

1 **Title:**

2 **Neural correlates of cognitive motor signals in primary somatosensory cortex.**

3

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26 **Contributions:**

27 M.J., T.A, and R.A.A designed the study, M.J. and T.A developed experimental tasks, M.J. and
28 T.A. designed analysis and analyzed the data, M.J., S.C., S.S.K, and M.A.S. collected the data,
29 S.L.N contributed code, M.J. and T.A. interpreted results and wrote the original draft, M.J., T.A.,
30 S.C., and R.A.A. reviewed and edited the paper, T.A. and R.A.A. provided mentorship, T.A.,
31 S.K., and R.A.A. acquired funding, K.P provided administrative and regulatory assistance,
32 C.Y.L. performed implantation surgery.

1 **Abstract**

2 Classical systems neuroscience positions primary sensory areas as early feed-forward processing
3 stations for refining incoming sensory information. This view may oversimplify their role given
4 extensive bi-directional connectivity with multimodal cortical and subcortical regions. Here we
5 show that single units in human primary somatosensory cortex encode imagined reaches centered
6 on imagined limb positions in a cognitive motor task. This result suggests a broader role of
7 primary somatosensory cortex in cortical function than previously demonstrated.

8

9 **Main**

10 Somatosensory cortex (S1) is largely studied and understood in its role as the primary sensory
11 region for processing somatic sensory signals from the body. However, recent work highlights a
12 more direct role in motor production: S1 neurons can respond to passive movements alone,
13 active movements alone, or both^{1,2} and neurons become activated prior to movement initiation^{1,3}.
14 S1 neurons project to the spinal cord^{4,5}, and electrical or optical stimulation of S1 elicits motor
15 movements⁶⁻⁸. These results indicate a direct role of S1 in the production of motor behavior.
16 However, in many of these studies, it is hard to dissociate whether neural signals reflect motor
17 variables or aspects of sensory processing.

18 To understand if S1 processes reach intentions in the complete absence of sensation or expected
19 sensations, we recorded single unit activity from multi-channel arrays implanted in the sensory
20 cortex (Fig 1B) of a 34-year-old tetraplegic male (FG) during a delayed imagined reaching task.
21 The arrays were implanted in S1 as part of an ongoing clinical trial in which we showed that
22 microstimulation delivered through these same multi-channel arrays evokes localized and
23 naturalistic cutaneous and proprioceptive sensations⁹. Our paradigm (Fig 1A), adapted from
24 previous non-human primate studies^{10,11}, systematically manipulated fixation, imagined initial
25 hand, and reach target locations at distinct points in the trial. Importantly, the subject is capable
26 of moving his eyes and thus can direct his gaze to the fixation targets. However, the paralyzed
27 subject did not move his arm, but instead used motor imagery to imagine moving his hand to the
28 initial hand cue location and subsequently imagine moving it to the final target location. This
29 design allowed us to: one, understand how activity in S1 relates to storing information about arm
30 location, movement plans, and movement execution, and two, characterize the reference frame of
31 these signals, e.g. whether movement variables are coded relative to the initial imagined position
32 of the hand, relative to the eyes, or relative to the body or world.

33 We performed a sliding window analysis to understand whether and when neurons in S1 become
34 active for our cognitive motor task. For each unit, we used a linear model with interactions to
35 explain firing rate as a function of fixation, initial imagined hand, and target locations (Fig 1C, p
36 < 0.05 FDR corrected for number of units per time slice, window size: 750 ms, step size: 500
37 ms). We find negligible selectivity following cueing of the hand and eye positions indicating no
38 neural coding for true eye position or the imagined position of the arm. We also found negligible
39 selectivity following target presentation, indicating no encoding of the spatial location of the
40 target or planning activity related to the upcoming imagined motor action. Finally, we found that

1 a significant proportion of the population was selective following the instruction to initiate the
2 imagined reach. Thus, sensory cortex is engaged during a cognitive motor task despite the
3 absence of overt movement and sensory feedback, but only during imagined movement of the
4 limb.

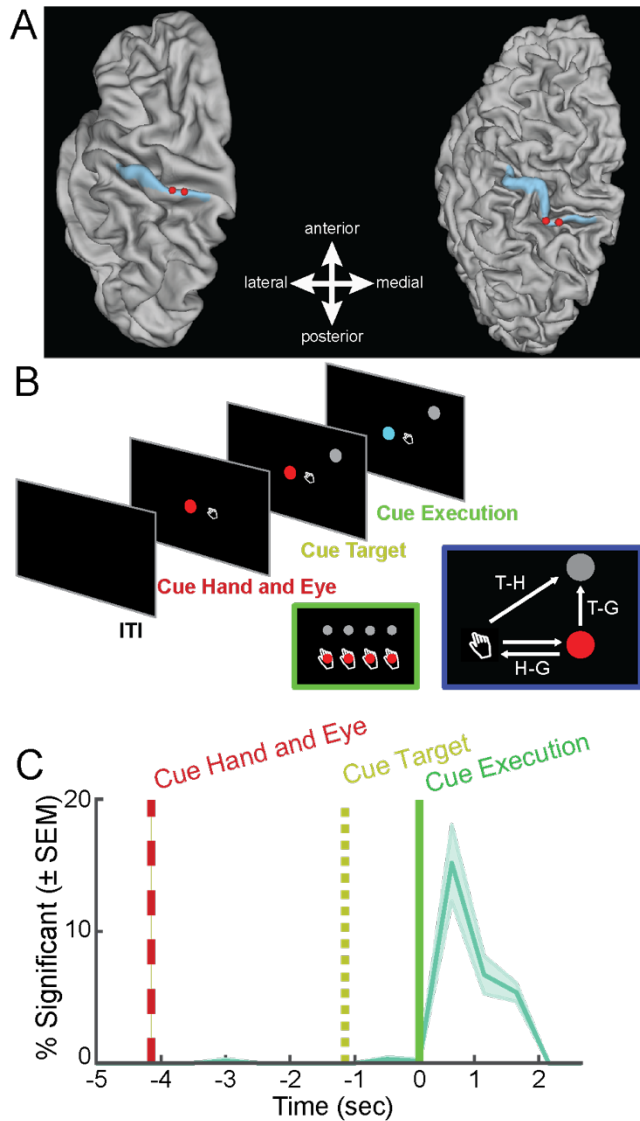
5 We found that nearly all the neurons selective during the movement execution phase coded
6 movement as the reach vector: the direction of imagined movement of the hand. In other words,
7 selective units coded the location of the target relative to the initial imagined hand position (or,
8 by symmetry, hand position relative to the target). This result was found using a gradient
9 analysis pioneered in NHPs¹²; neural responses for each unit were organized into response
10 matrices where the firing rate is coded for each hand, eye, and target position. A gradient field is
11 then computed which describes how the firing rate is sensitive to changes in the behavioral
12 variables. Finally, the resultant, or vector sum, of the gradient field summarizes the net effect of
13 behavioral manipulations which can be used to determine whether neural activity encodes target
14 position relative to gaze position (T-G), the target position relative to the hand (T-H), the hand
15 position relative to gaze direction (H-G), or some combination of these vectors (Fig S1). A
16 representative response matrix for a neuron coding the position of the target relative to the hand
17 and the population distribution of response gradients is shown in figure 2B and C. Interestingly,
18 despite no neural coding for imagined hand position prior to movement execution, our result
19 indicates that the neural coding during the imagined reach incorporates the internal estimate of
20 hand position when computing the reach response.

21 Single unit analysis shows that the population is dominated by units coding the reach vector. To
22 verify that this interpretation is an adequate summary of S1 encoding, we used complex principal
23 component analysis (cPCA) to characterize the full temporal dynamics of the reference frame of
24 the population as a whole (Fig S2). The gradient analysis described above summarizes the
25 sensitivity of a neuron to behavioral variables using the resultant of the gradient, a 2D vector that
26 can be described by a length and angle. We used cPCA for its capability to handle vector data
27 samples, i.e. described by both a length and angle for each observation¹³. We find that coding of
28 the reach vector strengthens and peaks around 750 ms after the cue to execute the imagined reach
29 (Fig 3A). Further, only the first cPCA component was significant (parallel analysis¹⁴, $\alpha < 0.05$).
30 This suggests that reach coding in S1 is dominated by a single homogeneous representation of
31 the reach vector that can be used to decode the subject's motor intent (Fig 3B).

32 We have shown the first single unit evidence that cognitive imagery of movements is represented
33 in the primary somatosensory area of human cortex. S1 neurons tracked motor execution
34 intentions in the complete absence of sensation exclusively during imagined execution. There
35 was negligible activity while the subject maintained the position of the limb in memory, fixated
36 distinct targets, or planned movements. These results suggest that the role of S1 in motor
37 production is restricted to the time of movement execution. Given the timing of S1 activity and
38 reciprocal connections with motor cortex, S1 activity may reflect an efference copy of execution
39 signals originating from motor cortex. Lastly, we show S1 activity codes motor intention relative
40 to the imagined position of the hand. A possible concern is that these results are unique to
41 individuals who have lost their main peripheral input. However, recent findings from our lab and

1 others have shown these representations are largely stable and reorganization does not result in
2 the production of novel functional sensory representations^{9,15-17}. These results implicate a role of
3 primary somatosensory cortex in cognitive imagery, a role of S1 in motor production in the
4 absence of sensation, and suggest that S1 can provide control signals for future neural prosthetic
5 systems.

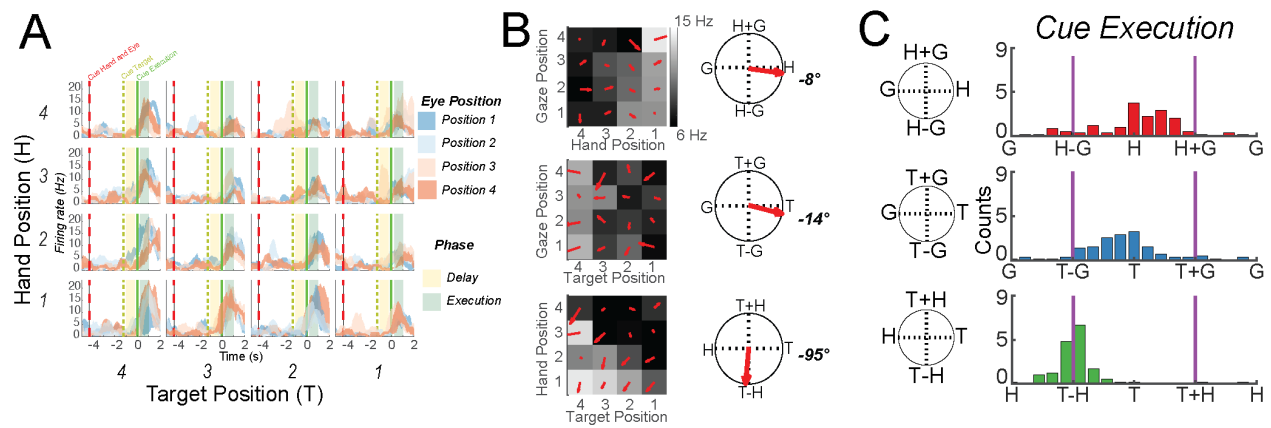
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8 Figure 1. Behavioral Task, Electrode Array Location, and Tuning Throughout Task. **A)** Group-
9 average brain map (left) and brain of subject FG (right) showing location of implanted
10 microelectrode array (red) and Brodmann Area 1 (blue). **B)** Time course of delayed reference
11 frame reaching task testing all unique combinations of four gaze, hand, and target positions
12 (green inset). Geometry of the reference frame task (blue inset). **C)** Percent of units in population
13 tuned (mean ± SEM, $p < 0.05$, FDR corrected). Units were considered tuned from the beta value
14 of the linear fit, and subsequently corrected for multiple comparisons.

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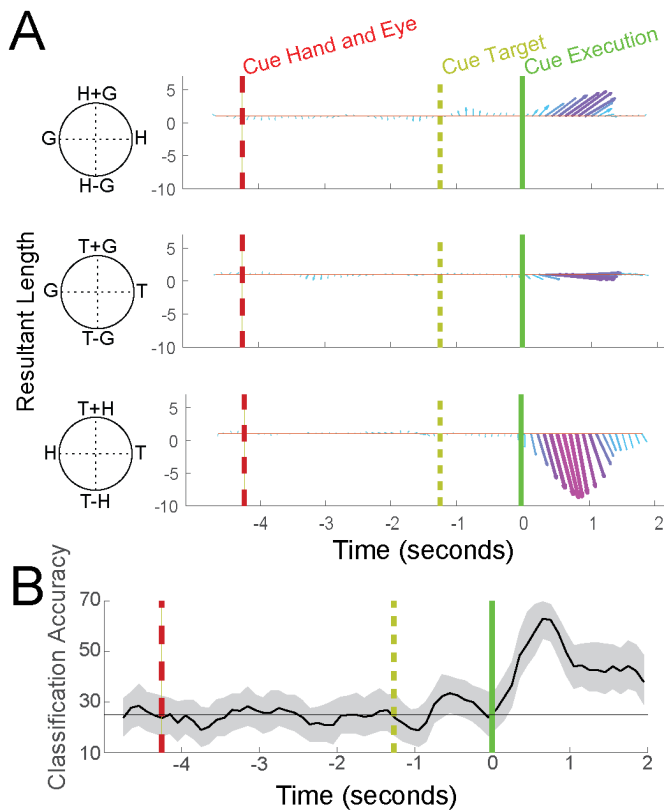
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4 Figure 2. Example S1 Unit, Gradient Analysis, and Distribution of Gradients of Tuned Units. **A)**
5 Peristimulus time histograms for all 64 conditions (3 trials; mean \pm SEM). Each of the 16
6 subplots shows the response of the unit to a particular combination of eye, hand, and gaze
7 position. **B)** matrices and gradient resultant orientations for the cell shown in 2A during the
8 execution epoch (Fig 2A, green). **C)** Histograms show gradient resultant orientations for the
9 population of tuned units.

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4 Figure 3. Population level reference frame coding and decode accuracy during a cognitive motor
5 task in S1. **A**) Temporal evolution of reference frame encoding across the population of S1 units.
6 Only the first component (shown) was found to be significant ($p < 0.05$; parallel analysis). Arrow
7 length, width, and color shows tuning strength. **B**) Temporal dynamics of imagined reach
8 decoding. Offline analysis depicting accuracy of target classification from the middle two hand
9 positions [750-ms sliding window, mean with 95% confidence interval (CI)]. Horizontal black
10 line is chance, 25%).

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22 Acknowledgments

23 This work was supported by the National Institute of Health (R01EY015545, 5U01NS098975-
24 02), the Tianqiao and Chrissy Chen Brain-machine Interface Center at Caltech, the Conte Center
25 for Social Decision Making at Caltech (P50MH094258), the David Geffen Medical Scholarship,
26 and the Boswell Foundation. The authors would also like to thank subject FG for participating in
27 the studies, and Viktor Scherbatyuk for technical assistance.

28

29 Data availability

30 All primary behavioral and neurophysiological data are archived in the Division of Biology and
31 Biological Engineering at the California Institute of Technology and are available from the
32 corresponding author on reasonable request.

33 Code availability

34 All custom-written analysis code is available from the corresponding author on reasonable
35 request.

1 **Materials and Methods**

2 **Subject Information**

3 Neural recordings were made from participant FG, a tetraplegic 32-year-old male with a
4 complete C5/C6 spinal cord injury. FG was implanted 1.5 years post-injury for a clinical trial of
5 a BMI system consisting of intracortical stimulation and recording. Neural recordings for the
6 current study were acquired 1-year post implantation. All of subject FG's sensations and motor
7 ability are consistent with the level of the sustained injury. The subject remains intact for all
8 other motor control and sensations above the level of injury. Surgical implantation took place at
9 Keck Hospital of USC.

10 Experiments were conducted in the framework of an ongoing neural prosthetics clinical study
11 (ClinicalTrials.gov identifier: NCT01964261) and were in compliance with all relevant clinical
12 regulations. We obtained informed consent after explaining the objectives of the study and the
13 possible risks involved. The study and all procedures were approved by the Institutional Review
14 Boards (IRB) of the California Institute of Technology (Caltech), the University of Southern
15 California (USC), and Rancho Los Amigos National Rehabilitation Hospital (RLA).

16

17 **Surgical Planning and Implantation**

18 Surgical planning for subject FG followed the protocols described in^{1,2}. In brief, functional
19 magnetic resonance imaging (fMRI) was used to measure the BOLD response while FG
20 performed imagined reaching and grasping movements in response to visual cues. The statistical
21 parametric analysis guided selection of implant locations in the left hemisphere of the ventral
22 portion of the premotor cortex (PMv), the supramarginal gyrus (SMG), and somatosensory
23 cortex (S1). PMv and SMG were implanted with 96-channel Neuroport microelectrode arrays
24 (Blackrock Microsystems, Salt Lake City, UT). S1 was implanted with two 7x7 microelectrode
25 arrays (48 channels per array, Blackrock Microsystems, Salt Lake City, UT) on the post-central
26 gyrus. Figure 1B shows the implantation locations for the two arrays. In addition, we estimated
27 the anatomical location of the implantation of S1 in terms of Brodmann's Area. To this end, we
28 used Freesurfer³ to perform a surface reconstruction of the individual subject's anatomy. The
29 subject's anatomy was then registered to the 164K fs-lr group-average template using
30 Connectome Workbench⁴. The subject's implants were determined to be localized to
31 Brodmann's Area 1 (BA1) according to the composite template of Van Essen et al 2012⁵ as
32 visualized within Connectome Workbench. Localizing the areal boundaries of BA1 within the
33 individual subject requires the registration of the individual subject's surface anatomy to a
34 group-average atlas. We therefore show implant locations both as they appear on the individual
35 subject's brain surface as well as where the arrays are estimated to be located on the fs-lr group-
36 average template brain (Fig 1A).

37

38 **Reference Frame Task**

1 Experimental sessions with subject FG were performed at Rancho Los Amigos National
2 Rehabilitation Center (RLA). FG performed the task in a dimly lit room seated in his motorized
3 wheel chair. Task stimuli were viewed on a 47-inch LCD monitor with the screen occupying
4 approximately 45 degrees of visual angle. The subject was asked to minimize head movements
5 throughout the task. At the beginning of each trial, FG was presented with a fixation cue and a
6 hand position cue. Each cue could be positioned at one of four locations resulting in 16 possible
7 hand and eye configurations. FG was able to move his eyes and thus fixate the fixation cue as
8 verified using eye tracking. In contrast, FG did not position his actual hand at the location of the
9 hand cue, but instead FG imagined moving his hand to the cue location and maintained imagery
10 of his hand until the go cue. After 3 seconds a reach target cue was shown at one of four spatial
11 locations arranged parallel to and above the cued eye and hand positions. The target cue was
12 shown for 1.25 seconds during which the subject continued to hold their gaze and imagined hand
13 positions. A change in the color of the fixation marker instructed the subject to begin an
14 imagined reach to the cued target location. The subject was asked to make an imagined reach and
15 maintain the imagined ending position (target location) until the execution epoch was over (2
16 seconds). The execution epoch was then followed by an inter-trial interval (ITI) of 2 seconds. A
17 schematic representation of the task is shown in figure 1B.

18 Experimental data was collected in three experimental runs. Each run consisted of a total of 64
19 trials, one trial for each unique combination of the four eye, hand, and target positions. This
20 resulted in 192 total trials, 3 repetitions for each unique trial type. Each experimental session
21 was separated out by at least a week.

22

23 **Neural Recordings**

24 Neural activity from each array was amplified, digitized, and recorded at 30 kHz using the
25 Neuroport neural signal processor (NSP). The Neuroport system, comprised of the arrays and
26 NSP, has received FDA clearance for less than 30 days of acute recordings. However, for
27 purposes of this study we received FDA IDE clearance for extending the duration of the implant
28 (IDE number: G130100).

29 Putative waveforms were detected at thresholds of -3.5 times the root-mean-square after high
30 pass filtering the full bandwidth signal (sampled at 30Khz), using the Blackrock Central software
31 suite (Blackrock Microsystems). Waveforms consisted of 48 samples, 10 prior to threshold
32 crossing and 38 samples after. These recordings were then sorted (both single and multi-unit)
33 using k-medoids clustering using the gap criteria to estimate the total number of clusters^{6,7}.
34 Offline sorting was then reviewed and adjusted as needed following standard practice⁸. On
35 average across 4 days of recordings in S1 we analyzed 163 sorted units per session. All sorting
36 was done prior to analysis and blind to channel or unit responses found during the task. Further
37 spike sorting methods can be found in Zhang et al., 2017.

38

39 **Eye Tracking**

1 Subject FG's eye position was monitored using a 120 Hz binocular eye tracking system (Pupil
2 Labs, Berlin, Germany). If the subject's gaze shifted off the cued eye position the task was
3 terminated and restarted to ensure that gaze position was correct and remained fixed to the cued
4 eye position throughout each appropriate epoch for a run (64 consecutive trials). Eye positions
5 were synced to the task and allowed online determination of eye position. We instructed the
6 subject to maintain a constant head position and to only move his eyes to fixate the target.
7 However, head position was not monitored and more conservatively we can say that we
8 manipulated gaze as opposed to eye position proper. In either case, our results showed no
9 dependences on eye/gaze and thus the distinction is not especially important given the pattern of
10 results.

11

12 **Linear Analysis for Tuning (Fig 1C)**

13 We defined a unit as selective if the unit displayed significant differential modulation for our
14 task variables as determined by a linear regression analysis: We created a matrix that consisted
15 of four indicator variables for each unique behavioral variable (e.g. one indicator variable for
16 each of the four initial hand positions) resulting in 12 indicator variables. Firing rate was
17 estimated as a linear combination of these indicator variables and their interactions: FR is firing
18 rate, X_c is the vector indicator variable for condition c , β_c is the estimated scalar weighting
19 coefficient for condition c , and β_0 is the intercept.

20

$$FR = \sum_c \beta_c X_c + \beta_0$$

21 Linear analysis was performed over a sliding window throughout the interval of the task.
22 Windows were 750 ms in duration and window start times were stepped every 500 ms.
23 Significance of each fit was determined using the p-value of the F-test of overall significance for
24 the linear analysis ($p < 0.05$, FDR-corrected for number of units). Units that were found to be
25 significant in this analysis were then determined to be selective and further analyzed in the
26 reference frame analysis.

27

28 **Reference Frame Analysis: Gradient Analysis (Fig 2)**

29 Gradient analysis was used to quantify how changes in the behavioral variables changed the
30 firing rate of each unit when comparing across each unique combination of variable pairs (Hand-
31 Gaze (HG), Target-Gaze (TG), and Target-Hand (TH))⁹⁻¹²: For each tuned unit (based on the p-
32 value of the linear regression model described above) we created a four by four matrix (response
33 matrix) representing neural activity for each unique combination of two behavioral variables;
34 thus, for example, the value at the HG response matrix location $[x,y]$ would be the neural activity
35 recorded for hand position x and gaze position y averaged across trial repetitions and repetitions
36 acquired for the different target positions. Gradients were determined using the gradient function
37 in Matlab 2019a (Mathworks Inc, Natick, MA). For each gradient, a resultant angle and length

1 was computed to summarize the net direction and magnitude of change across the entire response
2 matrix (Fig. S1). However, often times the gradients often show a symmetrical pattern that
3 would result in cancellation of symmetrical angles (Fig. S1A). To avoid this, we double each
4 angle in the matrix and represent each angle from 0° to $\pm 180^\circ$. Therefore, the summed resultant
5 angle is represented by 0° for gradients oriented left and right, $\pm 180^\circ$ for gradients oriented up
6 and down, and -90° for gradients oriented along the diagonal (Fig S1A). The summed resultant
7 angle and length however cannot be mapped directly onto the response matrix; thus, we have
8 notated the appropriate variable and combinations of variables to help with interpretation. For
9 example, in figure S1A hand only (H) modulation would be found at $\pm 180^\circ$, gaze only (G)
10 modulation is seen at 0° , H+G at 90° , and H-G at -90° . Therefore, we can use the angle of the
11 resultant angle as a proxy for overall orientation bias for a variable or variable pair.

12

13 **Dimensionality Reduction (Fig 3)**

14 We used population level dimensionality reduction analyses to determine the most common
15 modes of reference frame encoding over time. This was done in a three stage process (see Fig
16 S2): (1) Initial principal component analysis (PCA) on the time varying activity of the neural
17 population, (2) reference frame analysis on each time point of the resulting principal
18 components, (3) complex principal component analysis (cPCA) on the resultant angles and
19 magnitudes. The initial principal component analysis was used to denoise and improve the
20 calculation of reference frames at the level of the population. In order to perform PCA analysis
21 we constructed a matrix of neural data D that was (n) by $(t * c)$ in size, with n being the number
22 of neurons, t being the number of time points, and c being the number of conditions. For each
23 neuron, activity was averaged across repetitions of the same condition within a 100ms window.
24 The reference frame analysis was then applied to each temporal window for the first 20 principal
25 components. Note that following the initial principal component analysis, the population activity
26 still carries detailed information about neural selectivity properties unrelated to the reference
27 frame proper (e.g. preferred directions of movement or preferred hand locations.) Thus multiple
28 principal components may have the same reference frame, but simply prefer a different direction
29 movement direction. Computing the reference frame at this stage extracts the population level
30 reference frame, abstracting away tuning preference differences. The final cPCA was then used
31 to capture the main reference frame modes once the detailed aspects of tuning (e.g. such as
32 preferred direction of response) were abstracted away by the reference frame analysis. We used
33 cPCA given the fact that dimensionality reduction was performed on the resultant vectors, values
34 with both a magnitude and angle. We converted all resultant angles and lengths into complex
35 numbers to apply cPCA¹³. We used parallel analysis to determine which components from this
36 dimensionality reduction were significant¹⁴.

37

38 **Discrete Classification (Fig 3B)**

39 Offline classification was performed using linear discriminate analysis. The classifier took as
40 input a vector comprised of the number of spikes occurring within a specified time epoch for

1 each sorted unit. The following assumptions were made for the classification model: 1) the prior
2 probability across the classes was uniform, 2) the conditional probability distribution of each
3 feature on any given class was normal, 3) only the mean firing rates differ for each class (the
4 covariance of the normal distributions were the same for each class), and, 4) the firing rates of
5 each input are independent (covariance of the normal distribution was diagonal). Reported
6 performance accuracy was based on leave-one out cross-validation. To compute the temporal
7 dynamics of classification accuracy, the neural data was first aligned to a behavioral epoch (e.g.
8 cue execution onset). Spike counts were then computed in 750 ms windows spaced at 100 ms
9 intervals. Classification accuracy was computed independently for each time bin and
10 bootstrapped resampling was used to compute 95% confidence bounds.

11

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