal population code for sound localization. *Nature*, 388: 871–874.
- Gawne, T.J. and Richmond, B.J. (1993) How independent are the messages carried by adjacent inferior temporal cortical neurons? *J. Neurosci.*, 13: 2758–2771.
- Georgopoulos, A.P., Kalaska, J.F., Caminiti, R. and Massey, J.T. (1982) On the relations between the direction of two-dimensional arm movements and cell discharge in primate motor cortex. *J. Neurosci.*, 2: 1527–1537.
- Gochin, P.M., Miller, E.K., Gross, C.G. and Gerstein, G.L. (1991) Functional interactions among neurons in inferior temporal cortex of the awake macaque. *Exp. Brain Res.*, 84: 505–516.
- Hatsopoulos, N.G., Ojakangas, C.L., Maynard, E.M. and Donoghue, J.P. (1998a) Detection and identification of ensemble codes in motor cortex. In: H. Eichenbaum and J. Davis (Eds.), *Neuronal Ensembles: Strategies for Recording and Decoding*. Wiley, New York, pp. 161–175.
- Hatsopoulos, N.G., Ojakangas, C.L., Paniniski, L. and Donoghue, J.P. (1998b) Information about movement direction obtained from synchronous activity of motor cortical neurons. *Proc. Natl. Acad. Sci.*, 95: 15706–15711.
- Hess, G. and Donoghue, J.P. (1994) Long-term potentiation of horizontal connections provides a mechanism to reorganize cortical motor maps. *J. Neurophysiol.*, 71: 2543–2547.
- Kakei, S., Hoffman, D.S. and Strick, P.L. (1999) Muscle and movement representations in the primary motor cortex. *Science*, 285: 2136–2139.
- Lee, D., Port, N.L., Kruse, W. and Georgopoulos, A.P. (1998) Variability and correlated noise in the discharge of neurons in motor and parietal areas of the primate cortex. *J. Neurosci.*, 18: 1161–1170.
- Maynard, E.M., Hatsopoulos, N.G., Ojakangas, C.L., Acuna, B.D., Sanes, J.N., Normann, R.A. and Donoghue, J.P. (1999) Neuronal interactions improve cortical population coding of movement direction. *J. Neurosci.*, 19: 8083–8093.
- Murphy, J.T., Kwan, H.C. and Wong, Y.C. (1985a) Cross correlation studies in primate motor cortex: Event related correlation. *Can. J. Neurol. Sci.*, 12: 24–30.
- Murphy, J.T., Kwan, H.C. and Wong, Y.C. (1985b) Cross correlation studies in primate motor cortex: Synaptic interactions and shared input. *Can. J. Neurol. Sci.*, 12: 11–23.
- Nordhausen, C.T., Rousche, P.J. and Normann, R.A. (1994) Optimizing recording capabilities of the Utah intracortical electrode array. *Brain Res.*, 637: 27–36.
- Oram, M.W., Foldiak, P., Perrett, D.I. and Sengpiel, F. (1998) The 'ideal homunculus': decoding neural population signals. *Trends Neurosci.*, 21: 259–265.
- Oram, M.W., Hatsopoulos, N.G., Richmond, B.J. and Donoghue, J.P. (2001) Synchrony in motor cortical neurons provides direction information that is redundant with the information from coarse temporal response measures. (Submitted for publication.)
- Parker, A.J. and Newsome, W.T. (1998) Sense and the single neuron: Probing the physiology of perception. *Annu. Rev. Neurosci.*, 21: 227–277.
- Rieke, F., Warland, D., de Ruyter van Steveninck, R. and Bialek, W. (1997) *Spikes: Exploring the Neural Code*. MIT Press, Cambridge, MA.
- Sanes, J.N., Donoghue, J.P., Thangaraj, V., Edelman, R.R. and Warach, S. (1995) Shared neural substrates controlling hand movements in human motor cortex. *Science*, 268: 1775–1777.

- Schieber, M.H. and Hibbard, L.S. (1993) How somatotopic is the motor cortex hand area? *Science*, 261: 489–492.
- Singer, W. and Gray, C.M. (1995) Visual feature integration and the temporal correlation hypothesis. *Annu. Rev. Neurosci.*, 18: 555–586.
- Stopfer, M., Bhagavan, S., Smith, B.H. and Laurent, G. (1997) Impaired odour discrimination on desynchronization of odour-encoding neuronal assemblies. *Nature*, 390: 70–74.
- Van der Togt, C., Lamme, V.A. and Spekreijse, H. (1998) Functional connectivity within the visual cortex of the rat shows state changes. *Eur. J. Neurosci.*, 10: 1490–1507.
- Van Kan, P.L.E., Scobey, R.P. and Gabor, A.J. (1985) Response covariance in cat visual cortex. *Exp. Brain Res.*, 60: 559–563.
- Von der Malsburg, C. (1981) *The Correlational Theory of Brain Function*. Max Planck Institute for Biophysical Chemistry, Göttingen.
- Zohary, E., Shadlen, M.N. and Newsome, W.T. (1994) Correlated neuronal discharge rate and its implications for psychophysical performance. *Nature*, 370, 140–143.