New neural activity patterns emerge with long-term learning

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Learning has been associated with changes in the brain at every level of organization. However, it remains difficult to establish a causal link between specific changes in the brain and new behavioral abilities. We establish that new neural activity patterns emerge with learning. We demonstrate that these new neural activity patterns cause the new behavior. Thus, the formation of new patterns of neural population activity can underlie the learning of new skills.

Significance

Consider a skill you would like to learn, like playing the piano. How do you progress from “Chopsticks” to Chopin? As you learn to do something new with your hands, does the brain also do something new? We found that monkeys learned new skilled behavior by generating new neural activity patterns. We used a brain–computer interface (BCI), which directly links neural activity to movement of a computer cursor, to encourage animals to generate new neural activity patterns. Over several days, the animals began to exhibit new patterns of neural activity that enabled them to control the BCI cursor. This suggests that learning to play the piano and other skills might also involve the generation of new neural activity patterns.

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The authors declare no conflict of interest.

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are indeed learned by the formation of new patterns of neural activity, and that those patterns directly drive the new behavior.

**Results**

We conducted 15 multiday OMP learning experiments (ranging from 6 to 16 days per experiment, average 9.2 days) across two monkeys. Each of these novel OMP mappings was learned over several days (Fig. 1C and D). With multiday practice, the amount of OMP learning is substantially greater than single-day OMP learning (Fig. 1D; t-test \(P < 10^{-4}\)), and is comparable to the single-day learning we previously observed for WMPs (8) (Fig. 1D; t-test \(P = 0.53\)). To facilitate learning, we employed an incremental training paradigm (10) (SI Appendix, Materials and Methods, and Fig. S1A–D). Multiday exposure to an OMP with no incremental training led to inconsistent learning (SI Appendix, Fig. S1E–G). The incremental training approach was not effective within a single day (SI Appendix, Fig. S1G). For most experiments, learning proceeded in a manner that resembles skill
learning (11): gradual improvement in performance (Fig. 1E and SI Appendix, Fig. S1 C and D). The dips and rebounds likely reflect some combination of the natural skill-learning process, motivation during a difficult task, and day-to-day recording instabilities (12–14).

The second objective of our study is to detect whether new neural activity patterns emerged during multiday OMP learning. By construction, forming new patterns of neural activity is the optimal neural strategy for learning to control the cursor under an OMP mapping because this would lead to the fastest cursor speeds. However, it is possible that the brain is unable to form new patterns because constraints exist on the patterns of neural activity that a population of neurons can exhibit (8, 9, 15–18). If this is the case, the monkey could still show some limited behavioral improvements by learning to reassociate preexisting patterns of neural activity with different intended movements (9). Thus, behavioral improvements alone are not sufficient to conclude that new patterns of neural activity have emerged.

Detecting the appearance of a new pattern of neural activity in the high-dimensional neural space is difficult because we observe only a limited number of patterns relative to the dimensionality of the space. Instead, we leveraged our BCI framework to look for the emergence of new neural activity patterns within the low-dimensional space specified by the BCI mapping. We started by defining the patterns of neural activity observed before learning as the “intuitive neural repertoire” (9). Then we projected the ~90D neural activity patterns comprising the intuitive neural repertoire into the 2D velocity space defined by the OMP mapping (Fig. 2A). This defines the limits on cursor velocities the monkey could produce through the OMP mapping if he only expressed patterns of neural activity from within his intuitive neural repertoire (Fig. 2B and SI Appendix, Materials and Methods). We term this the brain’s “speed limit.” Any cursor velocities we observe after learning that exceed the speed limit must have arisen from neural activity patterns that are outside of the intuitive neural repertoire, and thus are new (Fig. 2 B and C). Over the course of many days, monkeys learned to move the cursor at velocities that exceeded the speed limit for many targets (Fig. 2 D–F). The percentage of neural activity patterns that are new significantly increased over days (t test, \( P = 0.0015; \) Fig. 2G). This shows that the brain can generate new neural activity patterns when learning to perform a new skill, but that it takes several days to do so.

The third objective of our study is to show that the new neural activity patterns caused the behavioral improvements. In conventional learning studies, neural changes are observed that

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Fig. 2. New neural activity patterns emerge with long-term BCI learning. (A–C) A schematic of the technique used to identify outside-repertoire activity patterns. The OMP maps ~90D neural population activity patterns to 2D cursor velocities. Here we illustrate using 3D neural activity patterns and a 2D OMP mapping. (A) The neural activity patterns (orange dots) generated by the animal while using the intuitive mapping define an intuitive neural repertoire (dark gray ellipsoid). Each neural activity pattern maps to a cursor velocity (orange X, as one example) through the OMP mapping (blue plane). (B) Velocities predicted from the intuitive neural repertoire (orange X) through the OMP mapping define a speed limit (dashed gray ellipse). (Right) After learning, cursor velocities are observed that exceed the speed limit (three Xs outside of gray ellipse). (C) If the monkey produces cursor velocities that exceed the speed limit, those velocities were generated by neural activity patterns that lie outside of the intuitive neural repertoire and thus are new. (D–F) Using the speed limit to detect new neural activity patterns for an example experiment (OMP 1 from Fig. 1). (D) Velocities generated from the intuitive neural repertoire mapped through the OMP mapping. Each dot is the velocity resulting from one neural activity pattern (45-ms bin). Dots are colored by instructed target location (Inset). The speed limit is defined as the 95% convex hull (gray dashed line). By definition, 5% of the neural activity patterns are outside of the speed limit. (E) Day 1 velocities, generated while using the OMP mapping, mostly fell within the speed limit. Dots shown are from the 40 consecutive trials when behavior was the best on day 1. On these trials, 6% of the neural activity patterns were outside of the speed limit. (F) On day 8, some velocities exceeded the speed limit (e.g., patterns corresponding to purple, blue, and teal targets). Same conventions as in E. (G) The percentage of neural activity patterns that were new on the last day of OMP learning exceeds the percentage seen on the first day of learning for most experiments. Each symbol is one multiday OMP learning experiment. OMP1 is indicated in black.
accompany learning, but it has been difficult to know if those changes are directly responsible for the learned behavior. A BCI allows us to assess the behavioral consequence of any given neural activity pattern. To assess the behavioral impact of each neural activity pattern, we measured the component of cursor velocity in the direction of the target, which we term “progress” (Fig. 3A). Higher progress indicates straighter and/or faster cursor movements. Over the course of a multiday experiment, progress improved (Fig. 3B). Increases in progress were positively correlated with the emergence of more new neural activity patterns (Fig. 3C). This indicates that the monkey learned to move the cursor faster and straighter to the target in part by producing new neural activity patterns.

Before we can conclude that new neural activity patterns emerge due to learning, we need to ensure that they do not emerge by chance or due to neural recording instabilities. We performed three key controls to address this. First, we show that the new activity patterns were specific to the OMP being learned, and not generally helpful through other OMP mappings. To test this, we mapped the neural activity patterns generated by the monkey after learning through 500 random OMP mappings to assess how much apparent learning would have occurred with mappings the monkey never experienced. The apparent learning rarely exceeded the learning observed with the OMP mappings which the monkey did experience (SI Appendix, Fig. S2). This rules out the possibility that the animal learned a general strategy that would work for any OMP.

Second, we show that new patterns do not emerge without substantial learning pressure. That is, they do not appear by chance or because of neural recording instabilities. To assess this, we conducted control experiments in which the monkey used the same intuitive mapping for several days. This is a low learning pressure scenario because while control is good from the beginning of the experiment, there may still be incentive for the animal to increase his reward rate. The recording instabilities during these control experiments were indistinguishable from our multiday OMP learning experiments (SI Appendix, Fig. S3), and importantly, they do not result in the same emergence of new patterns of neural activity (SI Appendix, Fig. S4B). We also mapped the neural activity recorded during multiday intuitive mapping experiments through 500 random OMP mappings, which the monkey never experienced (SI Appendix, Fig. S4C). This is a “no learning pressure” scenario because the monkey never received feedback about how his neural activity would have impacted behavior through these mappings. The day-to-day recording instabilities in a no learning pressure scenario did not manifest as learning (SI Appendix, Fig. S4D).

Third, we assessed the extent to which the new activity patterns moved outside of the speed limit during learning. If new neural activity patterns are formed by expanding the neural repertoire, the distance of the new patterns from the speed limit should increase with learning. We found that in multiday OMP learning, not only does the percentage of patterns that are new increase with learning (Fig. 2 and SI Appendix, Fig. S4A and D), but also the distance of the new patterns from the speed limit increases (SI Appendix, Fig. S5). Taken together these controls confirm that the new neural activity patterns that emerge during multiday OMP learning are specific to the learned mapping, are directly responsible for behavioral improvements, and cannot be attributed to recording instabilities or other chance events.

We have shown that learning can proceed by the formation of new neural activity patterns that directly drive behavioral improvements. We wondered what characteristics make these new neural activity patterns different from the existing patterns. It might be that the new patterns are well explained by the pre-existing correlation structure, which is captured by the intrinsic manifold. Such new patterns could arise from organized changes in neural firing rates that conform to the preexisting correlation structure. We characterize this as an inside-manifold change (Fig. 4A). Alternatively, it might be that the new patterns arise from changes in the correlations between the neurons. We characterize this as an outside-manifold change (Fig. 4B). To determine the extent to which the new patterns generated by the animal resulted from firing rate changes or correlation changes, we decomposed each neural activity pattern into an inside-manifold component and an outside-manifold component (SI Appendix, Fig. S6 A and B). This enabled us to separately determine the inside-manifold and outside-manifold contributions.

Fig. 3. New neural activity patterns drive behavioral improvements. (A) Illustration of the progress metric. Progress is defined as the component of cursor velocity in the cursor-to-target direction. The + represents the center of the screen. Gray circles are cursor positions at previous time points. (B) Mean progress toward each target on day 1 (thin) and day 8 (thick) for an example experiment (OMP 1). (C) The cursor movements showed more progress when there was a larger percentage of neural activity patterns that were new (Pearson correlation coefficient $r = 0.76, P = 6 \times 10^{-16}$), and generally increased with several days of practice. Each symbol is the mean progress averaged over all eight targets on 1 d of one multiday OMP experiment. The shading of the symbols indicates the day within a given multiday experiment. In general, earlier days showed relatively few new patterns, and later days showed more new patterns and better progress.
to progress (SI Appendix, Materials and Methods). The new neural activity patterns on the last day of a multiday learning experiment include patterns with both substantial inside- and outside-manifold contributions to progress (Fig. 4C and SI Appendix, Fig. S6 C–E). This means that animals learned to move the cursor to some targets by generating new neural activity patterns that were outside of the intuitive neural repertoire but within the manifold, whereas other targets were learned by generating new neural activity patterns that were both outside of the intuitive neural repertoire and outside of the intrinsic manifold. Thus, learning can occur by changing the correlation structure (SI Appendix, Fig. S6C; blue), and also by changing firing rates in a manner that preserves the correlation structure (SI Appendix, Fig. S6C, red). We conclude that the brain can overcome the neural constraints imposed by the intrinsic manifold that we previously observed during single-day learning (8), but doing so takes several days.

Discussion

We found support for our hypothesis that populations of neurons can produce new patterns of activity to enable new behavioral capacities. Our BCI approach allowed us to establish a causal link from changes in neural activity patterns to changes in behavior. We encouraged new neural activity patterns to form by presenting the monkey with novel BCI mappings (OMPs). We detected the emergence of new patterns of neural activity after several days of practice with each OMP mapping. These patterns led directly to improved behavior. Some new patterns conformed to the preexisting correlation structure among the population of neurons, whereas other new patterns represented changes in the correlation structure. We expect that skill learning in general may proceed in part by the formation of new neural activity patterns appropriate for the learned behavior (19).

We can interpret changes in the brain at other levels of organization in the context of changes in neural populations. For example, learning has been associated with synaptic plasticity and the expansion of cortical maps. The time course of learning that we observed is consistent with findings that cortical synaptogenesis and motor map reorganization occur during late phases of skill learning (20). We posit that OMP learning involves synaptic plasticity. In fact, a function of synaptic plasticity could be to permit a network of neurons to generate new patterns of activity. This plasticity may occur among the neurons in M1 from which we record, or among neurons from which we do not record, but that drive the recorded population.

Learning has been associated with changes in tuning properties of individual neurons in previous BCI (6, 7) and motor skill learning (21) studies. We posit that the formation of new neural activity patterns during long-term BCI learning may provide a parsimonious explanation for the tuning curve changes reported in earlier studies. In particular, our results combined with earlier BCI studies (6–9, 15, 16, 18, 22–26) and motor learning studies (27, 28) suggest that fast and slow learning are driven by different neural mechanisms. Fast learning can be accomplished by reassociating preexisting patterns of neural activity with new behaviors (9). This would result in neural tuning changes that are coordinated across the population (6, 29). Slow learning, as reported here for OMP mappings, can involve the formation of new patterns of neural activity. This would correspond to neural tuning changes that are specific to individual neurons (29). Other slowly learned phenomena that may also entail the creation of new patterns of neural population activity include motor skill, or de novo (30), learning (31, 32), cognitive learning (33, 34), and stroke recovery (35, 36). In the future, it might be possible to facilitate learning in those contexts by directly guiding the formation of new neural activity patterns appropriate for the desired behavioral capacities, as we have done here.

Materials and Methods

We used a BCI paradigm in which the monkey moved a computer cursor from the center of a screen to one of eight peripheral targets by voluntarily modulating the activity of a population of 90 neural units recorded with a multielectrode array chronically implanted in the arm region of primary motor cortex. Each experiment began by presenting the monkey with an “intuitive” mapping that relates neural activity to cursor velocities in a way that provides proficient control without requiring the animal to learn. Then, we induced learning by presenting the monkey with a novel mapping from neural activity to cursor velocity. The novel mappings encouraged the formation of new neural activity patterns. Subsequent analyses, demonstrate that the novel mappings are learned by the formation of new patterns of neural activity, and that those patterns directly drive the new behavior.

Fig. 4. Monkeys can produce new neural activity patterns outside of the intrinsic manifold. There are two types of new neural activity patterns: (A) those that are outside the repertoire, but remain within the manifold, and (B) those that are outside the manifold. Either type can yield performance improvements. (C) Animals learn using both inside-manifold and outside-manifold strategies for a given OMP mapping. Each bar shows one target from one multiday OMP experiment. The overall learning, defined as change in progress from day 1 to the last day, is represented by the green dot. Targets are ordered based on the amount of learning. The inside-manifold contributions to that learning are shown in red. The outside-manifold contributions are shown in blue. For visual clarity, data presented here show only targets with behavioral improvement and only the helpful contributions are shown. See SI Appendix, Fig. S6 for a full presentation of these data.
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Supplementary Materials for

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This file includes:

Materials and Methods

Figs. S1 to S7

Table S1

Caption for Movie S1

Other Supplementary Materials for this manuscript include the following:

Movie S1

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MATERIALS AND METHODS

All animal procedures were approved by the University of Pittsburgh Institutional Animal Care and Use Committee in accordance with the guidelines of the US Department of Agriculture, the International Association for the Assessment and Accreditation of Laboratory Animal Care, and the National Institutes of Health.

Electrophysiology and behavioral monitoring

We recorded neural activity from the arm region of the primary motor cortex (M1) in two male rhesus monkeys (Macaca mulatta, age, monkey L: 9 years; monkey N: 7 years) using 96-channel microelectrode arrays (Blackrock Microsystems, Salt Lake City, UT, USA). We recorded neural units as threshold crossings, where a threshold crossing was detected when the depolarizing phase of the voltage signal crossed a threshold of -3 times the root-mean-square voltage. We estimated the root-mean-square voltage of the signal on each electrode while the monkeys sat calmly in a darkened room. For multi-day experiments, we set the threshold on day one and did not adjust it again. Across multi-day experiments, we recorded 89.9±1.9 neural units (all quantities are listed as mean±SD unless otherwise noted) for monkey L, and 93.2±1.8 units for monkey N; within a given OMP experiment the number of recorded neural units was constant throughout. The number of threshold crossings were counted in non-overlapping 45-ms bins. The data were recorded between 18 and 41 months after array implantation for monkey L and from 2.5 to 8 months after array implantation for monkey N.

Both arms were loosely restrained throughout all experiments. While the monkeys could move their forearms slightly and there was no restriction on wrist and hand movement, the arm movements during the experiments were minimal.

Behavioral task

Throughout each experiment animals performed an eight-target center-out task under brain-computer interface control. Each trial began with the cursor appearing at the center of the workspace. A peripheral target 125 mm away appeared simultaneously. Target locations were uniformly spaced 45 degrees apart around a circle. Targets were presented in a random (monkey N) or a pseudo-random (monkey L) order. Pseudo-random target presentation consisted of 8-trial blocks, in which target location was randomly chosen without replacement, and the next block of trials began only after all eight targets were successfully acquired. The cursor was frozen at the center of the workspace for the first 300 ms of the trial. After this “freeze period” the cursor began moving under neural control. Details about the neural control are given in the Intuitive BCI mappings and Perturbed BCI mappings sections below. Target acquisition occurred when the cursor entered the target window (circle, radius = 14 mm, monkey L; 35 mm, monkey N). If the target was successfully acquired within 7.5 s, the trial was deemed a success, the monkey was given a water reward, and the next trial began 200 ms later. If the target was not acquired within the 7.5 s allotted time, there was a 1.7 s timeout before the next trial.
Identifying the intrinsic manifold

The Intrinsic Manifold is defined as the low-dimensional space that describes the neural activity patterns generated by the animal prior to learning. To estimate it, we used the data collected on day 1, while we calibrated the intuitive BCI mapping (as described below Intuitive BCI mappings). We used factor analysis to describe each high-dimensional spike count vector in terms of a low-dimensional set of factors. Under factor analysis, factors are described by a standard normal distribution:
\[ z_t \sim N(0, I) \]  

where \( I \) is the identity matrix. The neural activity is related to those factors by a normal distribution:
\[ u_t | z_t \sim N(\Lambda z_t, \psi) \]  

where \( u_t \in \mathbb{R}^{q \times 1} \) is the z-scored spike count vector across \( q \) simultaneously-recorded neural units at timestep \( t \). Each neural unit was z-scored separately. \( z_t \in \mathbb{R}^{p \times 1} \) is the set of \( p \) factors at timestep \( t \). \( \Lambda \in \mathbb{R}^{q \times p} \) and \( \psi \in \Sigma_{+}^{q} \) (a diagonal \( q \times q \) covariance matrix) were estimated using the expectation-maximization algorithm (37). The intrinsic manifold is defined as the column space of \( \Lambda \), where each factor corresponds to a column of \( \Lambda \). By z-scoring we ensure that animals are not required to produce firing rates that are outside of the observed physiological range of each neural unit in order to learn how to control the cursor while using the perturbed BCI mappings.

We set the dimensionality of the intrinsic manifold to be 10 for all experiments. This was the dimensionality used in Sadtler et al. (8), and is consistent with the dimensionality of the neural activity in the current study. Here, we computed the dimensionality as the number of dimensions needed to explain 95% of the shared variance (38). This method differs slightly from that used in Sadtler et al. (8). We used the method described in (38) because it returns a more reliable estimate of dimensionality, even though it tends to underestimate the “true” dimensionality. The underestimation occurs because it seeks only to explain 95% of the shared variance. Using this method, the multi-day experiments had a mean dimensionality of 8.4 (range: 5-11) across both monkeys (computed using 3500-5500 time points for each session). (For each monkey individually, dimensionalities were monkey N: mean = 9.6, range: 8 – 11; monkey L: mean = 7.4, range: 5 - 9). This distribution is consistent with the use of 10 dimensions in this study.

Given the neural activity \( u_t \), we extract the factors
\[ \hat{z}_t = E[z_t | u_t] = \Lambda^T(\Lambda \Lambda^T + \psi)^{-1} u_t = \beta u_t \]  

where \( \beta = \Lambda^T(\Lambda \Lambda^T + \psi)^{-1} \). A separate factor analysis model was fit for each experiment based on the neural activity recorded during the calibration trials (as described below Intuitive BCI mappings).
Intuitive BCI mappings

BCI mappings translated the neural activity into 2D cursor velocities \( v_t \) using a Kalman filter (8). A Kalman filter consists of a state model, which describes how cursor velocity changes over time, and an observation model, which describes how observed neural activity relates to cursor velocity. The state model is:

\[
v_t | v_{t-1} \sim N(Av_{t-1}, Q) \quad (4)
\]

where \( A = I \) and \( Q = 2(m^2/s^2) \times I \). \( Q \) controls the smoothness of cursor velocities over time, and was chosen based on the setting that yielded the best closed-loop performance. In a standard Kalman filter, the high-dimensional neural activity is directly translated into cursor velocities. Here, we first estimated the lower-dimensional factors using Eqn. 3, and then translated the factors to cursor velocities. The observation model is:

\[
\hat{z}_t | v_t \sim N(Cv_t + d, R) \quad (5)
\]

where \( C \in \mathbb{R}^{10 \times 2} \), \( d \in \mathbb{R}^{10} \), and \( R \in \Sigma_{+}^{10} \). These parameters were fit using maximum likelihood to relate the factors and intended cursor velocities (defined below) from the calibration trials at the start of each experiment. Taken together, the intuitive BCI mapping can be written as

\[
\hat{v}_t = M_1 \hat{v}_{t-1} + M_2 u_t + m_0 \quad (6)
\]

\[
M_1 = A - KCA
\]

\[
M_2 = K\beta
\]

\[
m_0 = -Kd
\]

where \( \hat{v}_t \) is the velocity used to move the cursor on the screen at time \( t \) and \( K \) is the converged Kalman gain. \( M_1 \) temporally smooths the velocities, \( M_2 \) describes the high-dimensional neural activity in terms of the low-dimensional factors and relates the factors to the cursor velocity, and \( m_0 \) is a constant offset.

Each experiment began with 80 trials to calibrate an intuitive BCI mapping. Calibration involved a mixture of passive observation of center-out cursor movements and closed-loop BCI cursor control, during which we gradually increased the animal’s level of control over the cursor, until all assistance was removed, and he had full control. Calibration began with 16 trials (2 to each target) of the monkey observing automatic center-out cursor movements straight to the target at a constant speed (0.15 m/s). Here, intended cursor velocity at each timestep was taken to be the observed cursor velocity (0.15 m/s) in the center-to-target direction. For the next 8 trials, the animal controlled the cursor using a mapping calibrated using the data from the 16 observation trials, but the cursor was restricted to move only along the center-to-target direction (velocity components perpendicular to the center-to-target direction were set to 0). The next 8 trials used a mapping calibrated from the previous 8 trials, and perpendicular velocity
components were scaled by a factor of 0.2. The next 8 trials used a mapping calibrated from the previous 16 trials, and perpendicular velocity components were scaled by a factor of 0.4. We repeated this procedure for a total of 40 to 80 trials until the animal was given complete control of the cursor (perpendicular scale factor = 1). All calibrations performed within this procedure defined intended cursor velocities to be straight to the target, with speeds taken from the cursor movements that were displayed to the animal. Animals demonstrated proficient cursor control using the intuitive BCI mapping from the very first intuitive trial of each experiment, as evidenced by success rates (100%), fast acquisition times (L: 678.7 ± 42.9 ms; N: 522.3 ± 23.8 ms), and relatively straight cursor trajectories (e.g., Fig. 1C). The data from these 80 calibration trials were used to determine the intrinsic manifold.

**Perturbed BCI mappings**

Perturbed BCI mappings alter the relationship between recorded neural activity and cursor velocities to induce learning. The OMP mappings are of the same general form as the intuitive mapping (Eqn. 6). OMP mappings modify an intuitive BCI mapping by permuting the elements of \( u_t \) (that is, the ~90 neural channels) before passing it into factor analysis. This changes the relationship between the neural activity and factors, but preserves the relationship between the factors and cursor velocity. The impact of this manipulation is that it encourages the monkey to change the way in which neurons co-vary in order to restore proficient cursor control. (In contrast, to generate a WMP mapping, the ten factors were permuted before passing them to the Kalman filter. This manipulation changes the relationship between the factors and cursor velocity, but preserves the relationship between the neural activity and the factors (8).) An OMP mapping can be described in terms of the high-dimensional neural activity by:

\[
\hat{v}_t = M_1 \hat{v}_{t-1} + M_2^{OMP} u_t + m_0,
\]

where \( M_2^{OMP} = M_2 \eta_{OM} \) and \( \eta_{OM} \) is \( q \times q \) permutation matrix defining the outside-manifold perturbation (where \( q \) indexes the neural channels).

The OMP mappings we chose were not orthogonal to the manifold, as this would result in essentially zero cursor movement, at least initially. Rather, each mapping was selected to be difficult enough to require substantial learning but not so difficult that the animal would give up (8).

Behaviorally, these perturbations had complex effects on cursor movements, which cannot be expressed as pure visuomotor rotations or gains. Before learning, the effects of a typical perturbation can be approximately summarized by a combination of per-target velocity rotations and speed scalings. Because the perturbations were implemented in high-dimensional space, these rotations and scalings need not be consistent across movement directions and speeds (as they would be in the case of a pure visuomotor rotation or gain). Perturbations often affected movement speeds more profoundly along one movement direction than along the perpendicular direction (as seen in Fig. 2D-F).
Incremental training paradigm

We developed an incremental training paradigm to facilitate learning. The incremental training paradigm consisted of giving the monkey a series of incremental mappings which were successively further from the intrinsic manifold and successively closer to the full OMP mapping, to guide the monkey through neural space to the new patterns of neural activity requested by the OMP mapping (Fig. S1A). The incremental mappings were a weighted combination of the intuitive mapping and the OMP mapping, such that

\[ M_{2\text{incremental}} = \left(1 - \frac{a}{5}\right) * M_2 + \left(\frac{a}{5}\right) * M_{2\text{OMP}} \]  

where \(a = 1, 2, 3, 4\) and 4.5. Incremental step 1 is closer to the intrinsic manifold and should be easier to learn to control and incremental step 4 is closer to the OMP mapping and is expected to be more difficult to learn to control. The inclusion of the additional half step (4.5) was made to increase the monkeys’ willingness to continue to attempt the task. The criteria for incrementing the mapping are described below.

Task flow

Each experiment began with a calibration block during which we identified the intrinsic manifold and determined the parameters of the intuitive mapping. The monkeys used the intuitive mapping for 206 ± 56 trials (monkey L) or 193 ± 3.68 trials (monkey N). We then ran one of four possible OMP experiment types (Fig. 1B): multi-day, incremental training (monkey L: n=9; monkey N: n=6); multi-day, no incremental training (monkey L: n=6; monkey N: n=5); single day, incremental training (monkey L: n=12; monkey N: n=15); single day, no incremental training (monkey L: n=13; monkey N: n=8). Single day WMP experiments are also included (monkey L: n=11; monkey N: n=11).

We conducted a total of 51 experiments with monkey L. The 13 single day OMP, no incremental training experiments and 11 single day WMP experiments from monkey L have been previously reported (8). We conducted a total of 45 experiments with monkey N. Single day WMP experiments from monkey N have been analyzed in previous studies (9, 15). Below, we detail the task for each experiment type. The number of each type of experiment is summarized in Table S1.

Multi-day OMP, incremental training

This section corresponds to the experiments described in Figs. 1-4 and Fig. S1C, D, G (lower right). The procedures for multi-day incremental training experiments differed somewhat for the two monkeys. For monkey N, on day 1 the intuitive mapping block was followed by that experiment’s full OMP mapping (434±81 trials). Day 2 began with 40 trials of the full OMP mapping before beginning the incremental training with the incremental step 1 mapping. (These
data were collected to test whether OMP learning simply required a night’s sleep. We did not observe this to be the case. These data are not included in the analyses.) The mapping was incremented when the monkey reached a success rate of 80% or greater over the prior 40 trials and target acquisition times appeared to asymptote according to visual inspection by the experimenter (E. Oby). On subsequent days, the monkey began with an incremental mapping (usually step 3) and incremental training continued in the same way. After arriving at the full OMP mapping, the experiment continued for another 2 to 3 days (2.8±1.2 days). At the end of the final day, the intuitive mapping from day 1 was re-introduced for a washout block (356±130 trials).

For monkey L, day 1 of a multi-day, incremental training experiment proceeded in the same manner as a single day, incremental training experiment (as described below) without a washout block. On subsequent days, the monkey began with an incremental mapping (usually step 3) and incremental training continued. That is, the full OMP mapping was not re-presented at the start of day 2, as it was for monkey N. There were not objective criteria for incrementing to the next mapping for monkey L; the mapping was incremented when he showed good performance as judged by the experimenter. This procedure was adopted in part because monkey L was more likely to give up when the task was difficult, and we felt that a fixed rule might actually disrupt learning. After reaching the full OMP mapping, the experiment continued for another 4.5±3.1 days. At the end of the final day, the intuitive mapping from day 1 was re-introduced for a washout block (425±283 trials).

**Multi-day OMP, no incremental training**

This section corresponds to Fig. S1E, F, G (upper right). In this type of experiment, on day 1 the intuitive mapping block was followed by a full OMP mapping block for 250 to 815 trials (L: 563±226 trials; N: 440±90 trials). The first day ended with no washout block. The same OMP mapping was presented for 3 to 7 days (L: 4.5±1.5 days; N: 5±0 days). On subsequent days the monkey saw only that experiment’s full OMP mapping, and he had at least 400 trials (L: 738±257 trials; N: 443±139 trials) of exposure to it each day. At the end of the final day of each multi-day OMP, no incremental training experiment the intuitive mapping from day 1 was re-introduced for a washout block (699±205 trials).

**Single-day OMP, incremental training**

This section corresponds to Fig. S1G (lower left). In this type of experiment, the intuitive mapping block was followed by a 40 to 160 trial block with that day’s full OMP mapping. Then incremental training began. The monkey saw each incremental mapping for the same number of trials regardless of performance: Incremental step 1 for 40 trials, incremental step 2 for 40 trials, incremental step 3 for 80 trials, incremental step 4 for 80 trials, incremental step 4.5 for 120 or 160 trials, and then the full OMP mapping for at least 160 trials. These block sizes were chosen to balance the number of trials it took for the monkey to improve performance and to minimize the number of rewards the monkey received when the task required less learning (i.e., when the
incremental mapping was closer to the intuitive mapping). Following the full OMP mapping block, the intuitive mapping was re-introduced for a washout block (342±99 trials).

**Single-day OMP, no incremental training**

This section corresponds to Fig. 1D (blue) and Fig. S1G (upper left). In this type of experiment, the intuitive mapping block was followed by a block with that day’s full OMP mapping for 116 to 600 trials (L: 365±85 trials; N: 575±70 trials). Following the OMP mapping block, the intuitive mapping was re-introduced for a washout block (206±83 trials).

**Single-day WMP**

This section corresponds to Fig. 1D (red). In this type of experiment, the intuitive mapping block was followed by a WMP mapping block for 189 to 800 trials (L: 331±98 trials; N: 616±58 trials). Following the WMP mapping block, the intuitive mapping was re-introduced for a washout block (L: 167±60 trials; N: 334±108 trials).

**Analysis**

**Amount of learning**

For each experiment, we computed the amount of learning (AoL) during OMP control, which provides a measure of the extent to which learning recovered intuitive levels of performance subsequent to the introduction of the BCI perturbation. The metric is based on reward rate (i.e. the number of successful trials per unit time when the cursor is under the monkey’s control) and accounts for the reward rate with the intuitive mapping, as well as the potential learning possible given the difficulty of the perturbed mapping. Reward rate (RR) was computed for a sliding window of 40 consecutive trials. Then, we quantified the amount of learning (Fig. 1) as

\[
AoL_T = \frac{RR_T^{OMP} - RR_T^{OMP \text{ intuitive}}}{RR_T^{intuitive} - RR_T^{OMP}}
\]  

where \(RR_T^{\text{intuitive}}\) is the reward rate calculated for the 40 trials with the intuitive mapping just before the perturbation is introduced, and \(RR_T^{OMP}\) is the reward rate with the OMP mapping calculated for a sliding window of 40 trials beginning at trial \(T\) after the OMP is introduced. A value of 1 reflects performance that was fully restored to intuitive levels of control, and a value of 0 reflects no performance improvement. This is a different learning metric than was used in Sadtler et al. (8), and was chosen because it better captures the learning across all targets when the monkeys had a particularly low success rate to a subset of the targets, which was common for the OMP mappings studied here.

For single day experiments, \(AoL = max_T(AoL_T)\). For multi-day experiments, we found \(AoL\) for each \(T\) on each day. The \(AoL\) values reported in the histograms in Fig. 1D are the maximum \(AoL\) across all days. Thus, it reflects the best 40 consecutive trials on the best day, to
showcase the learning. The results were qualitatively similar when we considered the best 40 trials from the first day the monkey saw the full OMP mapping after incremental training or if we considered the best 40 trials from the last day the monkey saw that OMP mapping. Because our effects were robust to these choices, this shows that the learning is not trivially dependent on the particular trials we chose.

**Neural analyses**

Because our goal here was to characterize changes in neural activity that facilitate learning, we focused on the trials that showed the greatest improvement in behavioral performance. For our neural analyses, we analyzed the successful trials from the 40 consecutive perturbation trials that showed the best AoL on each day. Failed trials interspersed within that block of 40 trials were not analyzed because it is difficult to determine whether the animal was actively engaged in the task during failed trials.

**Defining new patterns of neural activity with a speed limit**

To look for the emergence of new neural activity patterns, we defined a “speed limit”. To define the speed limit (Fig. 2), we first projected each intuitive neural activity pattern through the OMP mapping

\[ \hat{\theta}_t = M_2^{OMP} u_t + m_0 \quad (10) \]

Here we are interested in the impact of the neural activity patterns on the cursor kinematics and so do not include the previous timestep’s velocity (i.e., \( M_1 \hat{\theta}_{t-1} \) in Eqn. 6). We computed the 95% convex hull of the resulting velocities. This convex hull is a 2D representation of the intuitive neural repertoire (9) in the behaviorally-relevant space. The convex hull is the smallest polygon enclosing all the 2D points that also encloses all possible line segments between any two points within the polygon. To be robust to outliers, the outermost points were successively dropped until 5% of all the points had been excluded. Points nearest to the boundary of the hull were dropped in order from largest to smallest Mahalanobis distance from the centroid of all points in the 2D projection. Mahalanobis distances were computed relative to the covariance across all points in 2D.

We refer to the convex hull as a *speed limit* because it represents the maximum speed in each direction that neural activity patterns within the intuitive neural repertoire would have produced under the OMP mapping. By definition, cursor speeds exceeding the speed limit could not have been achieved by the previously-observed neural activity patterns. Therefore, we classified any neural activity patterns leading to cursor speeds exceeding the speed limit as new. This is a conservative definition of new patterns, in the sense that it does not capture patterns of neural activity outside the \(~90\text{D}\) neural repertoire that map to speeds within the speed limit. The percentage of new patterns (e.g., Fig. 2G) is the ratio of new neural activity patterns to total
neural activity patterns generated by the monkey during that 40-trial block (successful trials only).

In all figures except Fig. S7, we have used the 95% convex hull to define the speed limit and to identify the emergence of new neural activity patterns. To ensure that our results did not depend on the percentage of points contained within the convex hull, we repeated our analyses for 98% and 100% convex hulls (Fig. S7). The results were consistent across these definitions of the speed limit.

**Cursor progress**

To quantify the behavioral consequence of each neural activity pattern, we measured the component of cursor velocity in the direction of the target at each timestep. We termed this metric **progress**

\[
P_t = \begin{bmatrix}
\cos \theta_t \\
\sin \theta_t
\end{bmatrix}^\ast (M_2^{OMP} u_t + m_0)
\]

which is the projection of the single-timestep cursor velocity onto a unit vector in the cursor-target direction \(\theta_t\). This metric is depicted graphically in Fig. 3A. While our AoL metric (i.e., reward rate) provides an overall metric of learning, the change in progress provides a metric of the impact of each neural activity pattern on performance. Changes in progress provide a metric of per-target learning.

**Outside-manifold contribution to progress**

In Figures 4 and S6 we sought to assess whether the new patterns of neural activity that we observed were still subject to the constraints of the intrinsic manifold. Each population activity pattern can be decomposed into an inside- and outside-manifold component. Correspondingly, the observed progress at each timestep is the sum of the inside-manifold contribution to progress and the outside-manifold contribution to progress, as depicted Fig. S6B. We computed the progress that can be attributed to getting outside the intrinsic manifold according to the equation:

\[
P_t^{outsideManifold} = P_t^{total} - P_t^{insideManifold}
\]

where \(P_t^{total}\) is calculated from Eqn. 11. To calculate \(P_t^{insideManifold}\), first we found the orthogonal projection of each neural population activity pattern into the manifold

\[
\text{orthogonal projection into manifold} = U^T u_t
\]

where \(u_t\) is the z-scored spike count vector. Because the spike counts have been z-scored, the mean of \(u_t\) is 0. \(U\) contains the orthonormalized columns of \(A\) and is found using the singular value decomposition, such that \(A = USV^T\). The column space of \(U\) defines the intrinsic
manifold. Then we found the representation of the orthogonal projection in the high-dimensional space

\[ \tilde{u}_t = UU^T u_t \] (14)

where \( \tilde{u}_t \) is the inside-manifold component of the population activity pattern. Finally, we computed the progress from this inside-manifold component of the spike count vector.

\[ p_t^{\text{insideManifold}} = \begin{bmatrix} \cos \theta_t \\ \sin \theta_t \end{bmatrix} \ast (M_2^{\text{OMP}} \tilde{u}_t + m_0) \] (15)

Fig. S6C shows the \( p_t^{\text{insideManifold}} \) and \( p_t^{\text{outsideManifold}} \) for each of the new neural activity patterns expressed on the last day of OMP1. Some neural activity patterns produce large inside-manifold contributions to progress and small outside-manifold contributions to progress (Fig. S6C, red). Other neural activity patterns produce small inside-manifold contributions to progress and large outside-manifold contributions to progress (Fig. S6C, blue). To further show that learning is not constrained by the intrinsic manifold, in Fig. S6D we calculated the change in the mean \( p_t^{\text{insideManifold}} \) and mean \( p_t^{\text{outsideManifold}} \) across all neural activity patterns produced for each target relative to day 1. For this calculation we include all the neural activity patterns expressed for each target, not only the new neural activity patterns. For many targets learning occurs by increasing the \( p_t^{\text{outsideManifold}} \), thus demonstrating that learning can be driven by producing new neural activity patterns outside the intrinsic manifold. Note that even for some targets that show good learning, the inside-manifold or outside-manifold component can be unhelpful, but then be overcome by helpful progress in the other component (Fig. S6E).

**SI References:**


**Fig. S1.** Incremental training facilitates multi-day learning. (A) An incremental training approach was used to guide monkeys during learning of the OMP mappings. Incremental mappings spanned the neural space between the intuitive mapping and the OMP mapping. (B) Training scheme used for single- and multi-day experiments with incremental training and no incremental training. Each block indicates a day. (C) Learning curves for all multi-day OMP, incremental training experiments for monkey L. The amount of learning (circles) is shown only for days on which the full OMP was presented to the animal. Each line indicates a unique OMP mapping. (D) All multi-day OMP, incremental training learning curves for monkey N. Same conventions as in C. OMP 1 corresponds to the experiment highlighted in other figures. (E) All multi-day OMP, no incremental training learning curves for monkey L. (F) All multi-day OMP, no incremental training learning curves for monkey N. (G) The amount of learning for multi-day, incremental training OMP experiments (green) was greater than for all other training strategies we used (vs. single-day, incremental training OMP experiments (cyan; t-test, p=0.0019); vs. multi-day, no incremental training OMP experiments (light green; t-test, p=0.052); vs. single-day no incremental training (blue; t-test, p<10^{-4}).
**Fig. S2.** Changes in neural activity are specific to the OMP mapping presented to the monkey. (A) Mean progress (cf. Fig. 3) observed through the OMP 1 mapping increased from day 1 to day 8 (green). For comparison, we mapped the learned neural activity patterns through 500 random OMP mappings and measured progress. The gray dashed lines show the average progress through these random mappings. Progress does not improve through these random mappings over time. This shows that neural activity changed in a manner that is appropriate for the particular OMP mapping the monkey was learning. **(B)** The change in progress between day 1 and the last day (averaged over all targets) is plotted for the OMP mapping the animal experienced (green) and each of the 500 random OMP mappings (gray). **(C)** For each multi-day OMP, incremental training experiment we compared the observed learning (change in progress relative to day 1 averaged across targets, green dot) to the apparent learning distribution through 500 random mappings (box and whisker plot, where the center line indicates the median, the edges of the box indicate the 25th and 75th percentiles, and the whiskers extended to the smallest
and largest of the data points). For all but one experiment, the chosen mapping showed more learning than would have occurred for 75% of the random mappings.
**Fig. S3.** Recordings are stable on the timescale of several days. Here, stability is assessed during an example multi-day OMP learning experiment and a multi-day intuitive mapping experiment. (A) Waveforms of the threshold crossings used for decoding from six selected channels on day 1 and the last day (day 8) of OMP1 for Monkey N (green) and day 1 and the last day (day 5) of a multi-day intuitive experiment for Monkey N (gray). The waveform shape for each channel remains stable across days. (B) Waveform differences for OMP1. We quantified the difference in waveform shape by calculating the distance between the mean waveform on day 1 and that on the last day for each channel. Arrows correspond to the selected channels in panel A. (C) Waveform differences for a multi-day intuitive experiment. Arrows correspond to the selected channels in panel A. The waveform shape changes are not statistically different between the multi-day OMP learning and multi-day intuitive scenarios (K-S test, p=0.97). (D) ISI differences for OMP1. The difference in ISI histograms was calculated as the K-S statistic between the distribution of ISIs on day 1 and the last day. Arrows correspond to the selected channels in panel A. (E) ISI differences for a multi-day intuitive experiment. Arrows correspond to the selected channels in panel A. ISI changes are not statistically different between the multi-day OMP learning and multi-day intuitive scenarios (K-S test, p=0.99).
A Multi-day OMP: high learning pressure

B Multi-day intuitive mapping: “low learning pressure”

C Multi-day intuitive neural activity through random OMP: “no learning pressure”

D Multi-day OMP (high learning pressure)  
Multi-day intuitive (low learning pressure)
**Fig. S4.** New neural activity patterns preferentially emerge during OMP learning. (A-C) “New” neural activity patterns correspond to velocities that exceed the speed limit. As in Fig. 2, the “speed limit” is defined as the 95% convex hull of velocities generated from the intuitive neural repertoire projected through the OMP mapping (gray dashed line). The velocities generated while using the OMP mapping are colored according to the instructed target location. Each dot is the velocity resulting from one neural activity pattern (45 ms bin). (A) Multi-day OMP learning for OMP 1. This experiment is the same as in Fig. 2, but here we include all days for which the monkey used the full OMP mapping. On day 1, the velocities during OMP control mostly fell within the speed limit defined from the intuitive neural repertoire. On day 6, most of the velocities are still within the speed limit. However, the velocities have become more appropriate for successful target acquisition, as can be seen by the points for each target (color code given by inset). For example, when the monkey is instructed to move the cursor to the upper-left target (blue), he generates neural activity patterns that cause velocities in that direction. On days 7 and 8, velocities begin to consistently exceed the speed limit in the direction that is most beneficial for behavior (blue arrows). Thus, during OMP learning, new neural activity patterns emerge in a manner that increases the progress of the cursor toward the target. % new indicates the percentage of points that fall outside the speed limit. Δ prog refers to the progress relative to day 1. (B) Multi-day intuitive mapping. This is considered a “low learning pressure” scenario because while cursor control performance is high from the beginning of the experiment, there might still be motivation for the monkey to increase his reward rate by generating faster speeds. The speed limit (gray dashed outline) is identified on day 1. Each panel shows the velocities generated during subsequent days with the same intuitive mapping relative to the speed limit. Across all days there are only small changes in progress (which happen to all be negative, i.e., behavior has gotten worse relative to day 1) and few new neural activity patterns (that is, velocities which exceed the speed limit). The velocities that do exceed the speed limit do not occur in an appropriately target-directed manner, as was seen during OMP learning in row A. (C) For a “no learning pressure” scenario, we passed the neural activity from the multi-day intuitive experiment through 500 random OMP mappings. There is no learning pressure because the monkey did not receive any online feedback about these random OMP mappings. The speed limit (gray dashed line) and velocities corresponds to one representative random OMP mapping which the monkey never saw. In this scenario, it is not the emergence of new neural activity patterns that leads to apparent behavioral improvement. Rather, there is a slight shift of the velocities relative to the speed limit that leads to an increase in speeds in some directions and a decrease in speeds in other directions. (D) New neural activity patterns preferentially emerge during OMP learning. Increases in progress are plotted as a function of the percentage of new neural activity patterns for the three conditions of high- (green), low- (magenta), and no-learning pressure (density histogram across 500 random OMP mappings). There is significant correlation between the formation of new neural activity patterns and increases in progress for the high-learning condition (Pearson correlation coefficient r=0.67, p=1*10^{-11}).
Fig. S5. New neural activity patterns move progressively farther away from the speed limit with learning. In Fig. 2, we defined the speed limit as the 95% convex hull of the velocities generated when the intuitive neural repertoire is mapped through the OMP. We defined new neural activity patterns as patterns that generate velocities which exceed the speed limit. With learning, we observe more new neural activity patterns. One possible interpretation of this result is that the velocities that exceed the speed limit arise from visiting those 5% of points outside the speed limit progressively more often. If this were case, the percentage of “new” neural activity patterns identified by the speed limit metric might go up, but the distance of those points from the speed limit would remain unchanged. Here, we show that this possibility is not consistent with the data. (A) Instead, the points move progressively farther from the speed limit (gray dashed) during learning (i.e., the cursor velocities continue to get faster and more target-directed during learning). (B) With learning over days, neural activity patterns are further from the speed limit, and they contribute to greater progress. For the multi-day OMP experiments, there is a significant correlation between the extent of the points beyond the speed limit and increases in progress (Pearson correlation coefficient $r=0.40$, $p=0.0002$). Each symbol is the average over all 8 targets from one day of one OMP experiment relative to day 1. Symbols are shaded to indicate the day within a given multi-day experiment.
**Fig. S6.** New patterns of neural activity can be inside or outside of the intrinsic manifold. (A) A particular value of cursor progress can be produced by many different neural activity patterns (dashed cyan line), including both patterns inside and outside of the manifold. (B) Each neural
activity pattern (green dot) can be decomposed into an inside-manifold component (red dot) and outside-manifold component. Correspondingly, observed progress (green X) is the sum of inside-manifold contribution to progress (red arrow) and outside-manifold contribution to progress (blue arrow). (C) Animals learn using both inside-manifold and outside-manifold strategies for a given OMP mapping. Each dot shows a new (i.e., outside-repertoire) neural activity pattern observed on the last day of OMP 1. For each new neural activity pattern, the inside-manifold component is plotted against the outside-manifold component. Dots are colored according to the instructed target when that pattern was generated by the monkey (inset). Dots above the diagonal have largely outside-manifold contributions to progress. Dots below the diagonal have largely inside-manifold contributions to progress. We found that some targets (e.g., red) are learned using a largely inside-manifold strategy, whereas other targets (e.g., blue) are learned using a largely outside-manifold strategy. Most of the targets (e.g., teal) are learned using a mixed strategy. (D) Learning (i.e., change in progress relative to day 1) can arise from both outside-manifold and inside-manifold strategies for different targets. Each symbol shows the extent of inside- and outside-manifold contributions to learning for one target from one experiment. Each point is the average of all of the same-colored dots plotted in the space of panel C. Here all population activity patterns are included in the average, not just the new patterns. Colored symbols correspond to the targets represented in panel C. Equal Δ progress lines are plotted to emphasize that both inside- and outside-manifold strategies were used by the animals to achieve similar amounts of learning. (E) Animals learn using both inside-manifold and outside-manifold strategies. Each bar shows one target from one multi-day OMP experiment. This figure differs from Fig. 4C in that here all targets are shown, including those that show negative learning. The overall learning, defined as change in progress from day 1 to the last day, is represented by a green dot. The inside-manifold contributions to that learning are shown in red. The outside-manifold contributions are shown in blue. The overall learning is equal to the sum of the inside-manifold contribution (whether it be positive, i.e., helpful, or negative, i.e., unhelpful) and the outside-manifold contribution (whether it be positive or negative). Thus, it is possible for a bar to exceed the corresponding green dot if the inside-manifold and outside-manifold contributions take on different signs.
Fig. S7. Results do not depend on the specific definition of the speed limit. In all other figures, we define the speed limit as the 95% convex hull. Here we have repeated the key analyses that depend on the speed limit (Fig. 2G and Fig. 3C) for speed limits defined as the (A) 95% convex hull (reproduced here to facilitate comparison), (B) 98% convex hull and (C) 100% convex hull.
<table>
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<th>Monkey</th>
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<th>Multi-day OMP, no incremental training</th>
<th>Single-day OMP, incremental training</th>
<th>Single-day OMP, no incremental training</th>
<th>Single-day WMP</th>
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**Table S1.** Number of experiments of each type.
**Movie S1.** Example BCI trials to each target with the intuitive mapping on day 1 of a multi-day, incremental training OMP experiment (OMP 1), and the OMP mapping on day 1 and after 8 days of training.