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A framework for relating neural activity to freely moving behavior

Justin D. Foster, *Student Member, IEEE*, Paul Nuyujukian, *Student Member, IEEE*,
Oren Freifeld, *Student Member, IEEE*, Stephen I. Ryu, Michael J. Black*, *Senior Member, IEEE*,
Krishna V. Shenoy*, *Senior Member, IEEE*

***Abstract*— Two research communities, motor systems neuroscience and motor prosthetics, examine the relationship between neural activity in the motor cortex and movement. The former community aims to understand how the brain controls and generates movement; the latter community focuses on how to decode neural activity as control signals for a prosthetic cursor or limb. Both have made progress toward understanding the relationship between neural activity in the motor cortex and behavior. However, these findings are tested using animal models in an environment that constrains behavior to simple, limited movements. These experiments show that, in constrained settings, simple reaching motions can be decoded from small populations of spiking neurons. It is unclear whether these findings hold for more complex, full-body behaviors in unconstrained settings. Here we present the results of freely-moving behavioral experiments from a monkey with simultaneous intracortical recording. We investigated neural firing rates while the monkey performed various tasks such as walking on a treadmill, reaching for food, and sitting idly. We show that even in such an unconstrained and varied context, neural firing rates are well tuned to behavior, supporting findings of basic neuroscience. Further, we demonstrate that the various behavioral tasks can be reliably classified with over 95% accuracy, illustrating the viability of decoding techniques despite significant variation and environmental distractions associated with unconstrained behavior. Such encouraging results hint at potential utility of the freely-moving experimental paradigm.**

I. INTRODUCTION

A goal of motor systems neuroscience is to explain how cortical areas involved in movement control behavior. Extensive studies over the past several decades in monkeys have developed many models of motor behavior [1], [2], [3], [4]. These findings have fostered the development of translational work in brain-machine interfaces (BMIs). Such systems aim to decipher cortical activity into meaningful control signals such as computer cursors or robotic limbs [5], [6], [7], [8], [9], [10], [11]. Both bodies of research have led to many insights and show great promise, however a fundamental limitation is their applicability to less constrained movements. It is unclear whether neuroscientific findings and BMIs will generalize beyond the limited subset of behaviors tested experimentally. Investigations into such generalizations were hampered by the lack of experimental tools and techniques, limiting research to the restrictive, but highly controlled environment of neuroelectrophysiological experimental rigs. Only in such setups could accurate measurements of behavioral kinematics and neurophysiological activity be taken. However, with the continued evolution of wirelessly transmitting neural recording amplifiers and computer vision technology, preliminary research with unconstrained animal models may be possible [12], [13], [14], [15]. In this study we aim to show that basic motor systems neuroscientific findings of neurally tuned behavior are consistent in unconstrained behavior in one monkey. Further, we show preliminary evidence that general types of behavior can be differentiated and decoded quite accurately despite the lack of rigid behavioral restrictions. Both findings are important so that we may 1) verify the applicability of in-rig results to broader domains of behavior and 2) have confidence that BMIs may successfully translate to complex use cases such as ambulatory patients.

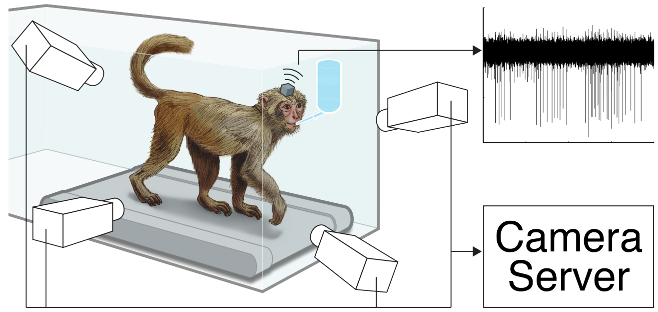

Fig. 1. **System overview.** Unconstrained behavior of a monkey is recorded synchronously with video streams while broadband neural activity is recorded and transmitted wirelessly.

*These authors contributed equally.

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J. D. Foster is with the Department of Electrical Engineering, Stanford University, Stanford, CA 94305 USA justinf@stanford.edu

P. Nuyujukian is with Bioengineering and Stanford Medical School, Stanford University, Stanford, CA 94305 USA paul@npl.stanford.edu

O. Freifeld is with the Division of Applied Mathematics, Brown University, Providence, RI 02912 USA freifeld@dam.brown.edu

S. Ryu is with the Department of Neurosurgery, Palo Alto Medical Foundation, Palo Alto, CA 94301 USA seoulman@stanford.edu

M. J. Black is with the Max Planck Institute for Intelligent Systems, 72076 Tübingen, Germany and the Department of Computer Science, Brown University, Providence, RI 02912 USA black@is.mpg.de

K. V. Shenoy is with the Departments of Electrical Engineering, Bioengineering, and Neurobiology, and the Neurosciences Program, Stanford University, Stanford, CA, 94305 USA shenoy@stanford.edu

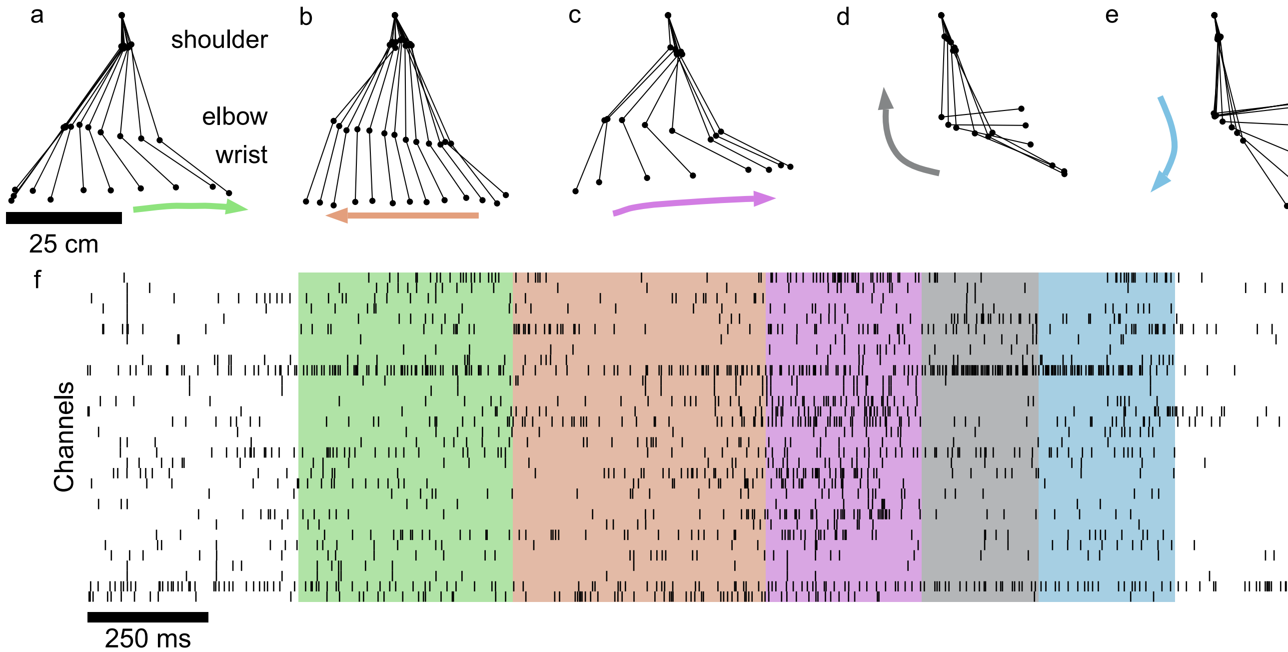

Fig. 2. **Behavior and spike raster.** Behavior was measured from 8 camera views as the monkey performed complex coordinated movements. Location of the wrist, elbow, and shoulder (contralateral to implant) are triangulated from video frames as the monkey moves through **a** the swing phase and **b** the stance phase of walking, **c** reaches for food, **d** brings food to his mouth, and **e** drops his arm down. Simultaneously, broadband neural activity was recorded from PMd. **f** Neural spiking from 32 channels is plotted with the behavior epochs highlighted.

II. Experimental Setup

A. Behavioral Task

All protocols were approved by the Stanford University Institutional Animal Care and Use Committee. We trained an adult male rhesus macaque (Monkey I) to walk on a treadmill at speeds ranging from 2.0 kph to 3.5 kph as shown in Fig. 1. Each session lasted approximately 10 minutes and was divided into blocks where the monkey walked continuously for up to 2 minutes before a break. During the break, the monkey reached for food at the front of the environment. In some blocks, labeled 'walk-reach' blocks, food was presented at the front of the environment while the animal was walking. After taking a step, the monkey would reach out with his right arm to grab food, put it in his mouth, and then continue walking. An example trajectory is presented in Fig. 2**a**-**e**. This study comprises one day's session (I120130) where the monkey walked at speeds ranging from 2.0-3.5 kph for 4 walking blocks and 2 'walk-reach' blocks.

B. Video Capture

Video was captured at 24 fps at a resolution of 1624×1224 pixels using eight Point Grey Grasshopper GRAS-20S4M/C cameras. These cameras were placed around the workspace of the monkey at various positions to capture multiple angles of view. Image acquisition and export was performed using a 4DViews 2DX Multi-Camera system.

C. Neural Recording

Monkey I was implanted with a 96-channel multielectrode array (Blackrock Microsystems, Salt Lake City, UT) implanted in dorsal premotor cortex (PMd) as determined by visual anatomical landmarks. Broadband neural activity on 32 electrodes was sampled at 30 kSamples/s and transmitted wirelessly using the HermesD system [13]. An OrangeTree ZestET1 FPGA was programmed to package the HermesD output datastream into a UDP Ethernet packet stream, which was saved to disk. In addition, the ZestET1 was programmed to record times when video frames were captured by listening to the video camera synchronization line. We tested the synchronization by illuminating distinct patterns on 4 LEDs visible in multiple camera views to guarantee accuracy between neural recordings and video frames. Thus, synchronization between the neural and video data streams was accurate to within +/-5 ms.

D. Neural Data Processing

Each channel of neural recordings was filtered with a zero-phase highpass filter to remove the local field potential (LFP), since LFP is not the focus of the present study. Specifically, a fourth order Butterworth filter with cutoff frequency of 250 Hz was used forward and reverse to ensure zero phase delay. Spike timing was determined with a single threshold. Points where the signal dropped below -4.0$\times$ the RMS value of the channel were spike candidates. Occasional artifacts, likely due to static discharge, were automatically rejected from the candidate spike set based on the shape and magnitude of the signal near the threshold crossing point.

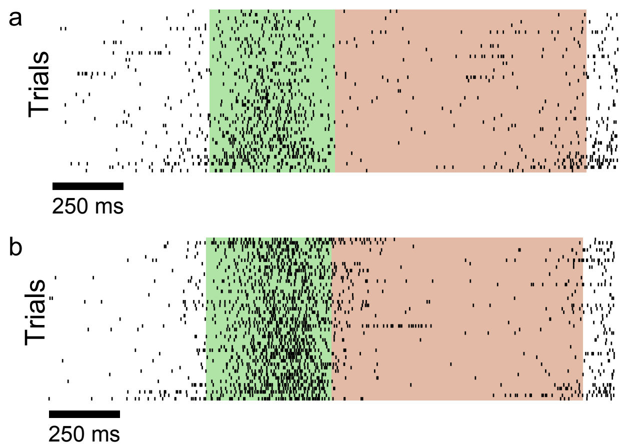

Fig. 3. **Modulation of neural activity during phases of walking.** Spike rasters of approximately 50 trials for two channels during the swing phase (green) and stance phase (orange). **a** Channel 7 **b** Channel 32

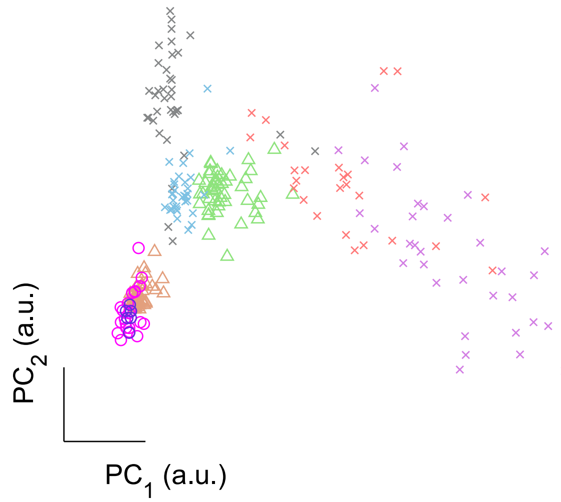

Fig. 4. **PCA plot of average firing rates.** Plot of epoch average firing rate categorized by behavior. Triangles represent walking epochs (swing phase in green, stance phase in orange), X's represent epochs reaching for food (reaching to food while sitting in pink, reaching to food while walking in red, bring food to mouth in gray, and returning his hand to the floor in blue), and circles represent idle epochs (sitting idly in pink and standing idly in purple).

III. Behavior Analysis

A. Hand-Tagged Kinematics

Kinematics were extracted from the recorded video manually via frame-by-frame analysis. A custom-written Python GUI was used to facilitate tagging of points and visualizing their location across all cameras. Four points were tagged on each frame of interest, as shown in Fig. 2. Ascending up the arm, these were: wrist, elbow, shoulder, and a reference point on the spine. These kinematics were linked at the spinal reference point to form the final kinematic profile.

B. Behavioral Epoch Tagging

Freely-moving behavior, and in particular walking, has no inherent trial structure. Therefore, to segment the neural data to make it amenable for subsequent analysis, an artificial trial structure was imposed on the behavioral data to label epochs of time that were similar across the recorded datasets. Eight distinct behavioral epochs were labeled in a frame-by-frame manner using a custom written Matlab GUI. Two of the epochs were related to the position of the right arm during walking: the swing phase (Fig. 2a) and the stance phase (Fig. 2b). Four epochs were related to acquisition of food: reaching for food while sitting, reaching for food while walking (Fig 2c), bringing food to mouth while sitting (similar to Fig. 2d), returning hand to floor while sitting (similar to Fig. 2e). Two epochs were related to idle times–one sitting and one standing. A total of 252 epochs were classified into one of the aforementioned eight categories. The corresponding times in the neural data were then pulled and assembled into their behavioral category, forming the basis of the trial structure (as shown in Fig. 2f) used for the subsequent analysis.

IV. Results

A. Behavioral Tuning

With the tagged epochs of behavior where the monkey was walking, the neural data was aligned at the swing-stance phase transition. Two channels of neural activity at this transition time are shown in Fig. 3. Note that for both depicted channels, neural firing rates increase during the swing phase and are relatively less active during the stance phase. The swing and stance phase across all channels was compared using a two sample t-test, and in 25 of the 32 channels there was a statistically significant difference ($p < 0.001$) in the firing rate of that channel between these epochs. This finding suggests that many of the channels in PMd are well tuned and modulated with walking activity.

B. Epoch Decoding

Having demonstrated neural tuning across epochs of walking, we next explored whether it was possible to differentiate among these eight categories using decoding techniques. To gain insight into the structure of the epoch firing rate, principal component analysis (PCA) was performed on the data. Fig. 4 plots the average firing rate of each epoch along its first two principle components. Significant clustering by epoch categories can be seen by visual inspection. This clustering suggests that decoding epoch categories may be possible. To decode, we used regularized discriminant analysis [16]. The neural data was regularized and fit to a multivariate Gaussian. Decoding was performed using maximum likelihood and leave-one-out cross-validation with a classification accuracy of 96%. The success of classifying and differentiating these categories suggests that real-time decoding of behavior may be possible.

V. Discussion

The results shown in the previous section highlight a few examples in which the freely-moving experimental model is useful for verifying generalizability. The segmentation of the walking trials along phases of movement revealed strong motion tuning, demonstrating that despite the lack of rigid constraints, such principles still appear to hold true. This supports the findings of basic motor systems neuroscience and suggests that despite the limitations of task conditions, the constrained experimental environment can uncover generalizable mechanisms.

Similarly, the success of decoding among the behavioral epochs despite significant postural variability, environmental distractions, or lack of controlled repeatable trial conditions, strongly support the applicability of decoding techniques to the freely-moving environment. This is rather surprising as there were no controls or enforcements of posture or position. Any of the aforementioned factors could have led to failure of decoding epochs due to contamination of the neural activity with aberrant and uncorrelated firing, yet the decoder was robust to such variability. This success holds promise for the translation of BMIs to the more generalized context where they will have to perform well under more strenuous conditions–where the neural signal may be masked by neural noise stemming from environmental demands.

The ability to perform experiments similar to those conducted in more traditional neuroelectrophysiological setups in the freely-moving context is a step towards an animal model that most closely resembles human behavior. These experimental techniques are exciting as they may aid in finding neuroscientific truths about the basis of generalized, unconstrained movement as well as for developing and testing BMIs in a strenuous fashion before translation to ambulatory patients.

A. Future Work

In the present study, hand-tagged images provided a relatively good ground truth for interpolating the kinematic position of the arm. However, hand-tagging is not feasible for more complex studies of natural behavior for a number of reasons: 1) it would be laborious to extend hand tagging to a more complete kinematic model of body posture, 2) it is somewhat qualitative and subject to user error, and 3) it does not scale to large datasets.

It is promising that a relatively simple model for decoding neural activity performed very well. At present these results are from one monkey (I), and experiments are currently under way with a second monkey (N) which will allow us to determine if, and hopefully confirm that, these one monkey results generalize. Subsequent work would incorporate more complex models and aim to decode kinematic parameters, ideally in real-time.

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References

[1] E.V. Evarts, "Pyramidal tract activity associated with a conditioned hand movement in the monkey.", *J. Neurophysiology*, vol. 29, no. 6, pp. 1011–1027, Nov. 1966.

[2] A.P. Georgopulous, J.F. Kalaska, R. Caminti, and T. Massey, "On the relations between the direction of two-dimensional arm movements and cell discharge in primate motor cortex.", *J. Neuroscience*, vol. 2, no. 11, pp. 1527–1537, Nov. 1982.

[3] E.E. Fetz, "Are movement parameters recognizably coded in the activity of single neurons?", *Behavioral and Brain Sciences*, vol. 15, no. Special Issue 04, pp. 679–690, 1992.

[4] C.E. Vargas-Irwin, G. Shakhnarovich, P. Yadollahpour, J.M.K. Mislow, M.J. Black, and J.P. Donoghue, "Decoding Complete Reach and Grasp Actions from Local Primary Motor Cortex Populations", *Journal of Neuroscience*, vol. 30, no. 29, pp. 9659, 2010.

[5] J.M. Carmena, M.A. Lebedev, R.E. Crist, J.E. O'Doherty, D.M. Santucci, D.F. Dimitrov, P.G. Patil, C.S. Henriquez, and M.A.L. Nicolelis, "Learning to control a brainmachine interface for reaching and grasping by primates", *PLoS Biol*, vol. 1, no. 2, pp. e42, Oct. 2003.

[6] Leigh R. Hochberg, Mijail D. Serruya, Gerhard M. Friehs, Jon A. Mukand, Maryam Saleh, Abraham H. Caplan, Almut Branner, David Chen, Richard D. Penn, and John P. Donoghue, "Neuronal ensemble control of prosthetic devices by a human with tetraplegia", *Nature*, vol. 442, pp. 164–171, 2006.

[7] G. Santhanam, S.I. Ryu, B.M. Yu, A. Afshar, and K.V. Shenoy, "A high-performance braincomputer interface.", *Nature*, vol. 442, pp. 195–198, July 2006.

[8] M Velliste, S Perel, MC Spalding, AS Whitford, and AB Schwartz, "Cortical control of a prosthetic arm for self-feeding.", *Nature*, vol. 453, no. 7198, pp. 1098–1101, 2008.

[9] J.E. O'Doherty, M.A. Lebedev, P.J. Ifft, K.Z. Zhuang, S. Shokur, H. Bleuler, and M.A.L. Nicolelis, "Active tactile exploration using a brain-machine-brain interface.", *Nature*, vol. 479, no. 7372, pp. 228–231, Nov. 2011.

[10] C. Ethier, E.R. Oby, M.J. Bauman, and L.E. Miller, "Restoration of grasp following paralysis through brain-controlled stimulation of muscles.", *Nature*, vol. 485, no. 7398, pp. 368–371, May 2012.

[11] L.R. Hochberg, D. Bacher, B. Jarosiewicz, N.Y. Masse, J.D. Simeral, J. Vogel, S. Haddadin, J. Liu, S.S. Cash, P. van der Smagt, and J.P. Donoghue, "Reach and grasp by people with tetraplegia using a neurally controlled robotic arm.", *Nature*, vol. 485, no. 7398, pp. 372–375, May 2012.

[12] C.A. Chestek, V. Gilja, P. Nuyujukian, R.J. Kier, F. Solzbacher, S.I. Ryu, R.R. Harrison, and K.V. Shenoy, "HermesC: Low-Power Wireless Neural Recording System for Freely Moving Primates", *Neural Systems and Rehabilitation Engineering, IEEE Transactions on*, vol. 17, no. 4, pp. 330 –338, Aug. 2009.

[13] H. Miranda, V. Gilja, C.A. Chestek, K.V. Shenoy, and T.H. Meng, "HermesD: A High-Rate Long-Range Wireless Transmission System for Simultaneous Multichannel Neural Recording Applications", *IEEE Transactions on Biomedical Circuits and Systems*, vol. 40, no. 3, pp. 181–191, June 2010.

[14] H. Gao, R.M. Walker, P. Nuyujukian, K.A.A. Makinwa, K.V. Shenoy, B. Murmann, and T.H. Meng, "HermesE: A 96-Channel Full Data Rate Direct Neural Interface in 0.13 um CMOS", *IEEE Journal of Solid-State Circuits*, vol. PP, no. 99, pp. 1 –13, 2012.

[15] J.D. Foster, O. Freifeld, P. Nuyujukian, S.I. Ryu, M.J. Black, and K.V. Shenoy, "Combining wireless neural recording and video capture for the analysis of natural gait", in *Neural Engineering (NER), 2011 5th International IEEE/EMBS Conference on*, May 2011, pp. 613 –616.

[16] J.H. Friedman, "Regularized discriminant analysis", *Journal of the American Statistical Association*, vol. 84, no. 405, pp. 165–175, Mar. 1989.