

Emergence of coordinated neural dynamics underlies neuroprosthetic learning and skillful control

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**Emergence of coordinated neural dynamics underlies neuroprosthetic learning
and skillful control**

by

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A thesis submitted in partial satisfaction of the

requirements for the degree of

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Committee in charge:

Professor Jose M. Carmena, Chair
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EMERGENCE OF COORDINATED NEURAL DYNAMICS UNDERLIES
NEUROPROSTHETIC LEARNING AND SKILLFUL CONTROL

Vivek Ravindra Athalye

Research Project

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Abstract

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Master of Science, Plan II in Electrical Engineering and Computer Sciences

University of California, Berkeley

Professor Jose M. Carmena, Chair

The Brain-Machine Interface (BMI) is an emerging technology which directly translates neural activity into control signals for effectors such as computers, prosthetics, or even muscles. Work over the last decade has shown that high performance BMIs depend on machine learning to adapt parameters for decoding neural activity, but also on the brain learning to reliably produce desired neural activity patterns. How the brain learns neuroprosthetic skill de novo is not well-understood and could inform the design of next-generation BMIs in which both the brain and machine synergistically adapt.

During both neuroprosthetic and natural motor skill learning, movements and underlying neural activity initially exhibit large trial-to-trial variability which decreases over training, resulting in consolidated movement and neural patterns. However, it is unclear how task-relevant neural populations coordinate to explore and consolidate activity patterns underlying behavioral improvement. Exploration and consolidation could happen for each neuron independently, across the population jointly, or both. We disambiguated among these possibilities by investigating how subjects learned de novo to control a brain-machine interface using a fixed motor cortex population. We decomposed population activity into the sum of private and shared signals, which produce uncorrelated and correlated neural variance respectively, and examined how these signals' evolution causally shapes behavior. We found initially large trial-to-trial movement and private neural variability reduce over learning. Concomitantly, task-relevant shared variance increases, consolidating a manifold containing consistent neural trajectories that generate refined control. These results suggest that motor cortex acquires skillful control by leveraging both independent and coordinated variance to explore and consolidate neural patterns.

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- 5.5 **Mean firing rate changes do not explain trial-to-trial variability and decoder-timescale variance changes.** 47

5.5 **Mean firing rate changes do not explain trial-to-trial variability and decoder-timescale variance changes.** **(A)** The mean firing rate increased over training (Monkey P: $R=0.79$, $p=5.1e-4$, early < late $p=7.1e-6$, 8 targets consistent; Monkey R: $R=0.49$, $p=2.7e-1$, early < late $p=6.1e-3$, 7 targets consistent). **(B)** We performed FA on a simulated data set of independent Poisson spike counts with window sizes used in Figure 4, the experimentally observed neurons' means, and 50 times the number of trials. Fitting FA on Poisson counts yields the best shared dimensionality as 0. In these plots, we used 1 shared dimension, matching our analysis of real neural data (Figure 4). Monkey P's simulated private trial-to-trial variability increased while Monkey R showed no trend (Monkey P, $r=0.78$, $p=5.1e-4$, late > early $p=2.3e-5$; Monkey R n.s. : $r=0.33$, $p=4.8e-1$, late > early $p=1.2e-1$). Both subjects' shared variance is close to 0 and showed no trend (Monkey P, $r=0.29$, $p=2.9e-1$, early vs late $p=4.9e-1$; Monkey R, $r=-0.06$, $p=9.1e-1$, early vs late $p=1.1e-1$). Because shared variance does not track changes in mean firing rate, we chose not to normalize shared variance by mean firing rate. **(C)** As mathematically expected, we observed that normalizing each simulated Poisson neuron's private variance by its mean yielded a value close to 1 with no significant trend over training. The value is expected to be less than 1, because some variance was absorbed as shared variance since we used a shared dimensionality of 1. **(D)** The trial-to-trial shared to total variance ratio showed no trend and is close to 0. **(E)** The trial-to-trial shared space alignment to the final epoch showed no trend (Monkey P: $r=0.21$, $p=4.7e-1$, early vs late $p=1.5e-1$; Monkey R: $r=-0.55$, $p=2.6e-1$, early vs late $p=6.9e-1$).

5.5	Mean firing rate changes do not explain trial-to-trial variability and decoder-timescale variance changes. (F) The experimentally observed data's decoder-timescale main shared, high-dimensional shared, and private variance, normalized by total variance. Normalized private variance decreased (Monkey P: $r=-0.92$, $p=1.4e-6$, early > late $p=1.3e-4$; Monkey R: $r=-0.38$, $p=4.1e-1$, early > late $p=7.6e-2$), and normalized high dimensional shared signal variance decreased (Monkey P: $r=-0.80$, $p=3.8e-4$, early vs late $p=1.2e-4$; Monkey R: $r=-0.76$, $p=4.8e-2$, early > late $p=8.7e-4$). Normalized main shared variance increased (Figure 5D). (G) Decoder-timescale shared variance changes are not explained by changes in mean firing rate. We applied FA on Poisson simulated neurons with 100 ms bins using experimentally observed average firing rates and shared dimensionality (Figure 5B). Private variance increased (Monkey P: $r=0.76$, $p=9.8e-4$, early < late $p=2.8e-4$; Monkey R: $r=0.42$, $p=3.4e-1$, early < late $p=2.3e-2$) and main shared variance was unchanged (Monkey P: $r=0.39$, $p=1.5e-1$, early vs late $p=1.7e-1$; Monkey R: $r=0.34$, $p=4.5e-1$, early vs late $p=4.8e-1$). High dimensional shared variance decreased slightly because the experimental shared dimensionality decreased (Monkey P: $r=-0.59$, $p=2.0e-2$, early > late $p=2.6e-4$; Monkey R: $r=-0.37$, $p=4.1e-1$, early > late $p=8.2e-3$). (H) Decoder-timescale Poisson simulated neurons' main shared variance to total variance ratio showed no trend (Monkey P: $r=0.27$, $p=3.4e-1$, early vs late $p=4.1e-1$; Monkey R: $r=0.039$, $p=9.3e-1$, early vs late $p=6.9e-1$). (I) Decoder-timescale Poisson simulated neurons' shared space alignment to the final epoch showed no trend (Monkey P: $r=0.32$, $p=2.6e-1$, early vs late $p=1.5e-1$; Monkey R: $r=0.14$, $p=7.9e-1$, early vs late $p=4.6e-1$).	49
5.6	Decoder-timescale main shared variance and control.	50
5.6	Decoder-timescale main shared variance and control. (A) The fraction of decoder-timescale main shared variance in the readout space increased for Monkey P ($r=0.86$, $p=3.9e-5$, late > early $p=2.2e-4$, 8 targets consistent) but not Monkey R ($r=-0.28$, $p=5.5e-1$, late < early $p=1.1e-1$). (B) Example trials driven by main shared variance and total activity from the final epoch for each target. (C) In late learning, successful movements driven by main shared variance are significantly faster (main shared minus total time-to-target; Monkey P: mean = -0.78 sec, main shared < total $p=4.2e-51$; Monkey R: mean = -0.66 sec, main shared < total $p=3.2e-11$). (D) In late learning, successful movements driven by main shared variance are significantly more direct (main shared minus total distance-traveled; Monkey P: mean = -2.8, main shared < total $p=5.38e-83$; Monkey R: mean = -5.1, main shared < total $p=1.8e-28$). For (CD), late learning trials were analyzed for which total activity and main shared variance were successful (Monkey P: epochs 8 to 15, 832 trials; Monkey R: epochs 4 to 7, 385 trials). . .	51
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Chapter 1

Introduction

When we begin learning a novel skill, we have no experience about how to move to achieve a particular goal. Early in training, movements exhibit variability from attempt to attempt, allowing the motor system to explore actions and select them based on consequences (Sutton and Barto, 1998; Tumer and Brainard, 2007; Wu et al., 2014). Gradually, movement variability decreases as the motor system consolidates particular movements that lead to success (Cohen and Sternad, 2009; Shmuelof et al., 2012). This suggests that a task-relevant neural population explores neural activity patterns to generate novel motor commands, and selects and consolidates those that achieve the desired goal. Indeed, neurophysiological motor learning studies have found that movement-related neural activity in various species follows a similar trend, exhibiting high variability in early training which reduces as particular ensembles and activity patterns are consolidated in late training (Arduin et al., 2013; Barnes et al., 2005; Cao et al., 2015; Costa et al., 2004; Kao et al., 2005; Mandelblat-Cerf et al., 2009; Peters et al., 2014; Santos et al., 2015; Zacksenhouse et al., 2007). However, it is unclear how exploration of particular patterns in a task-relevant neural population is accomplished, and also how goal-achieving patterns are refined and consolidated to improve performance.

The motor system is distributed and redundant, with parallel pathways and many more neurons than muscles, making it difficult to investigate the causal relationship between observed neural activity patterns and motor output (Briggman and Kristan, 2008). We therefore took advantage of a paradigm in which we could identify the output neurons that control behavior as well as the explicit transformation between output neuron activity and behavior. We used an operant learning brain-machine interface (BMI) in which stable recordings from ensembles of primary motor cortex (M1) neurons in macaque monkeys are input to a fixed mathematical transform (decoder) outputting prosthetic two-dimensional cursor movements. The BMI provided a closed-loop feedback system operating within the natural motor system (Figure 1.1). Because we defined the decoder to take input from observed cells (direct cells), this neuroprosthetic skill learning paradigm (Ganguly and Carmena, 2009, 2010) is uniquely advantageous to investigate how a task-relevant neural population coordinates to acquire skillful control.

Given that the decoder is novel, subjects must initially explore neural population activity

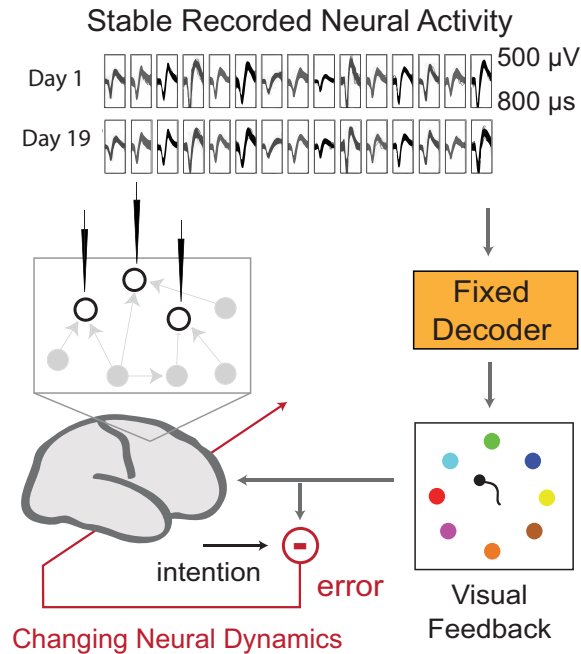


Figure 1.1: **Operant Learning BMI Paradigm Using Stable Neurons and a Fixed Decoder.** Monkeys use neural activity of stable neurons to control a fixed decoder over days, so improvement can only be driven by adaptive changes in neural population activity.

space. This is a non-trivial search because population activity space is high-dimensional, with each neuron’s activity represented as one dimension. Over training, subjects must use the behavioral consequences of explored activity patterns to select and refine goal-achieving patterns. This consolidation process is not well-understood, especially as there are many neural activity patterns which can elicit the same behavioral output in systems mapping many neurons to fewer outputs, such as a BMI or our natural motor system. How might this learning happen? We consider three possibilities.

In “independent neuron learning,” each neuron explores independently, as has been proposed in computational models (Héliot et al., 2010; Legenstein et al., 2010), and each neuron tunes its independent patterns over learning (Figure 1.2A). Because independent neuron learning explores every dimension of population activity space, this learning can acquire any firing rate configuration and thus control any decoder. However, this learning cannot explain how subjects rapidly acquire (within one day) decoders which leverage neural covariance (Sadtlter et al., 2014).

In contrast, “constrained-network learning” posits that the neural population possesses network connectivity constraints and thus preferentially produces covariation patterns within a fixed, lower-dimensional subspace of the full activity space. Indeed, both BMI and motor control studies have found that motor cortical neurons exhibit task-relevant, low-dimensional

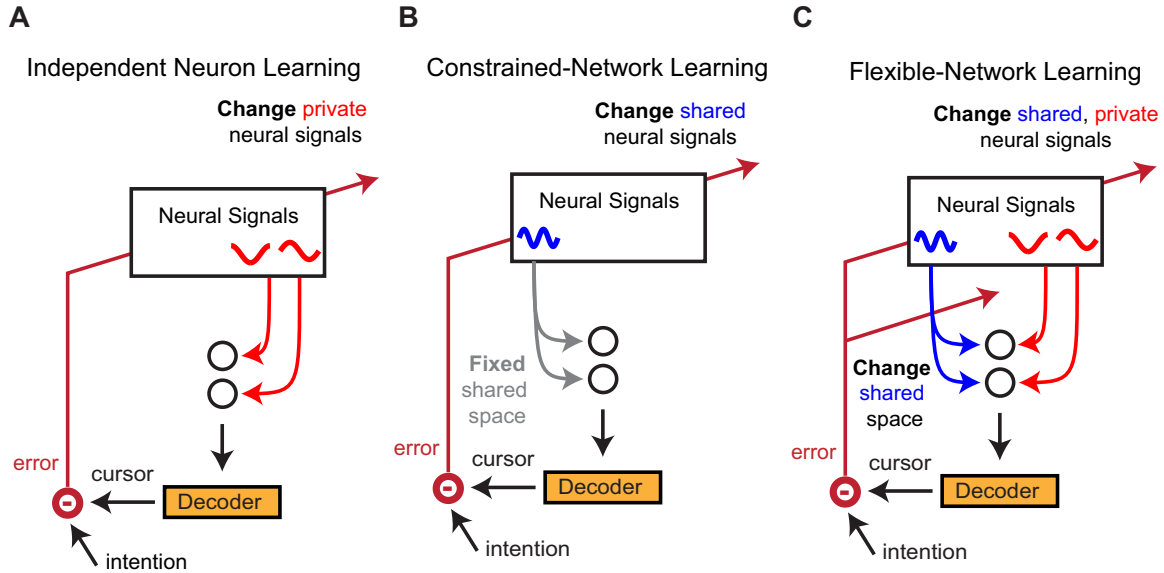


Figure 1.2: **Models of Learning.** (A) Independent Neuron Learning posits that each neuron explores and acquires independent patterns to control the BMI. (B) Constrained-Network Learning posits that the neural population learns BMI control by exploring and changing covariation patterns in a fixed shared space, e.g. because of network connectivity constraints. (C) Flexible-Network Learning posits that the neural population learns BMI control by exploring and changing both independent and covariation patterns and by using its exploration to change the shared space of covariation patterns. For intuition of how independent and covariation patterns can contribute to movement variability, see (Figure 5.1)

covariance during execution of well-learned behavior (Churchland et al., 2012; Kao et al., 2015; Sadtler et al., 2014). Under constrained-network learning, the neural population explores and changes covariation patterns within the fixed subspace (Sadtler et al., 2014) (Figure 1.2B). One limitation of the constrained exploration is that this learning can only acquire decoders reading out activity within the populations existing covariance subspace.

Finally, we consider “flexible-network learning,” which both permits the learning of many decoders and can explain the emergence of new covariance. In this model, the neural population explores and changes both independent and covariation patterns. Critically, independent exploration permits subjects to initially explore a higher dimensional space of activity patterns. Upon discovering patterns with rewarding consequences, subjects may shape their network to reliably reproduce rewarding patterns, constraining patterns to lie within a low-dimensional subspace. This mechanism thus enables consolidation of covariance in a different subspace from initial covariance (Figure 1.2C).

To determine which of these three possibilities best explains how the task-relevant neural population coordinates to acquire neuroprosthetic skill de novo, we sought to disentangle

how independent and coordinating sources of neural variance changed and contributed to BMI control over the course of learning. We used Factor Analysis (FA) (Everitt, 1984) to decompose population activity into the sum of private and shared signals, which estimate the effects of both private inputs to each cell and coordinating inputs which drive multiple cells simultaneously (Churchland et al., 2010; Yu et al., 2009). Using FA, we arbitrated between our three learning models in addressing how a task-relevant neural population explores, consolidates, and optimizes activity to acquire a neuroprosthetic skill *de novo*.

First, we asked how private and shared sources influence the exploration of different activity patterns from trial-to-trial. To isolate trial-to-trial variability from within-trial variance relevant for control, we focused on the variability of the population firing rate at coarse-timescale (time window ~ 1 s) for a fixed cursor state (the center of the workspace) with a fixed movement intention (the target). Second, we asked how private and shared sources contribute to within-trial control over the course of learning. To assess control-relevant neural activity, we focused on spike counts at the decoder-timescale of 100 ms. This decoder-timescale neural variance can be interpreted as signal strength for BMI control. Finally, we asked how the spatial and temporal structure of late-training neural activity supported skillful control. In particular, we asked whether neural activity preferentially occupied the control-relevant dimensions of the decoder, and whether a particular temporal sequence was consolidated which generated skillful control. We focused on fine-timescale trajectories at 50 ms resolution, faster even than the decoder-timescale.

Exploration and consolidation via independent neuron learning predicts that private trial-to-trial variability decreases and private decoder-timescale variance is used for control. Constrained-network learning predicts the opposite; shared trial-to-trial variability decreases and shared decoder-timescale variance is used for control. Combining these changes under flexible-network learning, we would expect that in early learning, private trial-to-trial variability contributes to activity exploration, and private decoder-timescale variance produces variable movements, while we would expect that in late learning, shared decoder-timescale variance consolidates and contributes to skillful control. Indeed, our analyses revealed that private and shared variance changed differentially to sculpt neural spatiotemporal patterns and improve movements, providing insight into how motor cortex coordinates to explore, consolidate, and optimize population activity underlying novel skills.

Chapter 2

Methods

Experimental model and subject details

Two adult male rhesus monkeys (*Macaca mulatta*) (Monkey P, age: 7 years 1 month, weight: 15 kg; Monkey R, age 6 years, weight: 10.7 kg) were chronically implanted in the brain with arrays of 64 Teflon-coated tungsten microelectrodes (35 μm in diameter, 500 μm pitch; Innovative Neurophysiology, Durham NC) in an 8×8 array configuration (Ganguly and Carmena, 2009). Monkey P was implanted in the left hemisphere in the arm area of both primary motor cortex (M1) and dorsal premotor cortex (PMd), and in the right hemisphere in the arm area of M1, with a total of 192 microwires across three implants. Monkey R was implanted bilaterally in the arm area of M1 and PMd (256 microwires across four implants). Only activity from M1 was used in these BMI experiments (Monkey P: right M1; Monkey R: left M1). Array implants were targeted for pyramidal tract neurons in layer 5. Localization of target areas was performed using stereotactic coordinates from a neuroanatomical atlas of the rhesus brain (Paxinos et al., 2000).

All procedures were conducted in compliance with the National Institutes of Health *Guide for the Care and Use of Laboratory Animals* and were approved by the University of California at Berkeley Institutional Animal Care and Use Committee.

Electrophysiology

Neural activity was recorded using the MAP system (Plexon) (Figure 2.1). Stable units were selected based on waveform shape, amplitude, relationship to other units on the same channel, inter-spike interval distribution, and the presence of an absolute refractory period. Only units from primary motor cortex were used which had a clearly identified waveform with signal-to-noise ratio of at least 4:1. Activity was sorted prior to recording sessions using an online spike-sorting application (Sort Client; Plexon). Stability of waveforms was confirmed by analyzing the stability of PCA projections over days (Wavetracker; Plexon).

Chronic Multi-Site Multi-Electrode Recordings

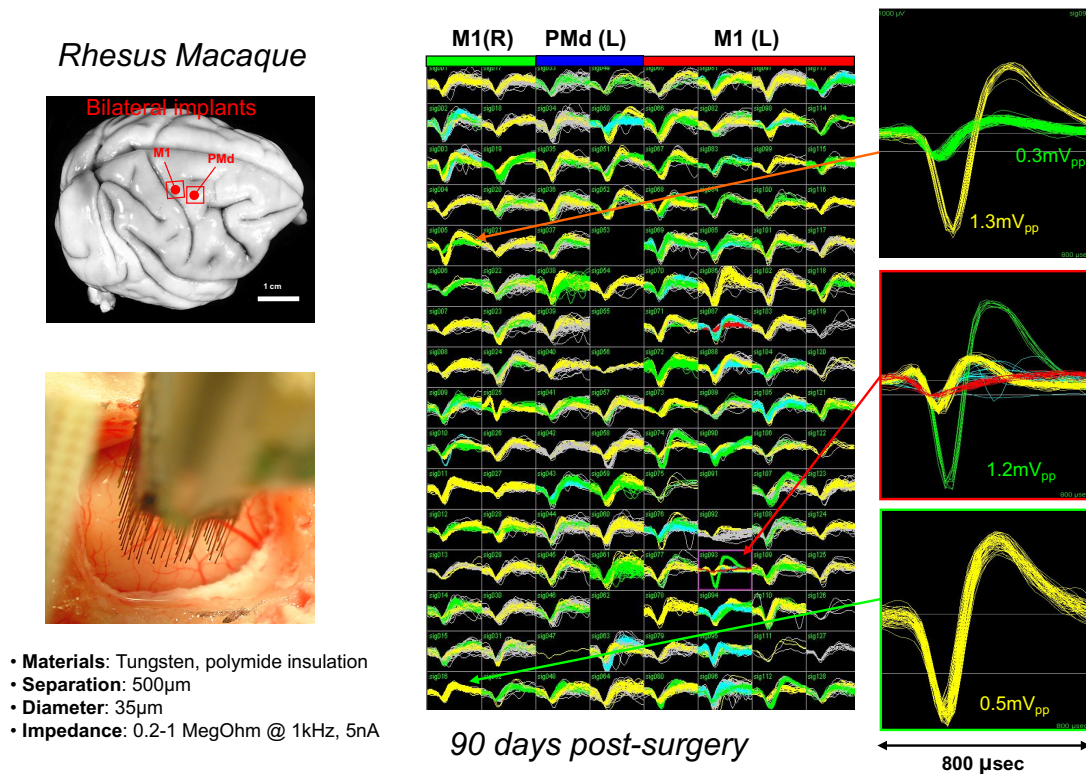


Figure 2.1: **Electrophysiology.** Electrophysiology in rhesus macaque M1 and PMd using 64 microwire arrays. Figure courtesy of Jose M. Carmena.

BMI Task

Subjects performed a center-out reaching task to eight targets (Figure 2.2A). The cursor was continuously controlled by neural activity. Subjects self-initiated trials by moving to the center target. Peripheral targets were presented in pseudorandom order. A successful trial required a short hold at the center, moving to the peripheral target within 15 seconds, and a brief hold at the target (Figure 2.2B). Successful trials resulted in a liquid reward; failed trials were repeated. During BMI control, both arms were removed from the workspace, lightly restrained, and thus unable to perform reaches. During selected sessions, video and surface electromyogram (EMG) recordings from proximal muscle groups were performed. Neither animal moved their upper extremity during brain control. Before starting the BMI learning experiments, subjects were overtrained on the task performed with arm movements using a Kinarm (BKIN Technologies) exoskeleton which restricted shoulder and elbow to move in the horizontal plane.

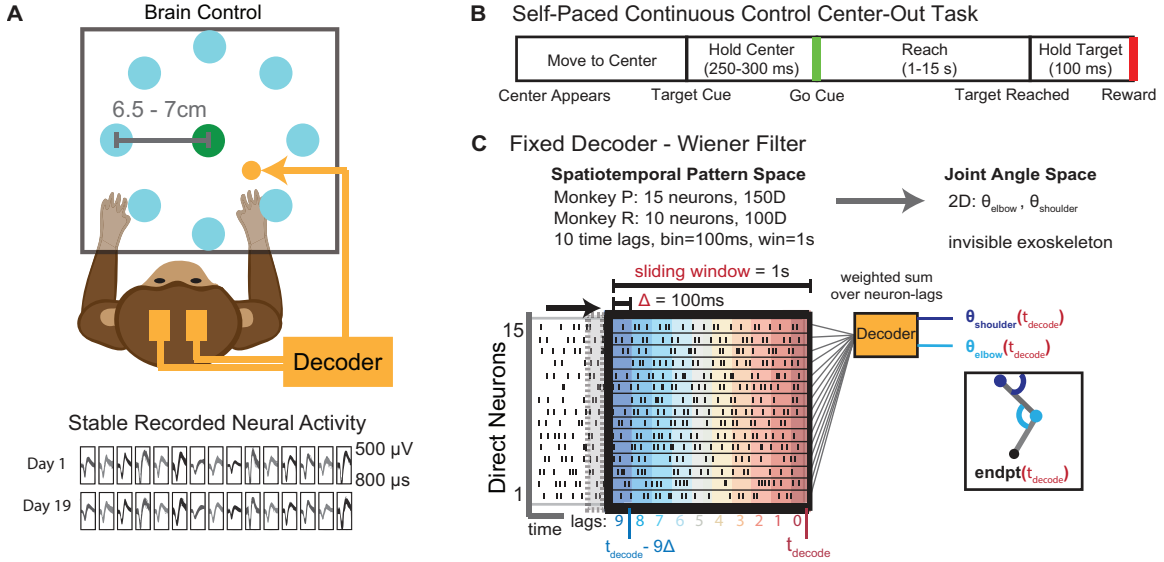


Figure 2.2: **Experimental Paradigm.** (A) Monkeys control a 2D cursor to one of 8 instructed targets using neural activity of stable neurons over days. (B) Center-out task timeline. (C) The task uses a position decoder, which maps a neural spatiotemporal pattern into a low-dimensional control signal that produces the cursor endpoint.

BMI Decoder

Decoding Algorithm

In this study, the decoder used neural activity to control the joint angles of a virtual, invisible two-link arm (Figure 2.2C). A Wiener Filter linearly mapped the binned spike counts of N neurons $x(t) \in \mathbf{R}^N$ in the last one second into virtual shoulder and elbow joint angles $y(t) \in \mathbf{R}^2$ via:

$$y(t) = \mathbf{b} + \sum_{k=0}^M \mathbf{a}(k\Delta)x(t - k\Delta) \quad (2.1)$$

The fixed decoder parameters $\mathbf{a}(k\Delta) \in \mathbf{R}^{2 \times N}$ for $k = 0, \dots, M$ and $\mathbf{b} \in \mathbf{R}^2$ used in this study were fit via least-squares linear regression to predict the subjects' actual shoulder and elbow joint angles in a calibration manual control session (Ganguly & Carmena, 2009). In this experiment, num lags = 10 = $M + 1$, and the spike count bin size was $\Delta = 100$ ms. The joint kinematics forward model mapped shoulder and elbow angles $y(t)$ to endpoint position, the only feedback signal the subjects received. The joint positions $y(t)$ and endpoint feedback signal were updated every $\Delta = 100$ ms.

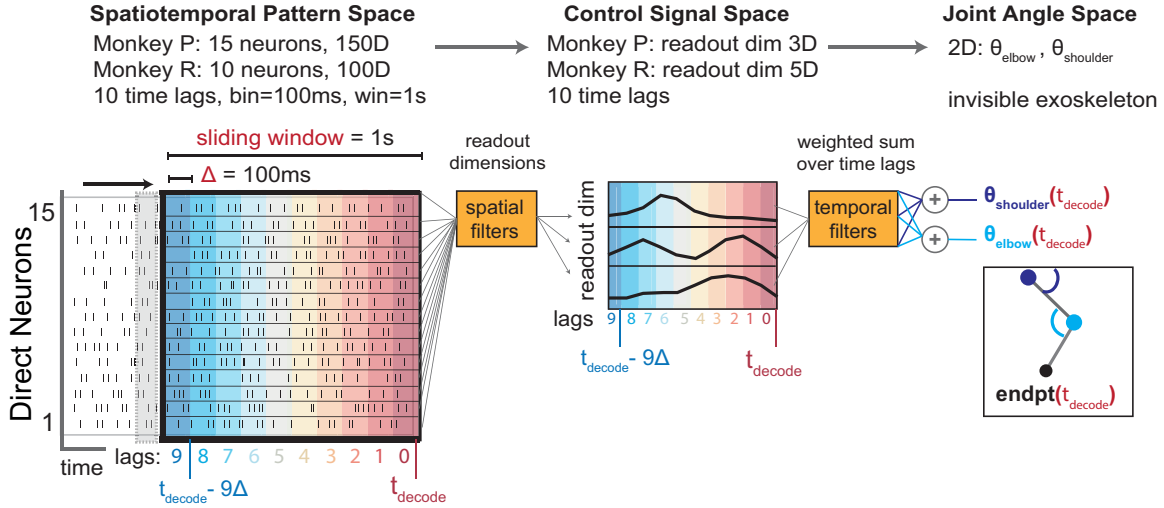


Figure 2.3: **Readout Space of Wiener Filter.** The decoder transforming neural activity into cursor position can be decomposed into two stages of filters. The first stage consists of “spatial filters” which project neural activity into a subspace termed the decoder’s “Readout Space.” The time series of neural activity projections are termed control signals. The decoder’s second stage consists of “temporal filters” which perform linear combinations of control signals over time lags.

Decoder Readout Space

We analyzed the decoder’s weights and determined that applying neural activity through the decoder is equivalent to first projecting neural activity into a subspace (the decoder readout space) and then applying it through the decoder (Figure 2.3). The decoder produced 2-dimensional output by summing num lags = 10 linear combinations of neural activity, so we analyzed how many neural dimensions the decoder primarily leveraged to produce control. At maximum, it could be 10, e.g. if each lag used a different individual neuron’s activity. We found the readout space dimensionality by evaluating the expression:

$$\mathbf{a}(k\Delta) \approx \mathbf{a}(k\Delta)\mathbf{P} \quad (2.2)$$

for $k = 0, \dots, M$, where $\mathbf{a}(k\Delta)$ are the decoder parameters, $\mathbf{P} \in \mathbf{R}^{N \times N}$ is a projection matrix of rank L , and num lags = 10 = $M + 1$. (Note that for $L = N$ we have perfect equality.) \mathbf{P} was found by performing PCA on the decoder parameters to compress neural dimensionality (as opposed to temporal dimensionality). $L = 3$ was sufficient for $\mathbf{a}(k\Delta)\mathbf{P}$ to capture $\sim 97\%$ of $\mathbf{a}(k\Delta)$ parameter variance for Monkey P, and $L = 5$ captured $\sim 99\%$ of parameter variance for Monkey R.

The “decoder readout space” is the column space of \mathbf{P} , as we can reproduce BMI cursor movements by first projecting neural activity into this space. Thus, we note that for our

decoder, the readout space dimensionality is not the same as the cursor dimensionality.

Quantifying Learning Over Training Epochs

We analyzed the behavioral and neural learning process for each target separately over “training epoch” blocks of a constant number of trials. We chose the “training epoch” rather than the more standard “training day” because we wished to eliminate the effect of variable trial numbers per training day on analysis results. Note that because subjects performed a different number of trials to each target overall, the number of trials in a training epoch differs for each target. For Monkey P (Monkey R), the smallest epoch size is 23 trials (31 trials) and the largest is 36 trials (56 trials).

Behavioral Metrics

We quantified task performance using percent correct (percent of initiated trials completed successfully) and success rate (successful trials per minute). Success rate combines accuracy and speed and is given by $\frac{\text{num successful trials}}{\sum_{\text{all trials}} \text{time to initiate trial} + \text{time to complete trial}}$.

Cursor Variability Analyses

To analyze cursor variability, we analyzed the cursor trial-to-trial Spatial Occupancy Map (SOM) by discretizing the workspace (each bin was 0.34% of the workspace) and computing the fraction of trials the cursor would enter each position bin. This was computed for each target and training epoch as: $\text{SOM}(\text{position}_{ij}) = \frac{\text{num trials cursor enters position}_{ij}}{\text{num trials}}$. We performed three analyses. First, we assessed control refinement via the fraction of workspace

entered per trial: $\frac{1}{\text{num trials}} \sum_{\text{trial}_i=1}^{\text{num trials}} \frac{\text{num bins entered}(\text{trial}_i)}{\text{num bins}}$. Second, we assessed the stabil-

ity of the learned cursor control strategy via the correlation between the final epoch SOM and previous epochs: $\text{corr}(\text{SOM}_{\text{epoch}_i}, \text{SOM}_{\text{epoch}_j})$, for $\text{epoch}_i = 1, \dots, \text{epoch}_{\text{final}-1}$, where

$\text{corr}(a, b) = \frac{\sum_{i=1}^N a_i b_i}{\|a\| \|b\|}$ is the standard vector correlation for $a, b \in \mathbf{R}^N$. Third and finally, we assessed the cursor’s trial-to-trial movement variability by considering each trial as a binary vector of 0’s and 1’s indicating the cursor’s spatial occupancy. We computed the covariance matrix using this parameterization of each trial and calculated the variability via the trace. We note that a decrease in trial-to-trial variability is not a mathematical consequence of reduction in workspace explored, as it is possible for subjects to enter the same large fraction of the workspace consistently as well as to enter different small fractions of the workspace from trial-to-trial. The trends found by these analyses are not sensitive to the discretization resolution; the same results were achieved with coarser resolution, e.g. bins 4 times larger (data not shown).

Factor Analysis

Model

We used FA to model the joint distribution of N neurons' spike counts $x \in \mathbf{R}^N$ as the sum of 1) a mean rate $\mu \in \mathbf{R}^N$, 2) private signals with diagonal covariance $\Psi \in \mathbf{R}^{N \times N}$, and 3) shared signals due to a low-dimensional latent variable $z \in \mathbf{R}^k$, $k < N$:

$$\begin{aligned} z &\sim N(0, I) \\ x|z &\sim N(\mu + Uz, \Psi) \\ x &\sim N(\mu, UU^T + \Psi) \end{aligned} \tag{2.3}$$

$U \in \mathbf{R}^{N \times k}$ are the weights (or factors) capturing how z drives x . We make explicit FA's decomposition of population activity x into shared signals $x^{\text{shared}} = Uz \in \mathbf{R}^N$ and private signals $x^{\text{private}} \in \mathbf{R}^N$:

$$\begin{aligned} x^{\text{private}} &\sim N(0, \Sigma^{\text{private}}) \\ x^{\text{shared}} &\sim N(0, \Sigma^{\text{shared}}) \\ x^{\text{private}} &\perp x^{\text{shared}} \\ x &= \mu + x^{\text{shared}} + x^{\text{private}} \end{aligned} \tag{2.4}$$

where $\Sigma^{\text{private}} = \Psi$ and is diagonal, $\Sigma^{\text{shared}} = UU^T$ and is low rank, and $\Sigma^{\text{total}} = \Sigma^{\text{shared}} + \Sigma^{\text{private}}$.

For each target separately, we fit the model's parameters by maximizing the log-likelihood of the data with the EM algorithm for a chosen shared dimensionality $k < N$. The best-fitting shared dimensionality k^* is estimated by using cross-validated log-likelihood to determine which k best describes held-out data (Dempster et al., 1977). To ensure we didn't choose too high of shared dimensionality, we analyzed the eigenvalues of the shared variance found using the dimensionality which maximized cross-validated log-likelihood and evaluated how many dimensions were needed to capture 90% of shared variance. We used this estimate of shared dimensionality throughout the work.

Comparison to Pairwise Correlation and PCA

To quantify correlated population activity, FA has advantages over more familiar measures such as average pairwise correlation and Principal Components Analysis (PCA). First, pairwise correlation addresses how well one cell's activity can predict another's, while the cell's shared-to-total variance ratio indicates how well that cell's activity can be predicted by the rest of the population together. Second, average pairwise correlation does not tell us the data's dimensionality. While PCA provides information about dimensionality, FA provides additional features. FA is a probabilistic model which posits total covariance as the sum of shared and private variance, permitting analysis of the two sources separately, while PCA analyzes dimensionality of total covariance.

Shared and Private Variance and the Shared-to-total Variance Ratio

Neuron i 's shared variance is $\Sigma_{ii}^{\text{shared}}$, private variance is $\Sigma_{ii}^{\text{private}}$, and total variance is $\Sigma_{ii}^{\text{total}} = \Sigma_{ii}^{\text{shared}} + \Sigma_{ii}^{\text{private}}$. The population-average variance is $\frac{1}{N}\text{trace}(\Sigma) = \frac{1}{N}\sum_{i=1}^N \Sigma_{ii}$. The population's shared variance to total variance ratio is $\frac{\text{trace}(\Sigma^{\text{shared}})}{\text{trace}(\Sigma^{\text{total}})}$.

Data Analysis using FA

Extracting Main Shared Variance

After fitting FA, we ordered shared signals by their variance by diagonalizing Σ^{shared} via the singular value decomposition (SVD) (Yu et al., 2009). Throughout the work we compared the decoder-timescale ‘‘main shared’’ variance. i.e. variance within the top p orthogonalized factors which provide the best rank- p approximation of Σ^{shared} . For both subjects, $p = 2$, as that was the shared dimensionality in late learning.

Shared Space Alignment

We used the ‘‘shared space alignment’’ to measure the similarity between the shared variance (or main shared variance) of epoch A and epoch B. The shared space alignment is the fraction of epoch A shared variance captured in epoch B's shared space and thus ranges from 0 to 1. For some geometric intuition, in the one-dimensional case (i.e., $\text{rank}(\Sigma^{\text{A, shared}}) = \text{rank}(\Sigma^{\text{B, shared}}) = 1$), the space alignment is equivalent to $\cos(\theta)$, where θ is the angle between epoch A and epoch B's one-dimensional shared space. We note that the shared space alignment is asymmetric when shared dimensionality is greater than 1, such that alignment of A with B need not be equal to the alignment of B with A.

Let $\Sigma^{\text{A, shared}}$ be epoch A's shared variance, and epoch B's shared space is $\text{col}(U^{\text{B}})$, the column space of epoch B's factor matrix U^{B} . We computed the shared space alignment in three steps:

1) Compute $P_{U^{\text{B}}} \in \mathbf{R}^{N \times N}$, the projection matrix into $\text{col}(U^{\text{B}})$. This is $P_{U^{\text{B}}} = VV^T$, where V is an orthonormal basis for $\text{col}(U^{\text{B}})$, e.g. calculated via the singular value decomposition $\text{SVD}(U^{\text{B}}U^{\text{B}T}) = VSV^T$.

2) Project $\Sigma^{\text{A, shared}}$ onto $\text{col}(U^{\text{B}})$, which is $P_{U^{\text{B}}}\Sigma^{\text{A, shared}}P_{U^{\text{B}}}^T$.

3) Compute the alignment via $\frac{\text{trace}(P_{U^{\text{B}}}\Sigma^{\text{A, shared}}P_{U^{\text{B}}}^T)}{\text{trace}(\Sigma^{\text{A, shared}})}$

This computation is used in Figure 3.4 E, 3.5 F, and 3.7 D. In Figure 3.7 D, main shared variance is projected into the readout space.

We computed the chance alignment by generating 100,000 random pairs of 1) a projection subspace of high dimensional neural space and 2) identity covariance in a random subspace of high dimensional neural space, and calculating the mean and 95th percentile of alignment. For Figure 3.4 E, the projection subspace and covariance are both 1-dimensional in a 15-dimensional ambient space (yielding mean chance alignment of 0.07 and 95th percentile chance alignment of 0.25). For Figure 3.5 F, the projection subspace and covariance are

both 2-dimensional in a 15-dimensional ambient space for Monkey P (yielding mean chance alignment of 0.13 and 95th percentile chance alignment of 0.28) and 10-dimensional ambient space for Monkey R (yielding mean chance alignment of 0.20 and 95th percentile chance alignment of 0.40).

Trial-to-trial Variability of Shared and Private Signals

We analyzed trial-to-trial variability by applying FA to a data matrix in which each column is one trial’s population spike counts in a window (~ 1 second) locked to Go Cue. For each monkey, we chose the window length to be the longest amount of time such that at least 70% of trials for every target and training epoch were longer (Monkey P 0.9 seconds; Monkey R 1.3 seconds) (Figure 5.4 A). We removed neurons with an average rate below 1.5 Hz because we had too few trials of non-zero activity to accurately estimate their variance. Over targets and epochs, a median of 11 out of 15 neurons were used for Monkey P and 9 out of 10 neurons were used for Monkey R. For all targets and epochs, the best-fitting shared dimensionality was 1, thus shared space alignment over training was between shared spaces of equal dimensionality (Figure 3.4 E).

We considered two components to spike count variability: fixed firing rate spiking variability (such as in a Poisson process) and underlying firing rate variability (Churchland et al. 2010). We analyzed whether neural variability changes differed from changes expected with Poisson spiking variability by 1) normalizing each neuron’s private variance by its mean rate and 2) performing FA on Poisson-simulated neurons (Figure 5.5 B-E). The ratio of shared variance to total variance was calculated without any normalization of private variance (Figure 3.4 C).

Decoder-timescale Private and Shared Variance

We analyze decoder-timescale population variance for each target and epoch by binning trials in 100 ms bins and applying FA. Neurons with firing rate below 1.5 Hz were excluded, as in the trial-to-trial variability analysis.

Sample-by-sample Contribution of Private and Shared Variance

Given an observed spike count at time t : $x(t)$, we used FA to estimate the shared and private variance contribution:

$$\begin{aligned}\hat{x}^{\text{shared}} &= E[x^{\text{shared}}(t) | x(t)] = E[Uz(t) | x(t)] \\ &= UU^T(UU^T + \Psi)^{-1}(x(t) - \mu) \\ \hat{x}^{\text{private}} &= x(t) - \hat{x}^{\text{shared}}(t) - \mu\end{aligned}\tag{2.5}$$

The main shared variance contribution is the linear projection of $\hat{x}^{\text{shared}}(t)$ into the main shared subspace (the top eigenvectors of Σ^{shared}).

Trial-to-trial Decoder Simulations

To test the how decoder-timescale main shared variance and private variance independently contribute to control, we separately supplied each trial’s main shared trajectory $\hat{x}^{\text{shared}}(t) + \mu$ and private trajectory $\hat{x}^{\text{private}}(t) + \mu$ as input to the decoder for the length of the observed trial. We quantified simulated performance using best progress to target, time to target hit (seconds), and normalized distance traveled to target hit. Best progress to target was computed for each trial as $\frac{\max(\text{closest distance to target} - \text{target radius}, 0)}{\text{distance from center to target}} \in [0, 1]$, such that a value of 1 indicates the target was reached and 0 indicates the cursor got no closer than the starting center point. Normalized distance traveled to achieve the target was normalized by the distance from center to target, such that a value of 1 indicates the cursor moved perfectly straight to the target. To compare late learning shared and private control, we used trials for which both were successful (Figure 3.6 E,F).

Relationship of Shared Variance to the Readout Space

We quantified shared variance in the decoder’s readout space via $\text{trace}(P_R \Sigma^{\text{shared}} P_R^T)$, where P_R is the projection matrix onto the readout space (Figure 3.7 B). It is the product of the shared variance magnitude: $\text{trace}(\Sigma^{\text{shared}})$ and shared space alignment with the readout space: $\frac{\text{trace}(P_R \Sigma^{\text{shared}} P_R^T)}{\text{trace}(\Sigma^{\text{shared}})}$, i.e. the fraction of shared variance captured in the readout space (Figure 3.7 D, 5.6 A). For each target and training epoch, we calculated the main shared variance magnitude and readout space alignment and normalized by training epoch 1 values to yield a “magnitude growth factor” and an “alignment growth factor” (Figure 3.7 D).

Shared Neural Trajectories at Fine-Timescale

To quantify shared neural trajectories, we zoomed in bin resolution to fine-timescale with 50 ms bins, performed FA on each target and epoch separately, and calculated

$$E[x^{\text{main shared}}(t) \mid x(t)]$$

on each spike count time sample. We then trial averaged each trial’s main shared trajectory (Figure 3.8 BC). We quantified the magnitude of the main shared trajectory by taking the squared Frobenius norm (Figure 3.8 D) and the stability of the trajectory by taking the correlation between each epoch’s main shared trajectory and the final main shared trajectory (Figure 3.8 E). The fraction of main shared variance explained by the average main shared trajectory was calculated as follows. We took the difference between each trial’s main shared trajectory and the trial-averaged main shared trajectory within a 2 second window and calculated how much main shared variance remained in these residuals. The main shared variance due to the trial-averaged main shared trajectory was $1 - \frac{\text{residual main shared variance}}{\text{main shared variance}}$ (Figure 3.8 F). Finally, we supplied the trial-averaged main shared trajectory as input to the decoder and quantified the progress to target (Figure 3.8 H).

Quantification and Statistical Analyses

All analyses were performed for each target separately, and each plotted trend shows the mean and s.e.m. over targets ($n=8$) for each training epoch, as indicated in the Results and figure legends. Trends were analyzed for significance with linear regression. Additionally, for both subjects we grouped the first 3 epochs into an early block and the final 3 epochs into a late block, resulting in $n=24$ in each group, from 3 epochs of 8 targets. For each analysis, we then performed a non-parametric one-sided Wilcoxon rank sum test of the appropriate comparison between early and late median. P values < 0.05 were considered statistically significant. All statistical analyses were performed with custom scripts in Matlab.

Chapter 3

Results

Neural control refinement increases movement success rate, directness, and consistency

We analyzed data from operant learning BMI experiments (Ganguly and Carmena, 2009) in which two rhesus macaques chronically implanted with microelectrode arrays in M1 learned to perform a two-dimensional, self-paced, continuous control center-out BMI reaching task (Figure 2.2A, B). Each trial, subjects drove the cursor under neural control to an instructed target (randomly selected from eight possible targets) for juice reward and controlled the cursor back to center to initiate the next trial. The decoder was optimized to predict upper limb movement using input from a fixed subset of recorded neurons (“direct cells”) chosen because of their stability over days (see Experimental Procedures) (Ganguly and Carmena, 2009). Because both the direct cells and the decoder parameters were held fixed for the duration of training (Monkey P: 19 days; Monkey R: 7 days), performance improvement could only be driven by adaptive changes in population activity (Figure 1.1).

The decoder transformed a neural activity sequence into the cursor’s x-y position (Figure 2.3). The direct cells’ activity in the last one second was binned into 10 time lags of 100 ms bins, and linear combinations of the neuron-lag activity produced the cursor’s position. Because the number of neurons exceeded the two cursor dimensions (Monkey P: 15 neurons; Monkey R: 10 neurons), (infinitely) many activity patterns could produce the same behavior, as is the case in our motor system which possesses more neurons than muscles. Changes in neural activity did not translate into changes in cursor position unless they occurred within the decoder’s control-relevant neural dimensions, the “readout space”, defined by the decoder weights.

Under these conditions, subjects gained proficient control, improving both accuracy and success rate for all targets (Figure 3.1 A,B). Changes over learning were analyzed over “training epochs,” where each epoch contains a constant number of trials. This division of trials ensured that analysis results were not influenced by unequal numbers of trials performed on each day. Observed trends were consistent with analyses performed across days (Figure 5.2, 5.3). Note that analyses of behavioral and neural changes were performed

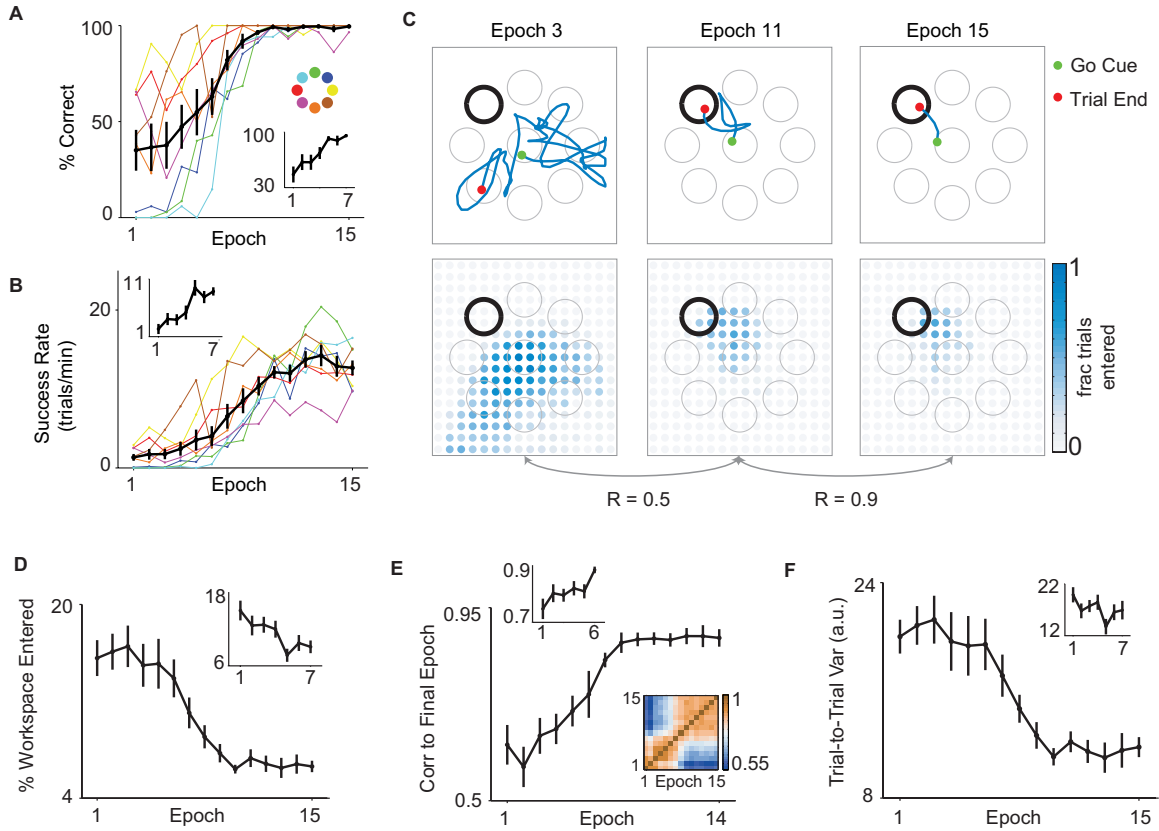


Figure 3.1: **Cursor control is refined.** Caption on next page.

for each target separately. All trends are plotted with error bars showing the standard error of the mean (s.e.m.) over targets.

We asked how control was refined on a trial-to-trial basis by analyzing the positions the cursor entered in each trial. We computed the cursor’s trial-to-trial workspace occupancy for each individual target, i.e. the probability that the cursor entered a given position within a trial (Figure 3.1 C). We found that the fraction of workspace entered per trial decreased as the cursor movements became increasingly direct (Figure 3.1 D), and that the subjects’ workspace occupancy became consistent over late-training epochs (Figure 3.1 E) (see Experimental Procedures). These two results show that the cursor’s trial-to-trial exploration of the workspace became refined and stable with training, extending previous reports on the straightening and stabilization of trial-averaged trajectories (Ganguly and Carmena, 2009). Finally, we found a decrease in the trial-to-trial variability of the entire set of positions entered within a trial (Figure 3.1 F) (see Experimental Procedures). These results show that neural control was refined and consolidated over long-term BMI training, increasing movement success rate, directness, and consistency.

Figure 3.1: (Previous page.) **(A,B)** Performance improved over training for Monkey P (main) and Monkey R (inset). Percent correct increased (Monkey P: $r=0.93$, $p=5.8e-7$, early < late $p=3.3e-10$; Monkey R: $r=0.96$, $p=4.7e-4$, early < late $p=1.5e-9$). Success rate in trials per minute increased (Monkey P: $r=0.96$, $p=1.6e-8$, early < late $p=1.4e-6$; Monkey R: $r=0.91$, $p=4e-3$, early < late $p=4.0e-6$). Targets (indicated by color) showed different time courses of improvement. Mean and s.e.m. error bars are shown over targets ($n=8$ for both subjects). **(C, top)** Single trial example trajectories over three epochs, for one example target. **(C, bottom)** Workspace occupancy maps for the example target over three epochs. Intensity indicates the fraction of trials a position was occupied. **(D)** Percent of workspace entered per trial decreased over training (Monkey P: $r=-0.94$, $p=3.2e-07$, early > late $p=4.1e-9$; Monkey R: $r=-0.87$, $p=1e-2$, early > late $p=2.0e-4$). **(E)** Similarity of workspace occupancy to the final workspace map increased and stabilized with training (Monkey P: $r=0.92$, $p=2.3e-6$, early < late $p=5.9e-9$; Monkey R: $r=0.88$, $p=2e-2$, early < late $p=1.2e-2$). **(E, bottom inset)** Heat map shows the similarity between each epoch pair's occupancy maps. A heat map was calculated for each target separately; the target average is shown here. The lower left red box indicates cursor scatter during gross exploration while the upper red box indicates late training stability of refined control. **(F)** Trial-to-trial variability of workspace occupancy decreased (Monkey P: $r=-0.93$, $p=4.6e-7$, early > late $p=1.7e-8$; Monkey R: $r=-0.54$, $p=2e-1$, early > late $p=2.4e-2$).

Modeling neural variance changes over learning with Factor Analysis

Having quantified control refinement over training, we sought to model how the direct cells coordinated to explore and change neural activity patterns underlying control. Under what conditions would independent patterns (described by private variance, Figure 1.2 A) or co-variation patterns (described by shared variance, Figure 1.2 B) be preferred for generating movement variability? When a subject has no idea which neural readout dimensions the decoder uses, private variance is beneficial because this high-dimensional exploration would generate variability in any readout space (Figure 5.1 A). Low-dimensional shared variance might be misaligned with the readout space and thus produce little movement variability (Figure 5.1 B). On the other hand, when the subject has experience with the readout space, low-dimensional shared variance aligned with the readout space is more efficient in generating movements because it concentrates more variance in fewer neural dimensions (Figure 5.1 C) and it leads to faster learning (Sadtlter et al., 2014). Thus, flexible-network learning combines these properties, allowing the population to expansively explore using private variance and then consolidate control-specific shared variance. Importantly, exploring the behavioral consequences of activity outside the initial shared space could guide the shared space to rotate or change dimensionality (Figure 1.2 C).

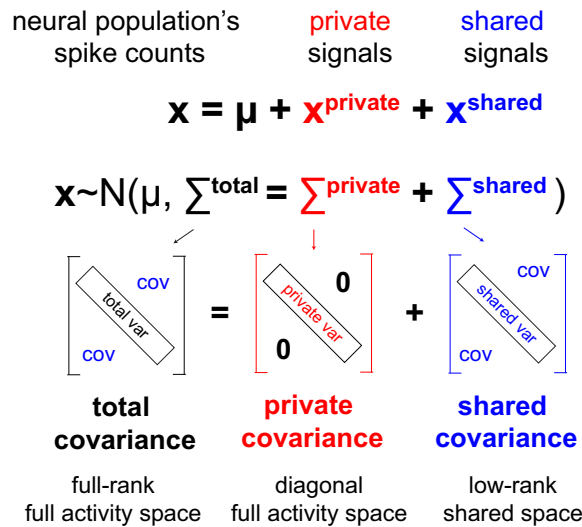


Figure 3.2: **Factor Analysis Covariance Decomposition.** Factor Analysis (FA) decomposes the spike count covariance matrix into the sum of a diagonal private variance matrix and a low-rank shared variance matrix.

Seeking evidence for these neural activity changes, we used FA (Figure 3.2) to decompose population firing rate activity into the sum of 1) a mean rate, 2) private signals which drive each neuron without correlation (Figure 3.3 A), and 3) low-dimensional shared signals which

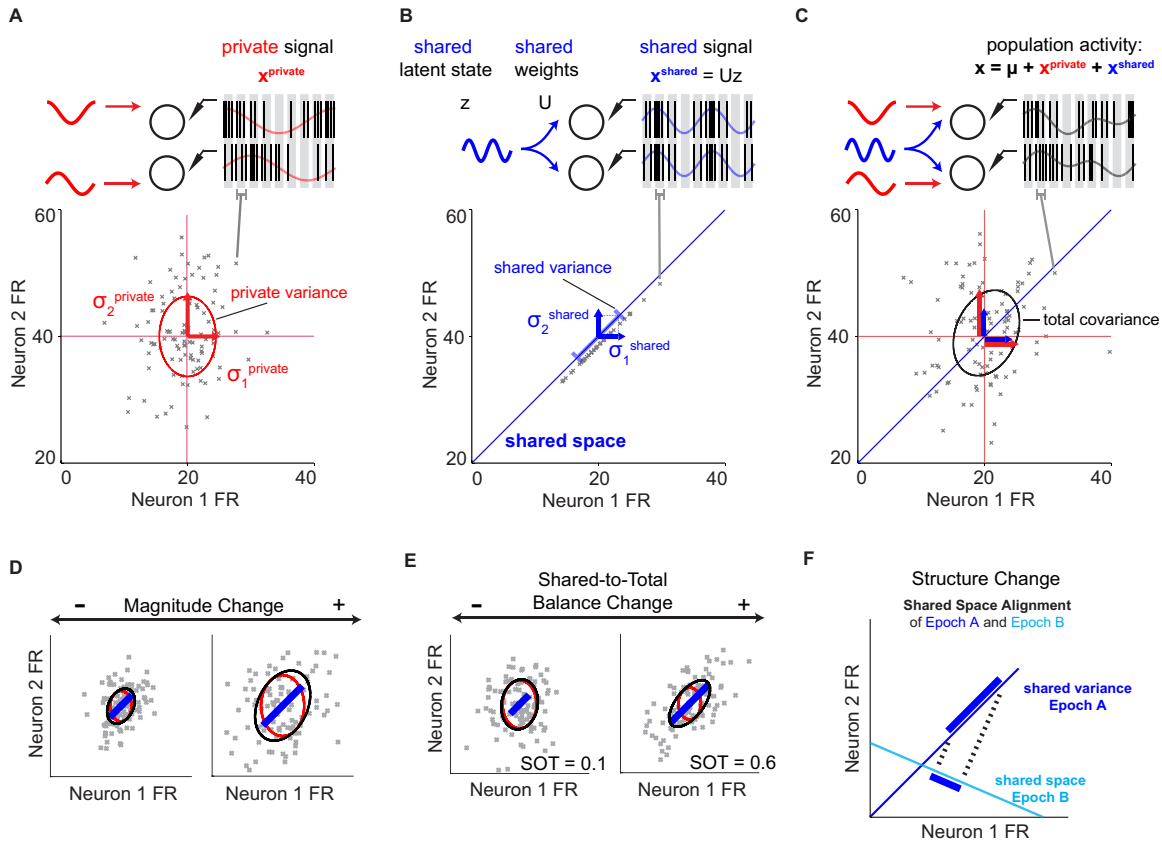


Figure 3.3: Variance Analyses via Factor Analysis.

Figure 3.3: Variance Analyses via Factor Analysis. (A) Private signals modulating two neurons’ firing rates. Each scattered gray ‘x’ is a binned population spike count. Neuron 2 has a larger private variance than neuron 1. (B) Shared signals modulating two neurons’ firing rates within a one-dimensional shared space. (C) FA describes the mixture of private and shared variance underlying population activity. (D) FA detects changes in the total magnitude of variance. (E) FA also detects changes in the shared-to-total variance ratio, quantifying how shared and private variance change in different proportions. The shared-to-total ratio plus the private-to-total ratio equals 1. (F) FA detects changes in how the population co-varies using the shared space alignment between Epoch A and B, which is the fraction of Epoch A’s shared variance captured in Epoch B’s shared space.

drive multiple neurons simultaneously, produce correlations, and constrain activity to the shared space (Figure 3.3 B). Thus, FA models the population’s total covariance matrix as the

sum of the diagonal covariance matrix due to uncorrelated private signals and the low-rank covariance matrix due to shared signals, permitting variance only within the shared space (Figure 3.2, 3.3 C). Our use of private variance and shared variance specifically refers to their respective covariance matrices. We emphasize that FA is fit for each target separately on the full simultaneously-recorded direct cell population, not just neuron-pairs as illustrated for geometric intuition (Figure 3.3). Model-fitting assessed the shared space dimensionality (number of shared signals) needed to best describe the firing rates (see Experimental Procedures).

We used FA to analyze how the neural population’s private and shared variance change over learning (Figure 3.2). First, the magnitude of total variance can change (Figure 3.3D). Second, the balance of shared and private variance can change, a measure of coordination which we quantified with the shared-to-total variance ratio (Figure 3.3 E). Third, the shared space containing shared variance can change, which we quantified by calculating the alignment between two epochs’ shared variances (Figure 3.3 F, Experimental Procedures). The shared space alignment, ranging between 0 and 1, asks how well Epoch B’s shared signals can approximate Epoch A’s shared signals. If Epoch A and B have perfectly aligned shared spaces, then the alignment is 1, and if the shared spaces are orthogonal, the alignment is 0. Thus, if the shared space stays fixed over learning as predicted by constrained-network learning, we expect alignment values to be high throughout training. In contrast, if the shared space consolidates with learning as predicted by flexible-network learning, we expect high alignment values only in late-learning. We used these three analyses to study how private and shared sources of variance contribute to the exploration and consolidation of activity patterns.

Over learning, private trial-to-trial variability decreases while the shared space changes and stabilizes

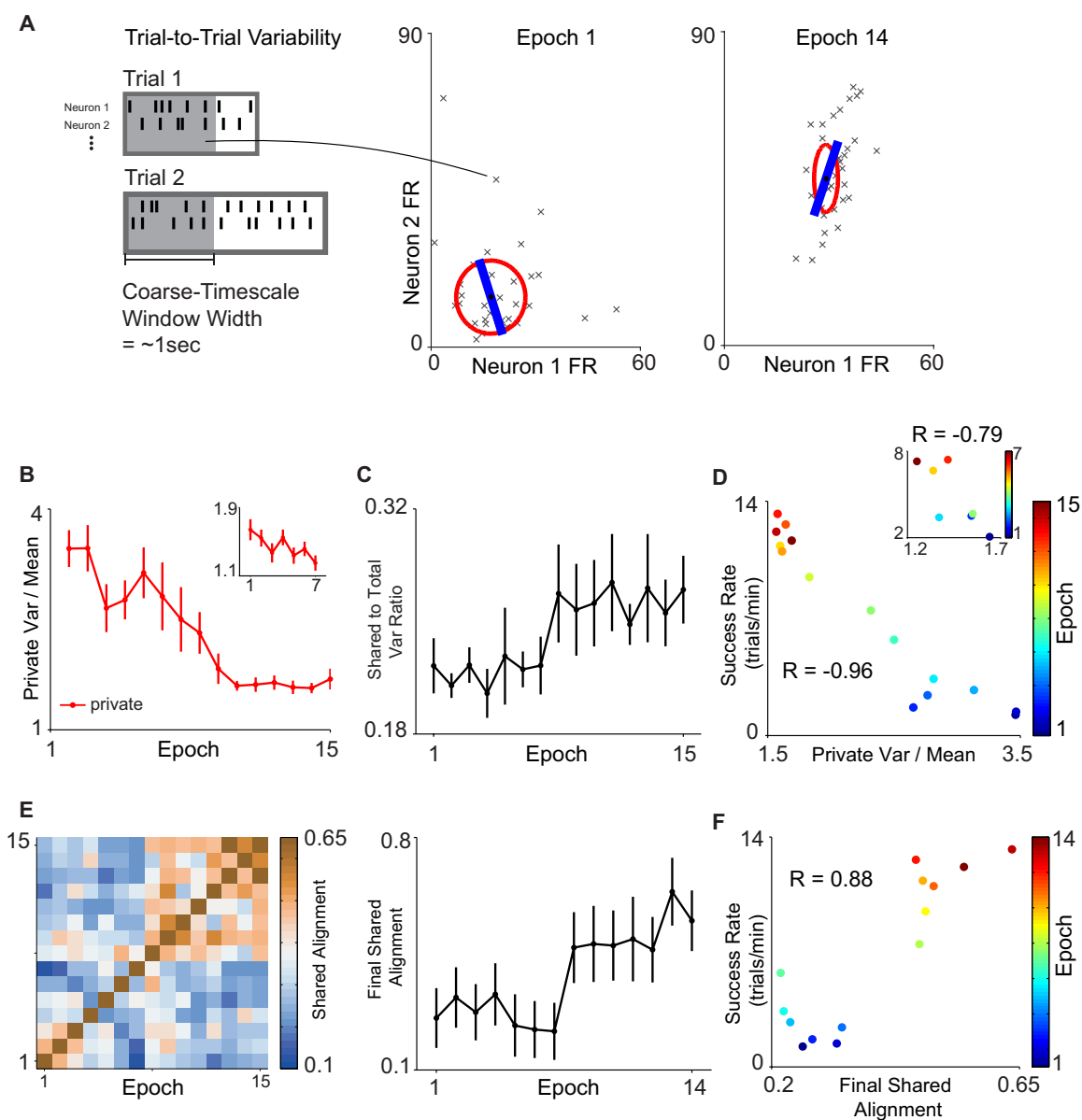


Figure 3.4: **Private Trial-to-Trial Variability Decreases and the Shared Trial-to-Trial Variability Consolidates a Shared Space.**

While previous studies have found trial-to-trial neural variability decreases for a particular intended action over motor learning, we used FA to ask how private and shared sources

Figure 3.4: **Private Trial-to-Trial Variability Decreases and the Shared Trial-to-Trial Variability Consolidates a Shared Space.** **(A)** Trial-to-trial variability example: FA fit on 2 direct cells in early and late training for Monkey P on one example target. **(B)** Private trial-to-trial variability for Monkey P (main) and Monkey R (inset) decreased (Monkey P: $r=-0.93$, $p=6.7e-7$, early $>$ late $p=1.1e-8$; Monkey R: $r=-0.81$, $p=2.7e-2$, early $>$ late $p=2.2e-2$). **(C)** The shared-to-total variance ratio increased over long-term training (Monkey P: $r=0.83$, $p=1.1e-4$, early $<$ late $p=8.1e-3$) but not significantly over shorter training (Monkey R: $r=0.27$, $p=5.5e-1$, early $<$ late $p=8.2e-2$). **(D)** The private trial-to-trial variability decrease correlated with success rate improvement (Monkey P: $r=-0.96$, $p=1.9e-8$; Monkey R: $r=-0.79$, $p=3.5e-2$). **(E, left)** The shared space alignment map indicated consolidation. Each element is the alignment of the row epoch’s shared variance with the column epoch’s shared space. The upper right red block indicates that the shared space becomes relatively stable, while the preceding blue indicates the shared space is unstable in early training. **(E, right)** The shared space alignment between the final epoch’s shared space and the preceding epochs’ shared variance increased with long-term training (Monkey P: $r=0.83$, $p=2.6e-4$, early $<$ late $p=5.8e-4$; Monkey R: $r=-0.12$, $p=8.2e-1$, early $>$ late $p=4.9e-1$). The mean chance variance alignment is 0.07, and the 95th percentile chance alignment is 0.25 for Monkey P (see Experimental Procedures). **(F)** The shared space alignment with the final epoch’s shared space correlated with success rate over long-term training (Monkey P: $r=0.88$, $p=3.3e-5$; Monkey R: $r=0.07$, $p=9e-1$). Changes in mean firing rate do not explain these results (Figure 5.5). These results also held for analyses over training days rather than epochs (Figure 5.2) and different window lengths (Figure 5.4).

influenced trial-to-trial variability. We analyzed firing rate variability at the start of trials for each target separately. To avoid capturing within-trial variance used for control, we extracted one spike count vector from each trial in a large ~ 1 second window locked to Go Cue (Figure 3.4 A, left). Subjects’ trial times determined the window size (Monkey P: 0.9s; Monkey R: 1.3s, see Experimental Procedures for details), but the results were insensitive to window choice (Figure 5.4 B-D). We assessed private trial-to-trial variability beyond that expected for a Poisson process by normalizing each neuron’s private variance by its mean rate (see Experimental Procedures). Shared trial-to-trial variability was calculated with each neuron’s un-normalized shared variance because in Poisson simulations, shared variance did not scale with the experimentally observed firing rates (Figure 5.5 B). This analysis enabled us to disambiguate between independent-neuron learning’s private trial-to-trial variability decrease, constrained-network learning’s shared trial-to-trial variability decrease, and flexible-network learning’s private trial-to-trial variability decrease and shared space consolidation. FA applied to a neuron-pair in early and late training is shown for illustration (Figure 3.4 A), showing a decrease in private trial-to-trial variability, an increase in shared-to-total variance ratio, and rotation of the shared space. At the direct cell population

level, FA found only 1 shared dimension was needed for each target and epoch. Consistent with the example, we found initially large private trial-to-trial variability which decreased prominently over training (Figure 3.4 B, 5.2 A). In contrast, shared trial-to-trial variability showed no significant trend, resulting in an increase in the shared-to-total variance ratio (un-normalized by firing rate) over long-term training (Figure 3.4 C, 5.2 C). These results suggest that neural activity space exploration in early learning was primarily accomplished with private trial-to-trial variability. The decrease in private trial-to-trial variability was correlated with success rate over training (Figure 3.4 D, 5.2 B), indicating the subjects produced desired activity as private trial-to-trial variability reduced. While the magnitude of shared trial-to-trial variability showed no change, its subspace consolidated over training. We assessed the shared space alignment between epoch pairs (Figure 3.4 E left, 5.2 D left) and found the alignment with the final epoch's shared space increased with training (Figure 3.4 E right, 5.2 D right), correlating with the subject's success rate (Figure 3.4 F, 5.2 E). Notably, the emergent shared space possessed a significantly different alignment from the initial shared space. Altogether, these results support flexible-network learning, showing that initial trial-to-trial variability is private to each neuron, and as private trial-to-trial variability decreased, the shared space evolved and consolidated.

Decoder-timescale shared variance strengthens and consolidates to coordinate population activity

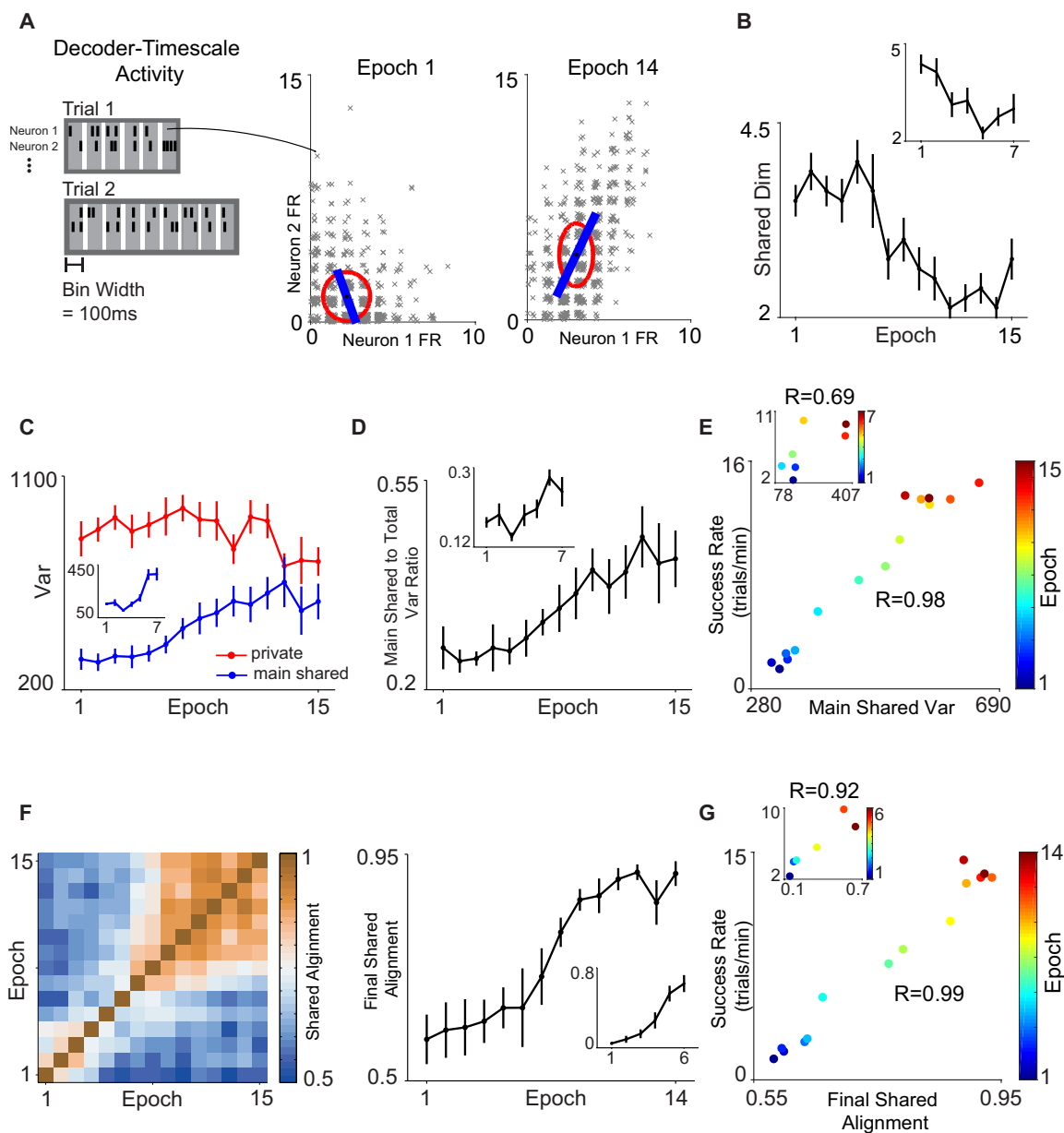


Figure 3.5: Decoder-timescale shared variance increases and consolidates a shared space.

Having analyzed coarse-timescale trial-to-trial variability, we next zoomed in temporal resolution and asked how private and shared sources contributed to control-relevant activity

Figure 3.5: **Decoder-timescale shared variance increases and consolidates a shared space.** **(A)** Decoder-timescale variance example: FA fit on 2 direct cells in early and late training for Monkey P on one example target. **(B)** The shared dimensionality decreased from 4 to 2 (Monkey P: $r=-0.85$, $p=5.7e-5$, early > late $p=1.4e-7$; Monkey R: $r=-0.80$, $p=3.1e-2$, early > late $p=9.8e-5$). We used a main shared dimensionality of 2 (see Experimental Methods). **(C)** Main shared variance increased with training (Monkey P: $r=0.92$, $p=8.1e-7$, early < late $p=1.9e-5$; Monkey R: $r=0.84$, $p=2.0e-2$, early < late $p=1.2e-5$). **(D)** The ratio of main shared variance to total variance increased with training (Monkey P: $r=0.95$, $p=7.1e-8$, early < late $p=2.2e-6$; Monkey R: $r=0.76$, $p=4.6e-2$, early < late $p=1.2e-4$). **(E)** Main shared variance correlated with success rate (Monkey P: $r=0.98$, $p=1.9e-10$; Monkey R: $r=0.69$, $p=8.6e-2$). **(F, left)** Shared space alignment map. The upper right red block indicates the shared space becomes stable, while the preceding blue indicates the shared space is changing in early training. **(F, right)** Alignment with the final epoch’s shared space increased with training (Monkey P: $r=0.95$, $p=1.8e-7$, early < late $p=9.6e-9$; Monkey R: $r=0.96$, $p=2.2e-3$, early < late $p=2.2e-6$). The mean chance alignment is (Monkey P: 0.13; Monkey R: 0.20) and 95th percentile chance alignment is (Monkey P: 0.28; Monkey R: 0.40). **(G)** Alignment with the final epoch’s shared space correlated with success rate improvement (Monkey P: $r=0.99$, $p=7.7e-11$; Monkey R: $r=0.92$, $p=8.3e-3$). Changes in mean firing rate do not explain these results (Figure 5.5). These results also held for analyses over training days rather than epochs (Figure 5.3) and different bin widths (Figure 5.4).

at the decoder-timescale of 100 ms bins (decoder bin size) for each target separately. Decoder-timescale neural variance can be interpreted as signal strength for BMI control, in contrast to our previous analysis on trial-to-trial variability. We thus use FA to study if the independent-neuron, constrained-network, or flexible network model best describes how learning changes decoder-timescale population activity driving control. We first observed population activity became lower dimensional, as the shared dimensionality describing the 100 ms spike counts within all trials to a single target decreased from 4 to 2 in late training (Figure 3.5 B). Because the brain found a two-dimensional neural solution in late training, we compared shared variance over training in the two neural dimensions which captured the most shared variance, which we call the “main shared variance” (see Experimental Procedures). Note that high-dimensional shared variance did not constitute a significant fraction of total variance (Figure 5.5 F). FA applied to a neuron-pair in early and late training is shown for illustration, in which shared variance increased and rotated (Figure 3.5 A). In concordance, in the entire direct cell population, we found main shared variance increased prominently while private variance decreased mildly over long-term training (Figure 3.5 C, 5.3 A), increasing the main shared-to-total variance ratio by a factor of 2 (Figure 3.5 D, 5.3 B). These results are not specific to our bin width selection, as they held over a range of bin sizes (Figure 5.4 E). Further, main shared variance correlated with success rate (Figure 3.5 E, 5.3 C), suggesting

that it was used for control. We next tested whether a shared space was consolidated over training for decoder-timescale variance. By analyzing the main shared space alignment, we found a period of relative instability in early learning followed by a period of stability in late learning (Figure 3.5 F, left). Notably, the stable main shared space of late training was significantly different from the main shared spaces explored in early training (Figure 3.5 F, right). Further, the alignment of main shared variance to the final epoch correlated with success rate (Figure 3.5 G), suggesting main shared variance consolidation supported learning. These results support the flexible-network learning mechanism, suggesting that learning proceeds by increasing shared variance within an emergent shared space which coordinates activity used for BMI control.

Decoder-timescale private variance contributes noisy yet successful control, while consolidated shared variance supports skillful control

Decoder-timescale private and shared variance changed differently over training, so we leveraged the decoder to ask how they contributed to cursor control. Mathematically, both sources are feasible strategies for generating a desired control signal (Figure 3.6 A, left). Private variance represents the limit of high-dimensional activity, such that the population exhibits no correlations, and still can possess the temporal structure to generate desired control signals in the readout space (Figure 3.6 A, middle). Shared variance captures low-dimensional covariation patterns and also can generate desired control signals in the readout space (Figure 3.6 A, right). For each target and epoch, we fit an FA model on decoder-timescale spike counts and used it to calculate the contribution of main shared and private variance to each individual trial of activity (see Experimental Procedures). We then used the main shared and private variance contributions as separate inputs to the decoder and compared the resulting control signals (Figure 3.6 B). Best trials produced by each source are shown, illustrating that both private and main shared variance could produce good control.

Under independent neuron learning, the population uses private variance for BMI control, while for constrained-network learning, the population uses shared variance. Because flexible-network learning permits both sources to contribute to control, we might expect private variance to dominate exploratory control in the beginning, while shared variance might contribute refined control in the end. Interestingly, both private and main shared variance improved how close they drove the cursor to the target (Figure 3.6 C). However, when we compared late training trials for which both sources achieved the target (Monkey P: 832 trials; Monkey R: 385 trials; Figure 3.6 D), we observed that main shared movements were faster (average time difference Monkey P: -0.80 sec; Monkey R: -0.66 sec) and more direct (average distance difference Monkey P: -1.6, Monkey R: -4.0, in units of distance from center to target) (Figure 3.6 EF). Thus, in late training, main shared variance contributed more skillful control. Indeed, offline analysis suggests main shared variance can even produce more skillful control than the total activity (Figure 5.6 B-D).

Main shared variance was not always better than private variance, however. In early training, private variance achieved positions closer-to-target (Figure 3.6 C), and total activity-driven movements explored more of the workspace than main shared movements (Figure 3.6 G). This suggests that initial main shared variance did not vary within the readout space, and that private variance served an exploratory role in early training by contributing behavioral variability. In support of flexible-network learning, private and main shared variance provided different contributions to performance improvement, with main shared variance contributing more skillful control in late learning.

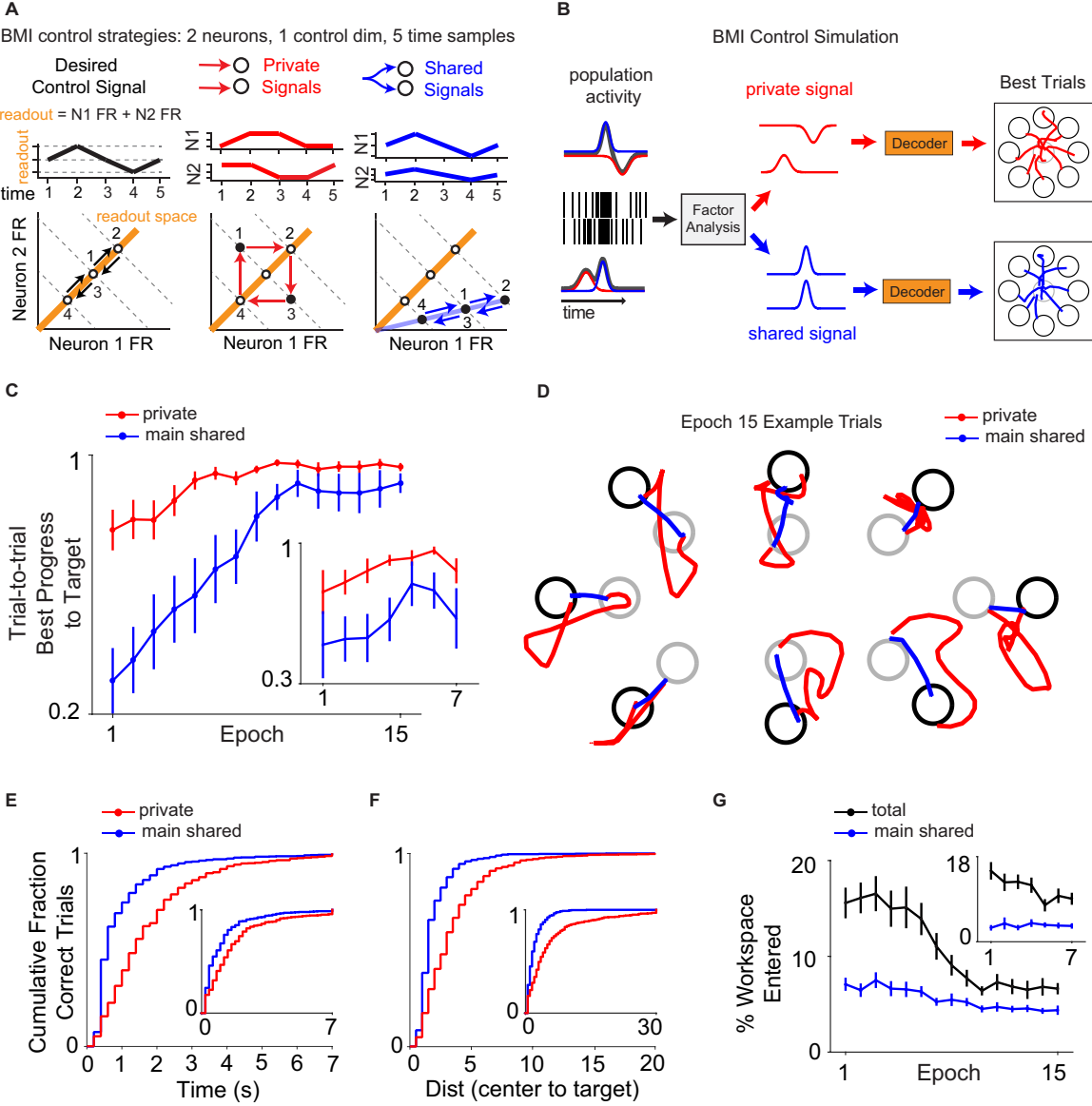


Figure 3.6: Decoder-timescale private variance produces noisy yet successful movements, while shared variance generate skillful movements.

Figure 3.6: **Decoder-timescale private variance produces noisy yet successful movements, while shared variance generate skillful movements.** (A) Both private and shared signals can mathematically produce the same desired control signal. (A, left) The desired control signal is shown over time, and its values are plotted on neuron firing rate axes. The readout value is the sum of the 2 neurons' firing rates. The dashed lines are contours which capture firing rates yielding the same sum. (A, middle) The neurons' activity is uncorrelated and produces the desired control signal. (A, right) The neurons' activity is perfectly correlated and produces the desired control signal. (B) The contribution of private and shared variance to each trial's activity can be estimated and simulated through the decoder separately to determine how they independently contribute to movement. (C) Both main shared and private variance increased best progress to target over training. (Private variance; Monkey P: $r=0.85$, $p=5.7e-5$, early < late $p=2.7e-6$; Monkey R: $r=0.75$, $p=5.3e-2$, early < late $p=3.0e-2$). (Main shared variance; Monkey P: $r=0.94$, $p=2.0e-7$, early < late $p=3.1e-8$; Monkey R: $r=0.74$, $p=5.8e-2$, early < late $p=9.6e-3$). (D) Example trials driven by main shared and private variance from the final epoch for each target. (E) In late training, successful main shared variance-driven movements were significantly faster than private variance-driven movements (main shared minus private time-to-target; Monkey P: mean = -0.80 sec, main shared < private $p=1.8e-56$; Monkey R: mean = -0.66 sec, main shared < private: $p=4.3e-11$). (F) In late training, successful main shared variance-driven movements were significantly more direct than private variance-driven movements (main shared minus private distance traveled; Monkey P: mean = -1.6, main shared < private $p=3.2e-52$; Monkey R: mean = -4.0, main shared < private $p=2.49e-22$). Interestingly, main shared variance achieved higher performance than even total activity (Figure S6). For (EF), late training trials were analyzed for which both private and main shared variance were successful (Monkey P: epochs 8 to 15, 832 trials; Monkey R: epochs 4 to 7, 385 trials). (G) Total activity-driven movements explored the workspace more than main shared variance-driven movements, especially in early training (main shared < total, Monkey P: $p=2.5e-9$; Monkey R: $p=3.2e-9$).

Control-relevant shared variance increases because of shared variance growth and re-alignment

How does decoder-timescale shared variance support skillful control (Figure 3.6 D)? We asked how main shared variance occupied the decoder’s readout space to produce control signals (Figure 3.7 A), finding that main shared variance in the readout space increased over training (Figure 3.7 B). Two independent mechanisms exist which increase readout space shared variance. First, shared variance itself can increase (magnitude growth, Figure 3.7 C left), as we already found (Figure 3.6 A). Second, the shared space can rotate to align with the readout space (re-alignment), thus making shared variance more efficient in producing control signals (Figure 3.7 C, right). We quantified the relative contributions of these two mechanisms by computing the factor by which main shared variance grew and the factor by which main shared space alignment with the readout space grew. The product of these two yields the factor by which readout space main shared variance grew. Interestingly, both mechanisms significantly increased over training (Figure 3.7 D). This provides one explanation for the changes in the main shared space; it can align with the readout space, making main shared variance more effective in producing control signals. These results provide a glimpse of how motor cortex can strengthen and optimize population coordination for neuroprosthetic control.

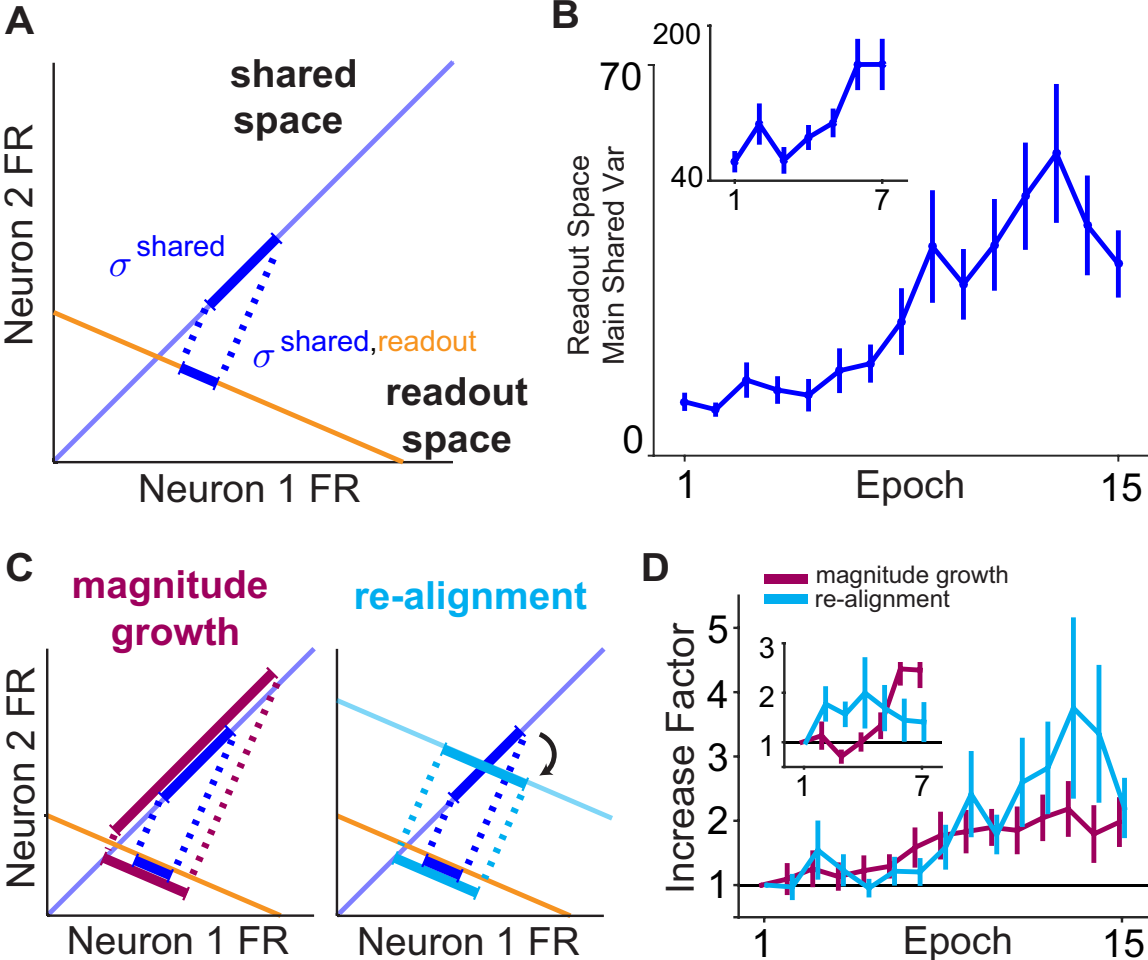


Figure 3.7: Task-relevant shared variance increases because of shared variance growth and re-alignment.

Figure 3.7: **Task-relevant shared variance increases because of shared variance growth and re-alignment.** (A) Shared variance can drive the decoder by producing variance in the decoder’s readout space. (B) Main shared variance in the readout space increased (Monkey P: $r=0.90$, $p=6.6e-6$, early < late $p=8.5e-9$; Monkey R: $r=0.85$, $p=1.5e-2$, early < late $p=8.4e-5$) (C) Shared variance can increase in the readout space by two mechanisms. (C, left) An increase in shared variance magnitude increases the readout space shared variance, as long as the shared space and readout space initially align. (C, right) Re-alignment of the shared space with the readout space increases the readout space shared variance. Readout space shared variance growth is the product of the magnitude growth and re-alignment. (D) Magnitude growth and re-alignment both increased for main shared variance, plotted as the ratio of each epoch’s value to the first epoch’s value. (Magnitude growth factor; Monkey P: $r=0.93$, $p=7.3e-7$, early < late $p=3.1e-4$; Monkey R: $r=0.82$, $p=2.4e-2$, early < late $p=1.6e-5$). (Re-alignment factor; Monkey P: $r=0.84$, $p=9.9e-5$, early < late $p=8.2e-6$; Monkey R: $r=0.17$, $p=7.2e-2$, early < late $p=6.2e-1$). While shared space alignment with the readout space increased, note that a significant fraction of shared variance remained outside the readout space in late learning (Figure 5.6 A).

Fine-timescale shared neural trajectories are consolidated which produce accurate movement

Having analyzed how the consolidated main shared variance relates to the readout space, we asked whether the covariation patterns consolidated a temporal sequence which supported skillful control, since shared variance can arise with or without consistent neural trajectories (Figure 3.8 A). To investigate temporal structure, we used finer bins (50 ms) than the decoder-timescale (100 ms), and for each individual target and epoch, we fit FA and calculated the main shared variance contribution to each trial’s activity and trial-averaged to form the main shared trajectory (see Experimental Procedures). Early epochs showed no pronounced pattern, while later epochs showed a large and consistent trajectory (Figure 3.8 BC). We found that the magnitude of each target’s main shared trajectory increased (Figure 3.8 D) and that the similarity of each target’s main shared trajectory to the final epoch increased (Figure 3.8 E), demonstrating neural trajectory consolidation. Was all the observed main shared variance due to these emergent neural trajectories? We took each trial’s main shared variance contributions and subtracted the trial-averaged main shared trajectory, leaving behind main shared variation beyond that due to the average trajectory, and calculated how much main shared variance remained. The large fraction of remaining main shared variance shows that the observed coordination of population activity is not simply explained by the activity’s average time-course. Interestingly, initial main shared variance showed no trial-averaged neural trajectory. The fraction of main shared variance due to the average neural trajectory increased with training (Figure 3.8 F), showing that main shared variance became increasingly temporally-structured over learning. Finally, we tested whether the main shared trajectories were sufficient for generating neuroprosthetic control. We applied them through the decoder and found that they evolved over learning to generate straight and accurate movements in late training (Figure 3.8 GH). These results show that emergent shared temporal structure produces control signals for skillful movement.

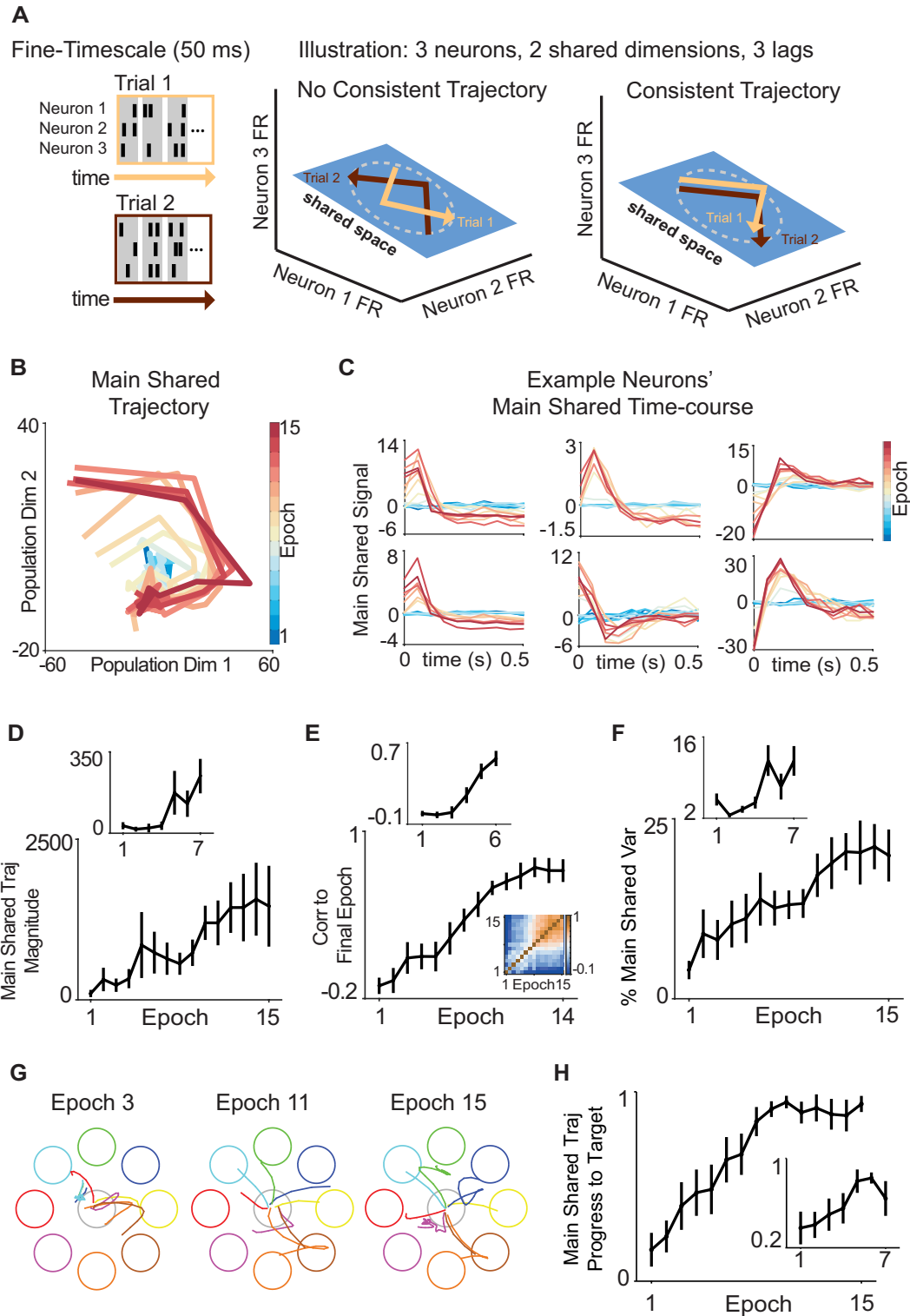


Figure 3.8: Shared neural trajectories are consolidated at fine-timescale which produce accurate movement.

Figure 3.8: **Shared neural trajectories are consolidated at fine-timescale which produce accurate movement.** **(A)** Shared variance can arise without a consistent neural trajectory (left) or with a consistent neural trajectory (right). **(B)** For one example target, every epoch’s trial-averaged main shared trajectory is plotted in the same informative 2D plane of the high-dimensional neural space (see Supplemental Experimental Procedures). **(C)** 6 example cells’ main shared time-course over training epochs for one target. **(D)** The magnitude of the main shared trajectory increased, as quantified by the squared norm (Monkey P: $r=0.95$, $p=8.8e8$, early < late $p=9.1e-7$; Monkey R: $r=0.86$, $p=1.3e-2$, early < late $p=1.0e-6$). **(E)** The correlation between each epoch’s main shared trajectory and the final epoch increased and stabilized (Monkey P: $r=0.98$, $p=3.0e-9$, early < late $p=2.2e-9$; Monkey R: $r=0.93$, $p=6.3e-3$, early < late $p=5.5e-8$). **(F)** The percent of fine-timescale main shared variance due to the trial-averaged main shared trajectory increased (Monkey P: $r=0.96$, $p=9.7e-9$, early < late $p=4.4e-6$; Monkey R: $r=0.77$, $p=4.4e-2$, early < late $p=7.1e-5$). **(G, H)** The trial-averaged main shared trajectory simulated through the decoder increased movement accuracy (Monkey P: $r=0.92$, $p=1.4e-6$, early < late $p=1.6e-8$; Monkey R: $r=0.84$, $p=1.8e-3$, early < late $p=5.9e-4$).

Chapter 4

Discussion

There are substantial challenges to investigating the neural basis of classical motor skill learning, as experimenters cannot observe all cells driving movement, cannot track the precise neural-movement transformation, and cannot analyze how a complete task-relevant population coordinates over learning. In this work, we leverage the reduced preparation of the BMI paradigm to study how the direct cells driving the decoder explored activity patterns from trial-to-trial, and how they consolidated control signals underlying skillful movement. Using FA, we uncovered that private and shared signals both evolve and contribute to control differently in a task-relevant population over training.

Private signals contribute initial neural and prosthetic variability

Previous studies have shown that neural variability reduction in motor brain areas accompanies motor adaptation (Mandelblat-Cerf et al., 2009), procedural learning (Barnes et al., 2005), skill learning (Costa et al., 2004; Kao et al., 2005; Peters et al., 2014; Santos et al., 2015), and neuroprosthetic learning (Arduin et al., 2013; Zacksenhouse et al., 2007), suggesting that the brain searches for goal-achieving patterns by modulating neural variability. We asked how a task-relevant neural population coordinates to search for goal-achieving activity patterns. By dissecting total trial-to-trial variability with FA, we found that initially large trial-to-trial variability which is private to each neuron decreases over training (Figure 3.4 B). This result extends (Zacksenhouse et al., 2007), which found that early neuroprosthetic training was accompanied by increased total firing rate variability which was unexplained by BMI kinematics. Thus, a task-relevant population can explore activity space by increasingly varying each neuron independently, suggesting that the brain possesses flexibility in finding goal-achieving patterns throughout population activity space.

How did initial decoder-timescale private variance contribute to cursor variability? We supplied shared and private variance separately as simulated inputs to the decoder and found that private variance contributed large cursor workspace exploration in early training (Figure 3.6 G) which achieved positions closer to the target, while shared variance initially had little impact on control (Figure 3.6 C). Thus, our findings suggest that each neuron in

the task-relevant population uses independent patterns to explore behavioral states in early learning.

Role of private signals in solving the credit assignment problem

Neuroprosthetic learning studies provide intriguing evidence that the brain can solve the credit assignment problem by specifically adapting the neurons which contribute to the global error signal provided by prosthetic cursor feedback (Ganguly et al., 2011; Gulati et al., 2014; Jarosiewicz et al., 2008; Koralek et al., 2013). To explain changes specific to the neurons driving errors, neuroprosthetic learning models require private neural noise to provide a beneficial exploratory signal for learning (Héliot et al., 2010; Legenstein et al., 2010). These models posited a fixed level of exploratory neural noise, and simulations indicated that this noise can hurt final cursor performance. Thus, our observation of initially large and later reduced private trial-to-trial variability is consistent with the view that motor cortex varies neurons independently to learn their contribution to control and then reduces this variability to generate refined control.

Shared variance consolidates for skillful neuroprosthetic control

It is known that particular neural ensembles (Cao et al., 2015; Peters et al., 2014) and spatiotemporal patterns are consolidated during natural motor learning (Costa et al., 2004; Peters et al., 2014; Santos et al., 2015) and neuroprosthetic learning (Carmena et al., 2003; Ganguly and Carmena, 2009; So et al., 2012a), but less is known about whether and how the population coordinates over learning. We asked: for skilled control, does each neuron use independent patterns, or does the population utilize covariation patterns? For both trial-to-trial variability and decoder-timescale activity, we found that that the shared-to-total variance ratio increased (Figure 3.4 C, 3.5 D) and that population activity is coordinated in a stable, low-dimensional shared space (Figure 3.4 E, 3.5 F). Using decoder simulations, we observed that emergent decoder-timescale shared variance contributed more skillful control than both private variance and total activity (Figure 3.6 EF, 5.6 CD). We hypothesize that the population finds this solution by selecting particular shared inputs which produce goal-achieving activity within a characteristic manifold.

Flexibility in acquiring neural patterns

Recent studies have asked how flexible the brain is in acquiring neural patterns for neuroprosthetic control (Hwang et al., 2013; Sadtler et al., 2014). (Sadtler et al., 2014) found that the structure of shared neural variance plays a causal role in neuroprosthetic learning; given one training session, it was easier for a subject to produce control signals within an existing BMI manifold of shared variance than outside the BMI manifold. Another study (Hwang et al., 2013) found that subjects can operate a BMI by re-purposing activity patterns associated with their physical movements. Thus, given a familiar task context, subjects more readily

select neural patterns within their pre-existing repertoire, facilitating rapid control. In our study, subjects possess no starting BMI control strategy as they learn a neuroprosthetic skill *de novo* over days of training. Using a decoder which permitted decoder-timescale variance from both private and shared sources as input, the neural population’s initial shared variance turned out to be small (Figure 3.5 C), misaligned with the decoder (Figure 3.7 B, 5.6 A), and produced neither significant cursor variability (Figure 3.6 G) nor accurate movements (Figure 3.6 C). Instead, the population initially generated private variance unconstrained to a manifold (Figure 3.5 C), and over training, shared variance increased and a BMI manifold emerged containing consolidated neural trajectories for skillful control (Figure 3.6 EF, 3.8 H). Because private variance permits subjects to observe the behavioral consequence of activity patterns outside the initial shared space, it may enable the consolidation of BMI manifolds and increase the space of patterns and thus decoders that subjects can learn. We hypothesize this flexible neural exploration and consolidation mechanism is employed for long-term novel skill learning, distinct from the more constrained neural exploration used for faster learning.

Refined control through matching of neural activity to the effector

To control a novel effector, subjects must discover motor control neural activity which is matched to the effector. A recent neuroprosthetic learning study found that changes in neurons’ mean firing rates across movement directions correlate with the decoder’s properties (Orsborn et al., 2014). In this work, we asked how neural dynamics for individual movement directions drive the decoder (Figure 3.7 A), finding that shared variance in the decoder’s readout space increased over training (Figure 3.7 B). This occurs both because shared variance increases overall, and because the shared space aligns with the readout space (Figure 3.7 D). Thus, neuroprosthetic skill emerges as subjects consolidate shared variance matched to the decoder. Given that subjects could also generalize control for untrained reaches (Ganguly and Carmena, 2009), these neural changes may reflect the development of an internal model for BMI control (Golub et al., 2015; Heliot et al., 2010). How might our findings extend to acquiring novel motor skill, which requires generating novel control signals to the body? The brain’s task in BMI approximates current models of the brain’s function in natural motor learning. Our decoder is a linear readout of neural activity into control signals, just as a common model posits muscles perform a linear readout of motor cortical activity (Churchland et al., 2012; Kaufman et al., 2014; Lillicrap and Scott, 2013). In analogy to motor cortical control of the decoder, motor control studies suggest that motor cortex generates neural control signals for our biomechanical plant, showing that motor cortical activity contains information about muscle-level dynamics as well as kinematics (Sergio et al. 2005) and possesses statistics which reflect the biomechanics it must control (Lillicrap and Scott, 2013). Thus, our findings on private and shared neural variance in motor cortex could apply to exploring and consolidating physical movements.

Refined control through consolidation of coordinated neural trajectories

Because we observed decoder-timescale shared variance could produce skilled cursor movements (Figure 3.6 D-F), we asked whether covariation patterns acquired a temporal sequence at a fine-timescale which supported learning. Interestingly, initial covariation patterns traverse no consistent trajectory (Figure 3.8 D). Over training as a shared space consolidates, neural trajectories consolidate within the shared space (Figure 3.8 EF) which are sufficient to drive straight and accurate cursor movements (Figure 3.8 GH). Future work will need to analyze whether these emergent temporal patterns obey dynamical rules such as those underlying natural motor control (Churchland et al., 2012; Kao et al., 2015). One interesting observation is that a large fraction of shared variance exists outside the readout space and thus does not directly drive the cursor (Figure 5.6 A), possibly reflecting internal neural dynamics necessary to generate the control signal to the decoder. This is consistent with motor control hypotheses that large neural populations exploit their high-dimensionality such that neural activity can obey lawful dynamics while a linear readout of the activity can produce flexible movements (Churchland et al., 2012) and can prepare movements without executing them (Kaufman et al., 2014). Interpreting neural data will be aided by modeling how neural networks might learn dynamics for BMI control as is being done for motor control (Hennequin et al., 2014; Sussillo et al., 2015).

Biological sources of private and shared variance: noise and supporting networks

We note that private variance in the direct cells can arise from multiple processes (Faisal et al., 2008): 1) “noisy” intrinsic spiking variance at a fixed firing rate, such as in a Poisson Process with fixed firing rate, 2) the action of private input activity changing the cell’s underlying firing rate, and 3) input activity structure which FA does not model, for example time-varying shared variance. We used Poisson simulations to ensure changing mean firing rate did not explain our observed trial-to-trial variability changes (Figure 5.5). In the latter two cases, some of the variance which is private in the population of direct cells may be shared with unobserved cells in connected networks. Thus, private variance need not be purely corruptive noise, a simplifying assumption sometimes made (Santhanam et al., 2009). Cells in M1 likely possess tens of thousands of synapses (Cragg, 1967); the input activity space is very high dimensional. Some of these inputs may be independent for each recorded cell while some may be coordinated across cells. These two classes of inputs would drive distinct statistical population variance, which FA attempts to describe with shared and private variance. There are many potential biological implementations for the observed increase in consistency and coordination in the direct cell population. Private trial-to-trial variability can decrease because variable private inputs become more consistent or their synaptic weights to direct cells weaken. Decoder-timescale shared variance can increase because anatomically shared inputs strengthen in signal or synaptic weight or because non-

anatomically-shared inputs become coordinated. Our FA results suggest new hypotheses about the neural substrate of skill learning in the direct cells and the supporting network. Indeed, a growing body of research indicates that during BMI control, the brain can enter a novel, wide-scale state producing new representations in indirect cells (i.e. not connected to the BMI) in primary motor cortex (Clancy et al., 2014; Ganguly et al., 2011; Gulati et al., 2014; So et al., 2012b), primary sensory cortex (Clancy et al., 2014), across cortical areas (Wander et al., 2013), and striatum (Koralek et al., 2013, 2012). These functional changes are subserved by ensemble re-activation during slow wave sleep (Gulati et al., 2014) and corticostriatal plasticity (Koralek et al., 2012), and suggest that emergent task-relevant coordination is driven by the formation of large-scale circuits including corticostriatal loops.

Implications for neural prostheses

Advances in neural engineering have produced algorithms to facilitate high performance even when decoders are re-trained frequently. How might decoder and neural adaptation synergize? Recent work shows closed-loop decoder adaptation (CLDA), which uses information about the task goal to fit the decoder to the subject's explored activity patterns (Dangi et al., 2013; Gilja et al., 2012; Shanechi et al., 2016), can improve performance in conjunction with neural learning (Orsborn et al., 2014). Future decoders might benefit from more detailed models of neural population dynamics and how they change with learning. Indeed, a recent algorithmic approach yielded significant performance improvement by modeling neural population dynamics underlying natural movements to decode the subject's intent while moving freely (Kao et al., 2015). Perhaps neural learning can help to generalize this approach to immobile patients, as we found coordinated neural dynamics can be consolidated over training in the absence of overt movement. Given our findings that main shared variance achieves better performance than total activity in simulations (Figure 5.6 B-D), a performance-motivated extension would be to design a decoder that is able to denoise neural observations based on learned neural dynamics (Shenoy and Carmena, 2014). In conclusion, this study uncovers the emergence and consolidation of coordinated dynamics for BMI control, highlighting the potential for neural prostheses to become more natural and automatic to the user, as well as an experimental tool for future investigations on the neural basis of skill learning.

Chapter 5

Supplemental Results

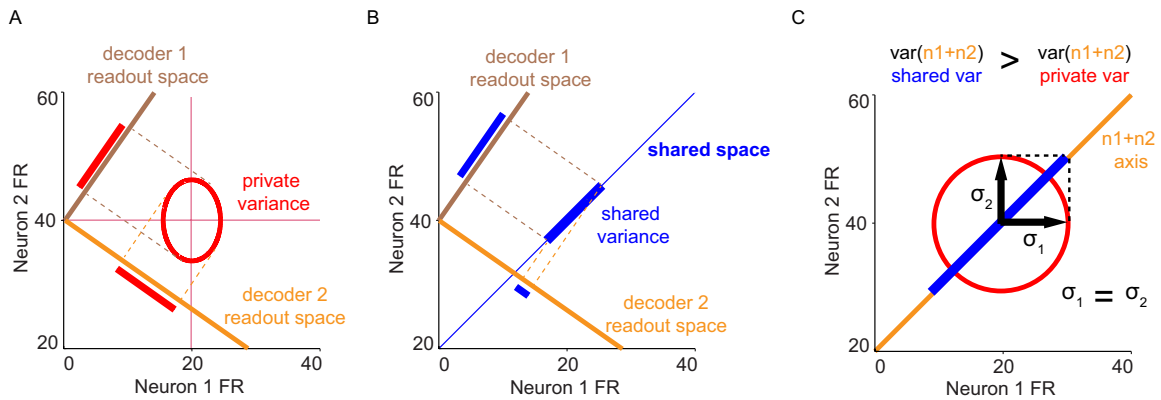


Figure 5.1: **Manners in which private and shared variance generate movement variance depending on the readout space.** (A) Private variance is high-dimensional and therefore generates variance in any readout space. (B) Low-dimensional shared variance generates significant variance only in readout spaces with which it is aligned. (C) Illustration of two neurons with equal variance. If the two neurons exhibit shared variance as opposed to private variance, they can concentrate more variance in the readout dimensions and thus generate movement variance more efficiently.

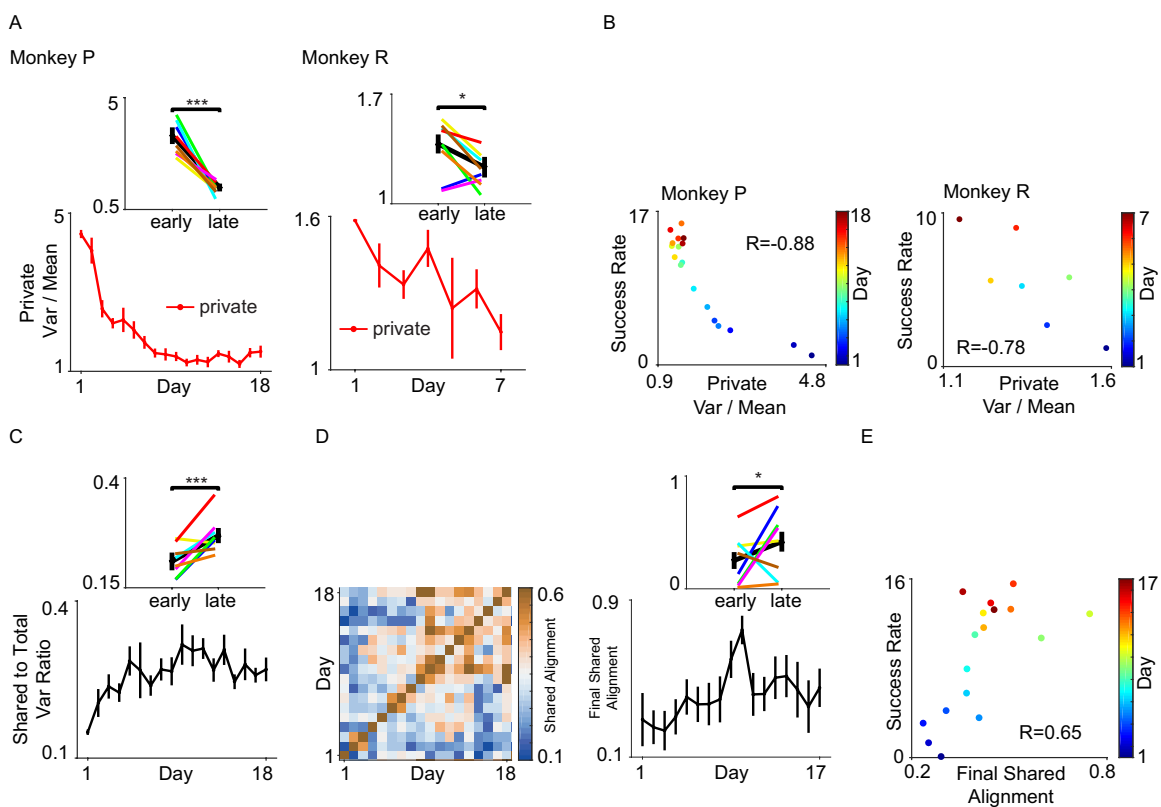


Figure 5.2: **Trial-to-trial variability over days of training.** (A) Over days, private trial-to-trial variability (private variance divided by mean rate) decreased (Monkey P: $r = -0.77$, $p = 1.7 \times 10^{-4}$, early > late $p = 2.2 \times 10^{-8}$, 8 targets consistent; Monkey R: $r = -0.84$, $p = 1.8 \times 10^{-2}$, early > late $p = 2.4 \times 10^{-2}$, 6 targets consistent). The window size was 0.9 sec for Monkey P and 1.3 sec for Monkey R as in Figure 4B. (B) Private trial-to-trial variability decrease correlated with success rate (Monkey P: $r = -0.88$, $p = 1.9 \times 10^{-6}$; Monkey R: $r = -0.78$, $p = 3.7 \times 10^{-2}$). (C) The ratio of shared variance to total variance increased (no normalization by mean rate) increased (Monkey P: $r = 0.58$, $p = 1.2 \times 10^{-2}$, late > early $p = 6.5 \times 10^{-4}$, 7 targets consistent). (D) The shared space stabilized (Monkey P: $r = 0.55$, $p = 2.3 \times 10^{-2}$, late > early $p = 4.5 \times 10^{-2}$, 6 targets consistent). (E) Shared space alignment to the final day correlated with success rate (Monkey P: $R = 0.65$, $p = 4.7 \times 10^{-3}$).

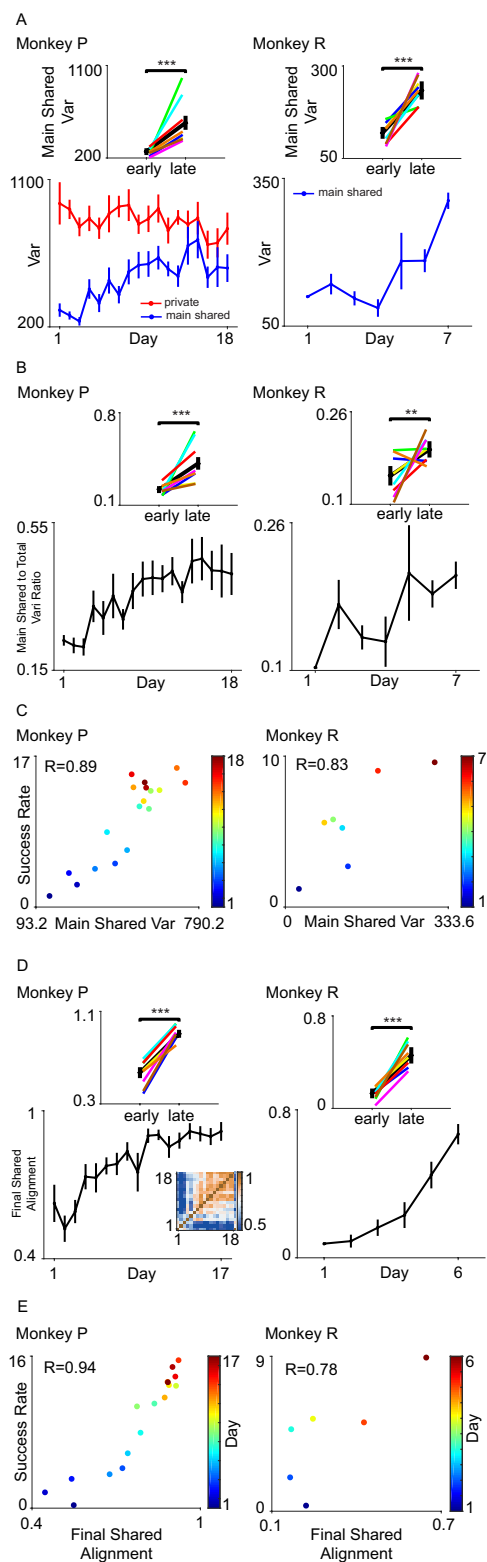


Figure 5.3: Decoder-timescale variance over days of training.

Figure 5.3: **Decoder-timescale variance over days of training.** **(A)** The shared dimensionality started at 4 and fell to 2 in late training, thus a main shared dimensionality of 2 was used. Main shared variance increased (Monkey P: $r = 0.79$, $p=1.1e-4$, late > early $p=1.1e-7$, 8 targets consistent; Monkey R: $r=0.77$, $p=4.2e-5$, late > early $p=5.2e-3$, 6 targets consistent). **(B)** The main shared to total variance ratio increased (Monkey P: $r=0.88$, $p=1.6e-5$, late > early $p=3.9e-7$, 8 targets consistent; Monkey R: $r=0.77$, $p=4.2e-5$, late > early $p=5.2e-3$, 6 targets consistent). **(C)** Main shared variance correlated with success rate (Monkey P: $r=0.89$, $p=5.4e-7$; Monkey R: $r=0.83$, $p=2.1e-2$). **(D)** Main shared covariance stabilized (Monkey P: $r=0.89$, $p=1.3e-6$, late > early $p=2.1e-8$, 8 targets consistent; Monkey R: $r=0.94$, $p=5.5e-3$, late > early $p=4.8e-5$, 8 targets consistent). **(E)** The main shared space alignment to the final epoch correlated with success rate (Monkey P: $r=0.94$, $p=2.3e-8$; Monkey R: $r=0.78$, $p=6.7e-2$).

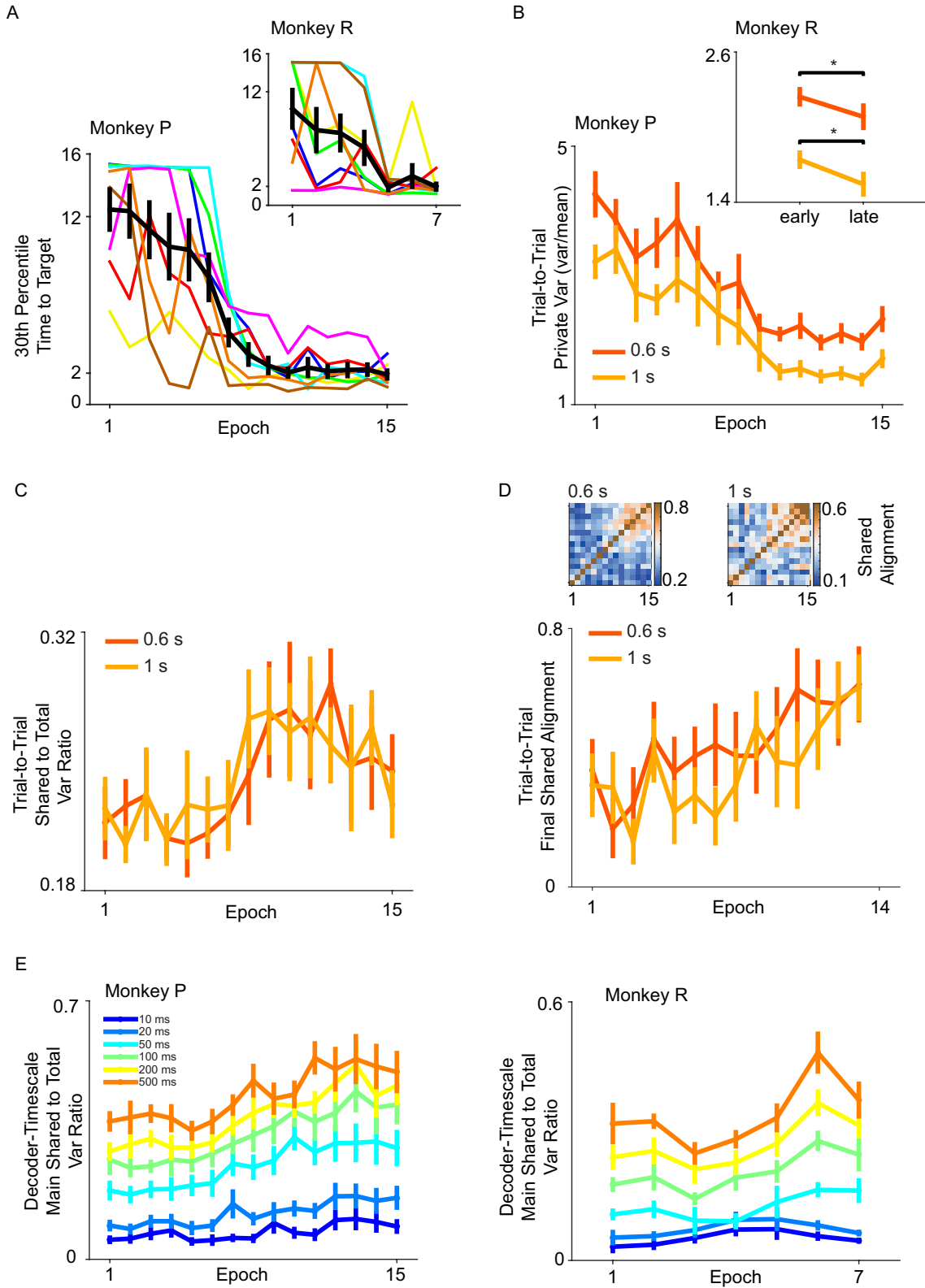


Figure 5.4: Variance results are robust to temporal parameter choice.

Figure 5.4: **Variance results are robust to temporal parameter choice.** **(A)** The 30th percentile of time to target over all targets. Minimum 30th percentile over all conditions was (Monkey P: 0.9 sec; Monkey R: 1.3 sec), which was used in Fig 4 for trial-to-trial variability. **(B)** Trial-to-trial private variability decreased for analysis window = 0.6 sec: (Monkey P: $r=-0.91$, $p=2.4e-6$, early > late $p=2.9e-12$, 8 targets consistent; Monkey R: $r=-0.45$, $p=3.1e-1$, early > late $p=4.4e-2$, 6 targets consistent), and for analysis window = 1 sec (Monkey P: $r=-0.93$, $p=4.3e-7$, early > late $p=1.2e-8$, 8 targets consistent; Monkey R: $r=-0.68$, $p=9.2e-2$, early > late $p=1.4e-2$, 6 targets consistent). **(C)** Trial-to-trial shared to total variance ratio increased for analysis window = 0.6 sec: (Monkey P: $r=0.67$, $p=6.5e-3$, late > early $p=1.0e-3$, 6 targets consistent) and window = 1 sec: (Monkey P: $r=0.60$, $p=1.7e-2$, late > early $p=2.7e-3$, 5 targets consistent). **(D)** The trial-to-trial shared space alignment to the final epoch increased for window = 0.6 sec (Monkey P: $r=0.87$, $p=5.4e-5$, late > early $p=6.7e-4$, 7 targets consistent) and for window = 1 sec (Monkey P: $r=0.67$, $p=6.5e-3$, late > early $p=1.0e-3$, 7 targets). **(E)** The decoder-timescale main shared to total variance ratio increased over a range of bin widths. Bin width = 10 ms: (Monkey P: $r=0.72$, $p=2.3e-4$, late > early $p=2.8e-3$, 7 targets consistent, Monkey R: $r=0.50$, $p=2.6e-1$ N.S., late > early $p=4.4e-2$, 7 targets consistent), 20 ms: (Monkey P: $r=0.89$, $p=1.1e-5$, late > early $p=5.9e-6$, 8 targets consistent; Monkey R: N.S. $r=0.47$, $p=2.8e-1$, late > early $p=0.11$, 7 targets consistent), 50 ms: (Monkey P: $r=0.93$, $p=4.9e-7$, late > early $p=4.3e-5$, 8 targets consistent; Monkey R: $r=0.75$, $p=4.9e-2$, N.S. late > early $p=6.6e-2$, 8 targets consistent), 100 ms: (Monkey P: $r=0.95$, $p=7.1e-8$, late > early $p=2.2e-6$, 8 targets consistent, Monkey R: $r=0.76$, $p=4.6e-2$, late > early $p=2.9e-2$, 7 targets consistent), 200 ms: (Monkey P: $r=0.92$, $p=8.0e-7$, late > early $p=2.0e-6$, 8 targets consistent, Monkey R: $r=0.72$, $p=6.7e-2$, late > early $p=2.3e-2$, 7 targets consistent), 500 ms: (Monkey P: $r=0.88$, $p=1.6e-5$, late > early $p=2.2e-4$, 8 targets consistent, Monkey R: $r=0.58$, $p=1.7e-1$ N.S., late > early $p=5.2e-2$ N.S., 7 targets consistent).

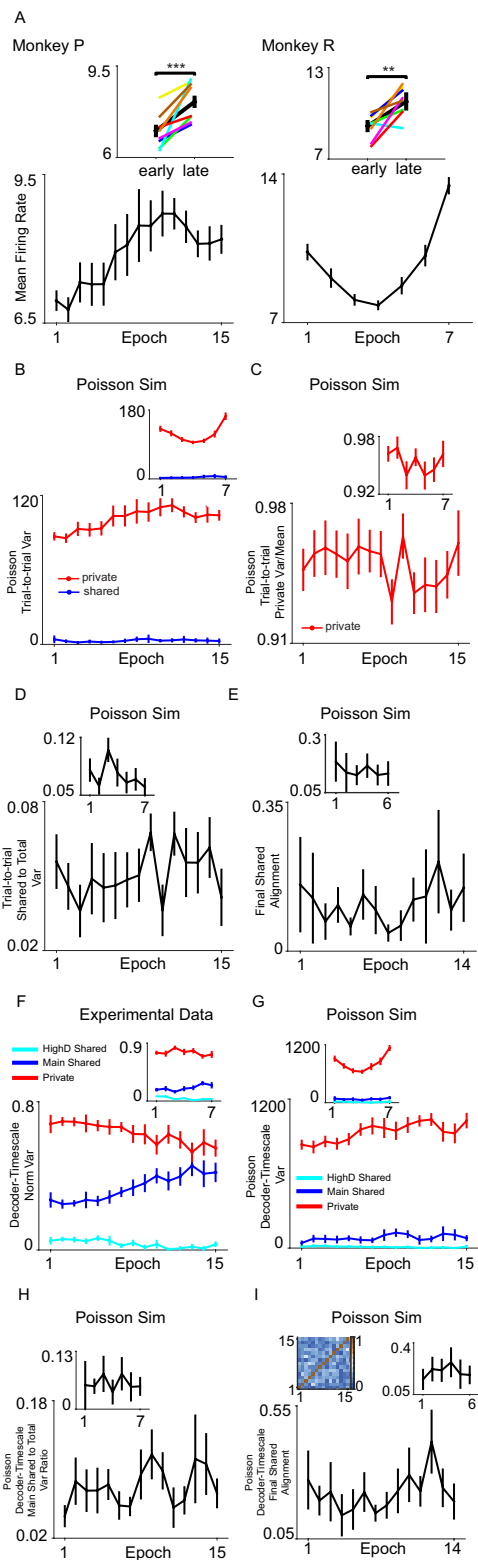


Figure 5.5: Mean firing rate changes do not explain trial-to-trial variability and decoder-timescale variance changes.

Figure 5.5: **Mean firing rate changes do not explain trial-to-trial variability and decoder-timescale variance changes.** **(A)** The mean firing rate increased over training (Monkey P: $R=0.79$, $p=5.1e-4$, early < late $p=7.1e-6$, 8 targets consistent; Monkey R: $R=0.49$, $p=2.7e-1$, early < late $p=6.1e-3$, 7 targets consistent). **(B)** We performed FA on a simulated data set of independent Poisson spike counts with window sizes used in Figure 4, the experimentally observed neurons' means, and 50 times the number of trials. Fitting FA on Poisson counts yields the best shared dimensionality as 0. In these plots, we used 1 shared dimension, matching our analysis of real neural data (Figure 4). Monkey P's simulated private trial-to-trial variability increased while Monkey R showed no trend (Monkey P, $r=0.78$, $p=5.1e-4$, late > early $p=2.3e-5$; Monkey R n.s. : $r=0.33$, $p=4.8e-1$, late > early $p=1.2e-1$). Both subjects' shared variance is close to 0 and showed no trend (Monkey P, $r=0.29$, $p=2.9e-1$, early vs late $p=4.9e-1$; Monkey R, $r=-0.06$, $p=9.1e-1$, early vs late $p=1.1e-1$). Because shared variance does not track changes in mean firing rate, we chose not to normalize shared variance by mean firing rate. **(C)** As mathematically expected, we observed that normalizing each simulated Poisson neuron's private variance by its mean yielded a value close to 1 with no significant trend over training. The value is expected to be less than 1, because some variance was absorbed as shared variance since we used a shared dimensionality of 1. **(D)** The trial-to-trial shared to total variance ratio showed no trend and is close to 0. **(E)** The trial-to-trial shared space alignment to the final epoch showed no trend (Monkey P: $r=0.21$, $p=4.7e-1$, early vs late $p=1.5e-1$; Monkey R: $r=-0.55$, $p=2.6e-1$, early vs late $p=6.9e-1$).

Figure 5.5: **Mean firing rate changes do not explain trial-to-trial variability and decoder-timescale variance changes.** **(F)** The experimentally observed data's decoder-timescale main shared, high-dimensional shared, and private variance, normalized by total variance. Normalized private variance decreased (Monkey P: $r=-0.92$, $p=1.4e-6$, early > late $p=1.3e-4$; Monkey R: $r=-0.38$, $p=4.1e-1$, early > late $p=7.6e-2$), and normalized high dimensional shared signal variance decreased (Monkey P: $r=-0.80$, $p=3.8e-4$, early vs late $p=1.2e-4$; Monkey R: $r=-0.76$, $p=4.8e-2$, early > late $p=8.7e-4$). Normalized main shared variance increased (Figure 5D). **(G)** Decoder-timescale shared variance changes are not explained by changes in mean firing rate. We applied FA on Poisson simulated neurons with 100 ms bins using experimentally observed average firing rates and shared dimensionality (Figure 5B). Private variance increased (Monkey P: $r=0.76$, $p=9.8e-4$, early < late $p=2.8e-4$; Monkey R: $r=0.42$, $p=3.4e-1$, early < late $p=2.3e-2$) and main shared variance was unchanged (Monkey P: $r=0.39$, $p=1.5e-1$, early vs late $p=1.7e-1$; Monkey R: $r=0.34$, $p=4.5e-1$, early vs late $p=4.8e-1$). High dimensional shared variance decreased slightly because the experimental shared dimensionality decreased (Monkey P: $r=-0.59$, $p=2.0e-2$, early > late $p=2.6e-4$; Monkey R: $r=-0.37$, $p=4.1e-1$, early > late $p=8.2e-3$). **(H)** Decoder-timescale Poisson simulated neurons' main shared variance to total variance ratio showed no trend (Monkey P: $r=0.27$, $p=3.4e-1$, early vs late $p=4.1e-1$; Monkey R: $r=0.039$, $p=9.3e-1$, early vs late $p=6.9e-1$). **(I)** Decoder-timescale Poisson simulated neurons' shared space alignment to the final epoch showed no trend (Monkey P: $r=0.32$, $p=2.6e-1$, early vs late $p=1.5e-1$; Monkey R: $r=0.14$, $p=7.9e-1$, early vs late $p=4.6e-1$).

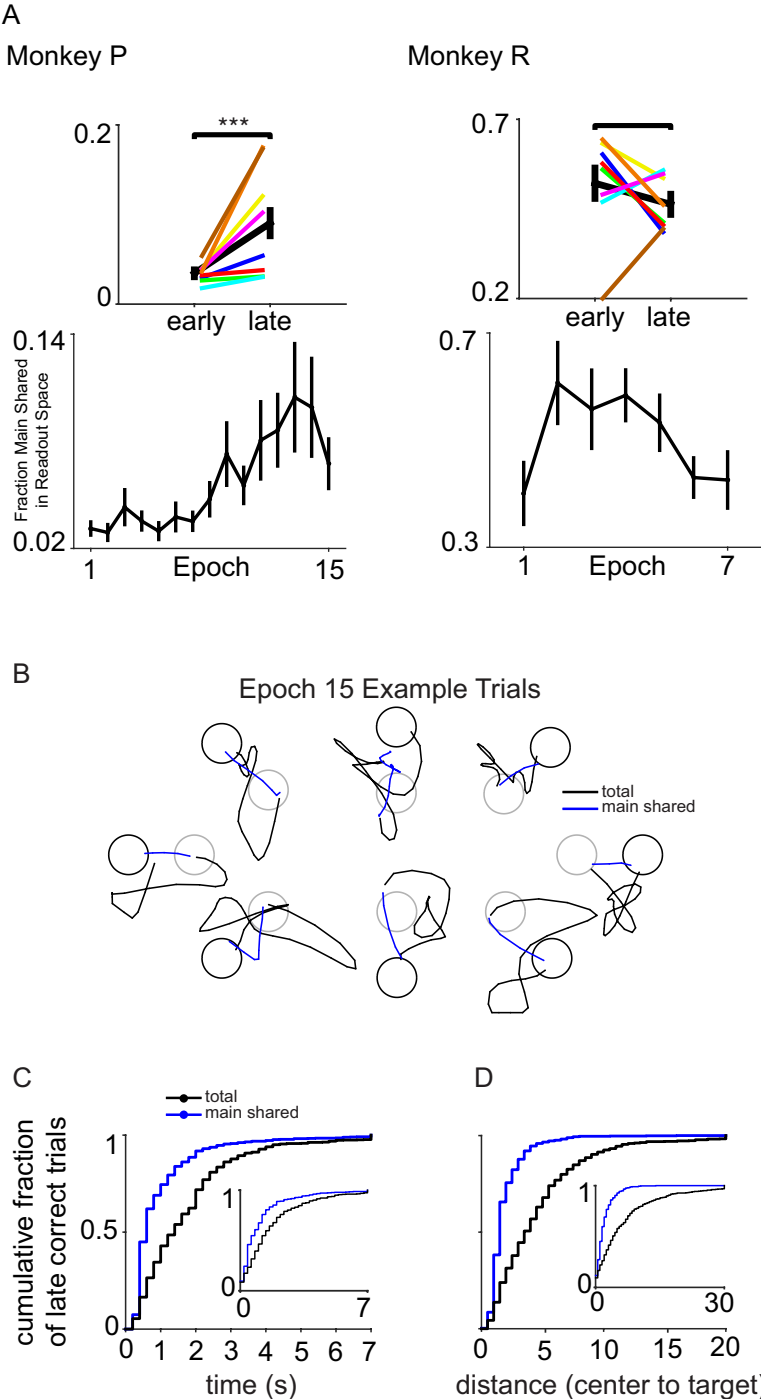


Figure 5.6: Decoder-timescale main shared variance and control.

Figure 5.6: **Decoder-timescale main shared variance and control.** **(A)** The fraction of decoder-timescale main shared variance in the readout space increased for Monkey P ($r=0.86$, $p=3.9e-5$, late $>$ early $p=2.2e-4$, 8 targets consistent) but not Monkey R ($r=-0.28$, $p=5.5e-1$, late $<$ early $p=1.1e-1$). **(B)** Example trials driven by main shared variance and total activity from the final epoch for each target. **(C)** In late learning, successful movements driven by main shared variance are significantly faster (main shared minus total time-to-target; Monkey P: mean = -0.78 sec, main shared $<$ total $p=4.2e-51$; Monkey R: mean = -0.66 sec, main shared $<$ total $p=3.2e-11$). **(D)** In late learning, successful movements driven by main shared variance are significantly more direct (main shared minus total distance-traveled; Monkey P: mean = -2.8, main shared $<$ total $p=5.38e-83$; Monkey R: mean = -5.1, main shared $<$ total $p=1.8e-28$). For (CD), late learning trials were analyzed for which total activity and main shared variance were successful (Monkey P: epochs 8 to 15, 832 trials; Monkey R: epochs 4 to 7, 385 trials).

	Monkey P		Monkey R	
	<u>pval</u>	<u>Num Targets</u>	<u>pval</u>	<u>Num Targets</u>
Trial-to-trial Variability				
trial-to-trial private var (<u>var/mean</u>)	early > late, p=6.7e-7	8	early > late, p=2.2e-2	6
trial-to-trial shared to total ratio	late > early, p=8.1e-3	7	<u>n.s.</u> : early < late	4
trial-to-trial shared align to final	late > early, p=5.8e-4	7	<u>n.s.</u> : early < late	3
Decoder-timescale Variance				
<u>decoder-ts</u> shared dim	early > late, p=1.4e-7	8	early > late, p=9.8e-5	7
<u>decoder-ts</u> shared main var	late > early, p=1.9e-5	8	late > early, p=1.2e-5	8
<u>decoder-ts</u> main shared to total ratio	late > early, p=2.2e-6	8	late > early, p=1.2e-4	7
<u>decoder-ts</u> main shared align to final	late > early, p=9.6e-9	8	late > early, p=2.2e-6	8
FA Simulations				
best progress to target, private	late > early, p=6.5e-6	7	late > early, p=3.0e-2	7
best progress to target, main shared	late > early, p=3.1e-8	8	late > early, p=9.6e-3	7
time to target	shared < private, p=1.8e-56	8	shared < private, p=4.3e-11	8
distance traveled to target	shared < private, p=3.2e-52	8	shared < private, p=2.49e-22	8
Shared Variance in Readout Space				
readout space main shared var	late > early, p=8.5e-9	8	late > early, p=8.3e-5	7
main shared mag ratio	late > early, p=3.1e-4	8	late > early, p=1.6e-5	8
alignment ratio	late > early, p=8.2e-6	8	<u>n.s.</u> : late > early, p=6.2e-1	3
Shared Trajectories				
main shared <u>traj</u> mag	late > early, p=9.1e-7	7	late > early, p=1.0e-6	7
main shared <u>traj corr</u> to final	late > early, p=2.2e-9	8	late > early, p=5.5e-8	8
<u>frac</u> main shared due to <u>traj</u>	late > early, p=4.4e-6	6	late > early, p=7.1e-5	8
main shared <u>traj</u> progress to target	late > early, p=1.6e-8	8	late > early, p=5.9e-4	8

Figure 5.7: **Summary Table.** Summary of number of targets consistent with analyzed trends.

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