Neuronal Representations of Learning Sensorimotor Skills

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Abstract

Psychophysical studies show that when humans learn new sensorimotor skills, an internal representation is formed in the brain. This “internal model” represents the new input (sensory) – output (motor) relationships that are required to perform the task. Often learning is confined to the movements experienced during training and generalizes only poorly to other untrained movements; hence sensorimotor learning is specific. From a global perspective, this is what learning is all about – it should be applied to similar situations but not interfere or hinder previously learned behaviors. This dissertation aims at directly investigating the neural mechanisms that underlie the specificity of sensorimotor learning.

A survey of recent behavioral paradigms shows that many use visually guided reaching movements and that the learning calls for adaptation to directional errors; i.e. errors experienced during learning shift the hand or the visual feedback in a consistent direction. Interestingly, a common finding in the motor system is that neurons show directional selectivity; that is, neurons show maximal activity only when the movement is in one direction in space. This has led me to the hypothesis that the specificity of learning is related to the actual properties of cells in motor areas. The experiments that were designed accordingly confirm this prediction and shed light on the mechanism of sensorimotor learning and transformations. The findings of this study are novel in three main ways. First, neurons in the primary motor cortex (MI) of monkeys alter their activity as a result of sensorimotor learning, signifying the formation of an internal representation of the newly acquired skill. Second, the specificity of the neuronal change is related and can explain the specificity of learning: only a subpopulation of cells increase their activity – those with directional preference close to the direction of movement experienced during learning, and these cells only alter their activity near the learned direction. Third, the formed internal representation persists between learning and re-performing the learned skill, providing direct evidence that MI participates in working memory that maintains newly learned sensorimotor skills.
A key characteristic in learning is that it improves performance. Although this is a trivial statement in itself, the neural changes that underlie and cause it are unknown. Two key features are required: a paradigm that provides inner control for learned vs. un-learned population of cells and a new approach to analyze the data – one that can provide insight into the information conveyed by their activity and how it is represented. This dissertation sheds light on such questions by applying measures from information theory for the first time to the activity of cells before and after learning. The study produced three main findings. First, the information contained in cell activity on movement direction indeed increased during learning; second, this increase took the form of an alteration of the slope of the cells' tuning curves thus showing an increased sensitivity to adjacent directions (rather than a reduction in noise); third, after learning, an external observer can more accurately predict hand direction based on neuronal activity. This suggests that simple learning tasks can improve reconstruction of movements and thus contribute to developing brain-driven devices ("neural prosthesis") to be used in the future for the motor disabled (paralyzed patients, amputees, and others).

The last part of this dissertation integrates my findings with previous knowledge and with knowledge from other fields of neuroscience. Here, I suggest a unified approach to the study of perceptual and motor learning. These two streams of neuroscience have traditionally been segregated and for the first time I highlight similarities and suggest common mechanisms for perceptual and motor learning algorithms. Such similarities suggest that unifying principles govern the neural code across different domains and provide clues to the transformation between sensory and motor representations in different areas.
Introduction

Specificity of sensorimotor learning and internal representations in the brain

Learning is a fundamental ability of animal behavior. To cope with a constantly changing environment, animals need to learn how to respond in different situations and adapt to the new requirements. The most common type of learning, for humans as well as for lower evolutionary species, is the acquisition of new sensorimotor skills. Here, animals learn to associate sensory cues such as visual (or auditory or haptic) feedback with a relevant motor response. For example, altered environmental conditions in an aquatic (in a swimming pool for instance), such as higher viscosity and lower body weight, requires different responses from our musculoskeletal system than on land. Our brain learns to produce new patterns of muscle activation to enable such performance. However, learning can also be “dangerous”: if our body produced these same newly learned muscle activations out of the water – walking would be impaired. On the other hand, we would like this newly learned skill to apply to other swimming pools or any other type of aquatic environment. In other words, learning should be transferable (generalized) to similar situations, but should not generalize to all conditions.

To study the generation and the internal representation of movement in the brain psychophysics has classically studied a relatively simple, yet very common behavior that we use when reaching for a piece of food or a cup of coffee, namely - reaching movements. It is now commonly agreed that targeted reaching movements are internally represented by specifying the direction of the movement and its extent; i.e. a vectorial representation (Bock, 1992; Gordon et al., 1994a; Vindras et al., 1998). An important tool used as a behavioral probe to assess the internal representation and its location in the brain is characterization of learning transfer and specificity. In particular, motor studies have assessed learning and adaptation to new sensorimotor environments and their generalization (Shadmehr and Mussa-Ivaldi, 1994; Imamizu et al., 1995; Ghahramani et al., 1996; Sainburg et al., 1999; Kawato, 1999; Thoroughman and Shadmehr, 2000). In such experiments, the experimenter can modify the relation between the extent or the direction of the hand movement and a movement of an
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object on a computer screen (cursor) by altering the visual feedback. For example, to study the extent element, in order to move a cursor on the screen for a distance of 2 cm, the hand must travel only 1 cm. These types of transformations are termed visuomotor gain transformation. A generalization study then tests whether movements to other untrained locations in space are also affected by this type of learning. Several studies have shown that this type of learning is transferred to other extents of movement (Bock and Burghoff, 1997) and even to other directions in space (Bock, 1992; Krakauer et al., 2000).

In contrast, when people are confronted with altered conditions that produce directional—visual deviations, learning is limited to the direction trained during the experiment. In such studies, when the hand travels in space, the visual feedback (cursor) is rotated in relation to it. Thus these transformations are termed visuomotor rotational transformations. During learning, movements are performed to only one or few proximal directions in space and then testing for transfer (or generalization) of learning is done for other directions in space. Such studies show that learning is limited to the trained direction (Imamizu et al., 1995; Krakauer et al., 2000). The specificity for direction is also evident when adapting to new dynamic properties; e.g. when an imposed force-field perturbs the hand directionally (Gandolfo et al., 1996).

These two types of transformation learning (gain and rotation) and their different patterns of generalization have led to the suggestion that the two properties of direction and extent are represented separately by two different channels in the brain (Vindras and Viviani, 2002). This separation could be helpful in the planning and generation of movements but also have relevance for the specificity of learning: it can be transferred to other extents because we need to rescale our natural movements easily (Goodbody and Wolpert, 1998), and indeed we can. Reaching for certain object located 5 cm from us should be the same as reaching for it when it is located 10 cm from us. Moreover, we can write and draw both on paper and on a blackboard while maintaining the same spatial properties of our impressions. On the other hand, obstacles and manipulations that hinder our hand when reaching to the left are less likely to be in our way when reaching to the right, thus different directions in space have different properties.

What are the underlying neuronal elements that constitute these changes in learning? To directly approach this question it is necessary to observe neuronal activity during motor performance and learning. The similarities in monkeys’ frontal
cortex architecture and their ability to perform accurate reaching movements with properties that are highly comparable to those found in humans serve as a basis for their use in studies that record single-cell activity during movement (Georgopoulos, 1995; Kalaska et al., 1997; Scott, 2003). However, before going any further, it is desirable to verify that monkeys do indeed plan and learn such complex tasks in the same way that humans do. Otherwise, there is a high risk of drawing inappropriate conclusions about our motor system without even realizing it. This is not trivial, since much is unclear about our closest ancestors and the “missing link” is still missing. It seems very probable that the prime leap in human evolution resides in the incredible ability to learn. For example, one widely accepted hypothesis posits that learning to use tools gave the early hominoids a relative evolutionary advantage. A prerequisite for tool use is the ability to learn new sensorimotor skills that demand complex eye-hand (visuomotor) coordination.

To conclude, these arguments show it is important to first demonstrate that non-human primates (monkeys) indeed plan, learn and generalize complex sensorimotor environments in the same way that humans do. Specifically, we need to show this capability for the learning and generalization of visuomotor transformations. The first section in the results chapter was designed for that purpose. Two monkeys were trained to learn rotational and gain transformation and then tested for other directions and extents. The study extends previous human studies by applying a wide variety of analysis methods and comparing learning and washout rates across conditions.

Having found that monkeys, like humans, learn rotational transformations locally with little generalization to unlearned directions, I attempted to look for the neuronal mechanisms that underlie this feature. One robust phenomenon that is widely accepted in the motor physiology literature is that cells in many motor areas have a directional preference (Georgopoulos et al., 1982; Caminiti et al., 1991; Schwartz, 1992; Fu et al., 1993; Johnson et al., 1999; Kakei et al., 1999). Namely, cells respond more vigorously when movements are in one direction in space (the “preferred direction” - PD) and respond less when movement is in another direction. This finding is especially prominent in the primary motor cortex (MI), which is considered a key area for generating movement and provide a large fraction of the projections to the spinal cord (Porter and Lemon, 1993). In contrast to the directional preference, neurons in MI modulate their activity as gain factors as a function of...
movement speed (Moran and Schwartz, 1999b) (or extent, naturally – movement extent and speed are coupled – “the isochrony principle” (Viviani and Schneider, 1991)).

These characteristics led me to the first main hypothesis of this thesis: that the spatial specificity of learning (i.e. to direction) is related to the spatial sensitivity of neurons (i.e. to direction). Formulating this more elaborately: when learning a directional task in one direction, only a subset of neurons (those with directional sensitivity to that direction) should “learn” the task. Thus when testing movements to other directions, a different “naïve” pool of neurons participates in the movement and the learning will therefore not generalize (or transfer) to it. The second section in the results chapter (Paz et al., 2003) describes the experiments that support my hypothesis, confirm its predictions and shed light on the mechanism of sensorimotor learning and transformations.

**Learning improves the neural code**

In Webster’s dictionary the term “learning” is defined as “to gain knowledge or understanding of or skill in by study, instruction, or experience”. Unfortunately, the only way to confirm that knowledge has been gained is to seek relevant changes in behavior. Learning is therefore tested by observing changes in behavior and we say that something was learned if a relevant improvement in behavior is observed. This raises fundamental issues for the neuroscience field: what is the neuronal correlate of improvement in behavior? Traditionally, learning tasks were shown to cause several types of changes in neuronal activity and changes were shown to correlate on a time course with the improvement in behavior. However, how can we say that something has “improved” in the neural representation as a result of learning? Namely we lack a definition of improvement in the neural code itself.

In this thesis, I approach this issue for the first time by applying measures from information theory, such as mutual information (MuI) (Cover T.M. and Thomas J.A., 1991; Rieke et al., 1997). This measure quantifies the amount of information (in bits) that the knowledge of one variable tells us about a second variable. It uses the independent and mutual distributions and is therefore a model-free measure of the relation. In the third section in the results chapter (Paz and Vaadia, 2004), MuI was used to assess how much neuronal activity (firing rate) tells us about the movement
direction; and I compared the amount of information before learning to after learning. The scheme presented in the previous section provides a task with an inner control. The specificity of learning to only one direction in space allows for a comparison of the information gained during learning on one trained direction to the information (presumably unchanged) on other, untrained directions.

A fundamental question in neuroscience is the nature of the neural code. Many descriptions of neuronal activity and many measures of it exist in the literature but the aspect of neuronal activity that is being used by the brain itself for communication remains unclear (Perkel and Bullock, 1968; Abeles, 1991; Rieke et al., 1997). Learning induces changes in behavior as well as changes in neuronal activity. I have exploited this and correlated the change in information gained during learning to several properties of neural activity. The hypothesis was that if we can identify what aspect of activity was altered and correlates with the increase in information, then this is the aspect that interests the neurons further downstream and is thus part of the language spoken by the neurons; i.e. an element of the neural code.

Further motivation comes from the desire for simplicity and structuralism: whereas measures from information theory use the full distribution matrix, it is desirable to formulate a “simpler” aspect of the neural code, one that can be quantified and formulated as general rule. I therefore examined changes in the tuning curve of neurons (i.e. their responses as a function of movement direction). Two canonical ways exist for neurons to increase their information content (Dayan and Abbott, 2001): a. increased sensitivity (Zohary et al., 1994; Gold et al., 1999), by increasing the slope of their tuning curve at a certain point thus increasing the difference in activity between adjacent values; and b. increased reliability by reducing the noise (Poggio et al., 1992); i.e. neuronal responses are more similar to the mean response. Intuitively, both aspects allow for a better discrimination between adjacent values because the first draw the mean responses to two values farther apart and the second narrows the two distributions.

Thus far, we have dealt with the way in which neurons encode the direction of movement and how this encoding improves as a result of learning. Naturally, the activity of neurons must also be decoded by the “next” group / network of neurons. In the case of generating movement, the activity of neurons in the primary motor cortex is read out by several areas. The first is the spinal cord which uses it to generate the final muscle activations and as a result – the movement itself (Porter and Lemon,
The complexity of the inter-neuronal network and its neuronal responses (Prut and Fetz, 1999) indicates that the performed computation is rich and therefore that the input from MI must be well interpreted. Moreover, other computational loops inside the brain, such as cortico-cortical connections, cortex-basal-ganglionic loops and cerebellar loops, receive and send projections from MI, and participate in motor functions (Alexander et al., 1986; Houk and Wise, 1995; Middleton and Strick, 2000). Thus, many brain areas should be able to decipher the activity of neurons and networks of neurons in MI. Although higher information content should theoretically make for a better readout (Dayan and Abbott, 2001), a direct demonstration that biologically plausible decoding algorithms can extract this information and use it is appropriate. I therefore used two possible algorithms that are based solely on neuronal responses to extract the actual movement direction, and compared the quality of prediction after learning to that before learning. An additional use of this process, the use of learning for designing neural prostheses, is extensively described in the discussion section of this thesis.

To conclude, the third section (Paz and Vaadia, 2004) addresses these questions of neural code from its two end points – encoding and decoding: 1. by using information theory to show that the encoding of movement direction by single neurons is improved due to learning. 2. By showing which aspect of the neural code is changed: the sensitivity to adjacent directions. 3. By decoding the actual direction of movement from the population activity and demonstrating that a better readout can be achieved after learning.

**Similarities of learning algorithms in perceptual and motor systems**

When posing global scientific questions, we usually seek unifying rules; namely, a small set of rules that apply to all areas and systems in the brain. This is the objective of the most common scientific approach: reductionism – which attempts to reduce a large set of observed phenomena into a much smaller set of principles. The brain is comprised of many areas which are classically divided into sensory areas (such as the visual, auditory, somatosensory areas) and motor areas. These two systems reflect two sides of one tightly connected loop that mediates interactions with the world. Whereas seemingly these are two different systems that control different entities, they are both parts of the same system, i.e. the brain. The fundamental
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The question is: do similar principles govern both systems? To the best of my knowledge, this question has never been directly posed and reviewed from a neurophysiological point of view.

Further motivation comes from the sensory-to-motor transformations that are performed continuously in our brain. Similar principles in both systems may ease these tasks. An intuitive analogy is the biblical story about the Tower of Babel; better work could be done if all the workers had continued to speak the same language.

Over the course of my work, I have observed that many similarities exist between properties of learning new motor skills and properties of learning new perceptual skills. Such similarities come to light when reviewing results from psychophysical studies, many of which have recently received direct confirmation from electrophysiological studies. When trying to identify the computation being performed in sensory and motor areas, it is worth applying the distinction between (1) representational level and (2) algorithmic level (Marr D, 1982). For example, a computer can use either a binary representation or a hexadecimal representation of numbers; and aside from this it can use different algorithms to perform a division operation. To take another example, two people can speak either Hebrew or English, but can solve problems similarly in both languages or differently with the same language.

At the level of representation, both systems resemble each other closely: almost all brain areas have neurons with activity fields, also known as receptive fields or tuning curves. In primary cortical areas, neurons possess tuning curves to simple physical features, such as orientation of a light bar in visual areas, tone frequency in auditory areas and direction of movement in motor areas. A population of neurons with different activity fields can provide the basis for representing sensory or motor parameters, and as such they can serve as the primitives—the fundamental components—of a neural representation (Pouget and Snyder, 2000). The nature of these primitives and their locations in the brain can be inferred by measuring how learned skills transfer to situations other than those experienced previously (Ahissar and Hochstein, 1997; Gilbert et al., 2001; Chou and Lisberger, 2002). For example, in the learning scheme presented earlier - adapting to directional perturbations for one direction in space and then testing for untrained directions - the width of the generalization function can point to the underlying neuronal primitives; e.g. by
comparing it to the shape and width of the tuning curve for direction of movement in certain motor areas (Donchin et al., 2003).

A closer investigation of learning paradigms and learning-related changes suggests more complexity in the representational level and clues as to the algorithmic level. The fifth section in the results chapter (Paz R et al., 2004) synthesizes recent findings from sensory and motor research and develops a new perspective that finds common ground in these (traditionally) different fields. Specifically, these similarities suggest that similar learning algorithms are used across different areas of the brain.
Methods

Subjects

The data were collected from two female Rhesus monkeys (W and X, Macaca Mulatta), approximately 4.5 kg each. The monkeys were approximately 1 year old when the training sessions began. All animal care and surgical procedures complied with the NIH Guide for the Care and Use of Laboratory Animals (rev. 1996) and with the Hebrew University guidelines supervised by the Institutional Committee for Animal Care and Use.

The behavioral setup

On each recording and training session, the monkeys were brought from the animal house to the recording room in a plastic primate chair. The recording room was dark (except for the visual display). The monkey controlled the position of a cursor on the workspace with its hand by a two joint low-friction manipulandum (constructed at the mechanical workshop in Hadassah) and wore a wrist cuff to minimize distal movements; thus movements were made predominantly with the elbow and shoulder. The head was also restrained during recording sessions.

A screen was located 50 cm from the monkey and two manipulanda controlled 2 cursors on the screen, one cursor (+ sign) was used for the right hand and one for the left (x sign). The basic idea of the task is to position the cursor inside a circle that appears on the screen. Upon successful termination of a trial, a juice or water reward was administered through a metal tube. A detailed account of the behavioral task is given in the Materials and Methods sections of sections I and II in the Results chapter.

To implement the complex learning task needed for this study and to allow for more flexible design of future learning tasks, I designed and implemented a new behavioral setup (see the behavioral program section below). In a nutshell, this software possesses a tailored (yet flexible) programming language that allows for full design and control of the task performed by the monkey as well as realtime control of its execution by the experimenter. It was written in Visual C++ and implemented on a PC (Windows 98/2000/XP) computer. The program was designed to communicate directly with the data acquisition system (MAP, Alpha Omega Instruments, Nazareth Israel), send all the behavioral signals and controls, and the manipulandum data to it.
Surgical procedure

After the monkeys were trained, they were anesthetized with Ketamine-Xylazine anesthesia. During surgery (performed by Prof. Eilon Vaadia and myself), the monkey’s head was fixed to a stereotaxic frame and a square piece of bone was excised using an electrical drill from the region overlying the motor and premotor cortex of both hemispheres. Titanium screws were implanted in adjacent skull locations and a 27mm x 27mm plastic chambers were placed over the drilled hole. The chamber was then fixed to the skull and the titanium screws using dental acrylic. For the two monkeys, chamber location with respect to skull landmarks was determined using magnetic resonance imaging (MRI) performed at the Hadassah Medical School, with the generous help of Dr. Gadi Goleman.

Extra-cellular recording

On each recording session, sixteen (eight in each hemisphere) glass-coated tungsten electrodes with an impedance of 0.2-1 MΩ at 1kHz (prepared by Varda Sharkansky) confined to a common guide tube with a 1.5mm inner diameter were used to record extra-cellular activity of 1-3 cells each. The guide tube and electrodes were mounted on a positioning apparatus which allowed for horizontal positioning of the guide tube (MT, Alpha Omega Instruments, Nazareth Israel). Before inserting the electrodes on each daily session, the recording chamber was filled with 4% agarose solution in saline to constrain brain movements due to blood pressure fluctuations. During recording, electrodes were lowered by a PC controlled mechanical driving system (EPS, Alpha Omega Instruments, Nazareth Israel) at steps of a 100-200 μm until the brain surface was encountered. Then, a pause of about 10 minutes was taken to allow the brain tissue to reach a stable state with respect to the electrodes. Subsequently, electrodes were lowered in smaller steps (~10-50 μm) until extra-cellular neuronal activity was discerned. Neuronal activity was monitored both by listening to the signal from each electrode through headphones, and by viewing it on oscilloscopes. After signals were found in all (or most) electrodes, spikes were isolated using the MSD system. While searching for neuronal activity, no explicit selection was made for neurons with specific activity characteristics, so that sampling was relatively unbiased. However, this procedure is inherently biased towards locating neurons with high firing rates and large extra-cellular electric fields. Once
spikes have been isolated from each of the electrodes, the behavioral program was activated and the session started. During the session, the experimenters continuously monitored the spike signals as detected by the MSD and graded the units according to how distinct their spike shapes were from other neurons recorded by the same electrode.

Approximately every 4 weeks, when the dura mat thickened (due to tissue growth) and consequently electrodes broke as they were advanced through it, the external tissue on the dura was scraped. During scraping, the monkey was seated in a primate chair with its head fixed, anesthetized with Ketamine-Xylazine anesthesia, and the overlying tissue was scraped using sterile metal instruments.

**Identification of the arm area**

Positioning of the electrodes within the arm area of MI was verified by somatosensory examination and intra cortical micro-stimulation (ICMS). At the end of each daily session, the responsiveness of the recording site to passive manipulations of the limbs was assessed. ICMS stimulation was applied (50ms of 200-μs cathodal pulses at 300Hz) through individual electrodes, and the threshold current for eliciting visible movements was noted. ICMS and somatosensory examination were also applied in preliminary mapping sessions conducted before initiation of the recording sessions. Only penetration sites where ICMS evoked single joint shoulder or elbow movements at ≤40μA were further used for analysis.

For surface mapping, Monkey X was killed with an overdose of pentobarbital, and then perfused transcardially with 0.9% saline followed by 4% formaldehyde in 0.1M phosphate buffer. After fixation, pins were inserted in defined chamber locations to allow for reconstruction of chamber coordinates, and the locations of penetration sites relative to cortical landmarks were determined. All penetration sites were located in MI (see figure 1 in section II of the Results chapter). In monkey W, we verified penetration locations using MRI after inserting electrodes in the boundaries of the recording locations. The monkey was then released and now lives happily with several of its friends in an animal shelter.

**EMG recordings**

To identify muscle activations, surface electro-myograms (EMGs) were recorded in several sessions (in both monkeys) from the following proximal and distal
arm muscles: *flexor carpi ulnaris* and *radialis, extensor carpi ulnaris* and *radialis, biceps brachii, triceps brachii, deltoid, trapezius, pectoralis major, latissimus dorsi, rhomboid, teres major* and *oblique abdominal extensors*. EMG was sampled at 24kHz.

**Data collection**

Data were fed from extra-cellular electrodes to x25 pre-amplifiers (Headstages, Alpha Omega Instruments, Nazareth Israel) positioned on the MT. Signals were then amplified to an overall gain of x10000 using signal conditioning hardware (MCP+, Alpha Omega Instruments, Nazareth Israel) and then logged at 24KHz on the data acquisition system based on a micro-star board (MAP, Alpha Omega Instruments, Nazareth Israel). In addition, data was bandpass filtered (0.3-8kHz) and fed to online spike-sorters (MSD, Alpha Omega Instruments, Nazareth Israel) in which spikes were detected with a template matching algorithm. These detected spikes as well all behavioral events were logged on the MAP data acquisition system PC at 10kHz. In addition, manipulandum angular positions were fed to the behavioral computer, transformed to XY coordinates, and logged on the MAP at 1kHz.

**Basic data analyses**

Online detected spikes, behavioral events and hand position data were saved with the continuous spike signals. Subsequently, the data were rearranged in cuts corresponding to each of the behavioral conditions. A cut comprises neuronal and hand position data in all trials from a given behavioral condition (e.g. all single movements to the left). For my analysis, I considered cuts made on the time of the appearance of the cue signal and of the go signal, starting 750 miliseconds before and ending 750 milisecond – 1.5 seconds afterwards. Cuts were derived using "Cut Engine" software programmed by Itay Gat. Data from individual neurons were then analyzed for stability (software developed by Yoram Ben-Shaul). In the stability analysis, sections of data exhibiting non-stationary activity across trials (from each neuron separately) were excluded.

In each recording session, information about the recorded neurons as well as general information about the session (penetration coordinates, monkey behavior, etc) were fed to a Microsoft Excel sheet. The benefit is that MATLAB has built-in
functions to access Excel sheets. Since a database is comprised of many days of recordings and large amounts of data, I designed and implemented in MATLAB code an environment that facilitates the analysis and order of the neuronal and behavioral data. This environment is now being used by all students in the lab. The library of functions in this environment supports and implement basic and complex analysis tools.

The basic neuronal data used for analysis in the first and second manuscripts are spike counts in behaviorally defined intervals. These spike counts were derived by MATLAB scripts from the data in the cuts, so that for each session we obtained the spike counts in each trial, for each recorded neuron, in each behavioral condition in various behaviorally defined epochs. The behavioral epochs are described in the Materials and Methods section and the first figures of the first and second manuscripts in the Results of the dissertation. Hand position was low pass filtered offline (10Hz) prior to subsequent analysis.

**Non basic data analyses**

Following the procedures in the previous section I obtained only the basic data, namely spike counts and peri-stimulus time histograms (PSTHs) in behaviorally defined epochs in each of the trials. Most subsequent procedures comprised various analyses performed on these spike count data. Many of these procedures; e.g., statistical parametric and non-parametric methods (Analysis of variance –ANOVA, Kruskal-Wallis test, Kolmogorov-Smirnov test, Mann-Whitney test, and others ); circular statistics (Mardia, 1972; Fisher, 1993); are standard for the analysis of neuronal data. However, I also used several non-standard methods for data analysis. Some of these methods are briefly described below with appropriate references.

**Bootstrap.** One of the benefits of this experimental design is that it allowed for comparison of two similar behavioral states, separated only by a learning period. I therefore compared behavior and neuronal activity in the post-learning to the pre-learning, two periods in which the monkey performed the same behavioral task (reaching to 8 directions under standard mapping conditions). Because this demands a comparison of parameters whose underlying distribution is unknown, the most convincing way to do so is to use bootstrap methods (Efron and Tibshirani, 1993). For this purpose, I shuffled trials from pre-learning and post-learning and divided them
each time into two new arbitrary groups. The difference in the compared parameter was then calculated. This procedure was repeated 100-1000 times (see the results section for specific calculations) and to obtain a distribution of differences. The actual difference between the true groups of pre-learning and post-learning was then compared to this distribution and a p-value was obtained. This method was applied to a series of selected parameters (preferred directions, mutual information, population vectors, firing rates, prediction accuracy, etc.). This procedure estimates the probability of a difference under the null hypothesis; i.e. what is the probability of obtaining a difference under a no-change hypothesis. It therefore estimates the alpha error (i.e. when a false hypothesis is accepted - a false positive in terms of the null hypothesis). Another procedure used in the motor literature (Sergio and Kalaska, 2003) resamples with replacement trials in each direction separately, calculates the difference in the parameter between the two and repeats the procedure to obtain a distribution of differences. This procedure estimates the probability of obtaining a difference which is equal to zero under the alternative hypothesis. It therefore estimates the beta error (i.e. when a true hypothesis is rejected - a false negative in terms of the null hypothesis).

Preferred direction and tuning curve. Preferred direction of cells (i.e. the direction of movement associated with the maximal response) is traditionally calculated by a linear regression on the normalized Cartesian coordinates (Schwartz et al., 1988). An alternative is fitting a cosine function to the activity of the cell and obtaining its phase (Georgopoulos et al., 1982). The quality of the fit is assessed by the correlation between the activity and the fitted function (i.e. the $r^2$). Another alternative is summing the activity vectors for each tested direction. All methods are similar and only extract the phase of the first Fourier component (Sanger, 1994). They provide different (important) insights into the goodness of fit and the representation of direction in the population. A more thorough investigation of tuning functions was recently performed by fitting a family of functions from the Von-Mises distribution (Amirikian and Georgopoulos, 2000), such as bi-modal, asymmetric, different widths. In my study, I tested all options, but since the learning-related change was mainly evident at a small range of the tuning curve (its peak), it was better to focus on quantifying the change by local firing rates (sections II & IV) and to quantify local parameters that could be related to learning and improved performance: the slope
(discriminability) of the tuning curve and the noise (reliability). This is detailed in section III.

**Behavioral measures.** To test for aftereffects in movement trajectory I used several methods that extend previous human studies. Because there were two types of visuomotor transformations, gain and rotation, it was important to differentiate temporal components and spatial components. Three methods were used: 1. a Pearson correlation between the complete speed profile of movement after learning to the typical (average) movement before learning. This method reveals similarities and differences in the temporal domain; 2. a figural distance measure (Conditt et al., 1997). This measure captures the difference in the shapes of the respective paths and is insensitive to differences in speed. It therefore probes the spatial domain; 3. a tailored measure for the appropriate type of learning. For the gain transformation I obtained the peak velocity, and for rotational transformation the deviation (in angles) at the peak velocity. Parameters were taken at peak velocity to reflect the feedforward mechanism of the planned movement rather than feedback corrections. Each measure was normalized by the transformation in its session to allow for comparisons between days. More details and results are described in section I.

**Mutual information.** Borrowed from information theory (Cover T.M. and Thomas J.A., 1991), the mutual information quantifies how much a neuron's activity tells us about another parameter (Rieke et al., 1997; Dayan and Abbott, 2001)-- direction of movement in this study. It does so by measuring the reduction in uncertainty about direction/activity due to the knowledge of activity/direction. Uncertainty is measured as the entropy of the distribution. Careful use of this measure requires bias correction and I have tested several methods, from analytical methods (Panzeri and Treves, 1996), bootstrap, assuming different underlying distributions and different approaches to the actual calculation. The benefits of using mutual information and the results are explained in detail in section III.
Decoding methods. To examine the ability of an external observer to decode the actual movement direction from neuronal spike trains I used two methods. The first is the widely used population vector (Georgopoulos et al., 1988; Zohary, 1992). This method is actually a radial-basis function method (Sanger, 1994). In a nutshell, this estimator weights the preferred direction of each cell by its momentary activity and sums it linearly over the population. The resultant vector is expected to converge under certain conditions (Georgopoulos et al., 1988; Seung and Sompolinsky, 1993; Sanger, 1994; Snippe, 1996) to the direction of the actual movement. However, whether these conditions are met by neurons in the motor cortex is still under debate (Scott et al., 2001). Because of all these reservations, I also applied a probabilistic method, the maximum aposteriori estimator (MAP) (Sanger, 2003). This method is a Bayesian-inference variant of the maximum-likelihood estimator (ML). The only assumptions made were independence between neurons and Poisson distribution of firing rates. More details and results are described in section III.

Simulations. To assess the plausibility that the observed learning-related changes are not only correlated but can also cause the observed changes in behavior, I performed simulations of neuronal tuning curves and used the population vector algorithm to approximate the actual hand movement under these conditions. Simulations included a population of standard, cosine-tuned (or Von-Mises) tuning curves with preferred direction homogenously distributed. To simulate the learning-related changes, a Gaussian shaped hill of activity was added to the appropriate sub-population of neurons. Simulations then used the population vector algorithm to obtain alleged-actual hand movement under the two conditions. The methods and results are briefly described in section IV.
Methods

Miscellaneous. I tested several hypotheses that are not described in this report because they did not yield any important results. E.g. Cross-correlations (Perkel et al., 1967; Aertsen et al., 1989) between pairs of neurons recorded in the same session were compared before and after learning with the hope of identifying changes in connectivity. Although some pairs exhibited significant changes, no systematic phenomenon was observed. Signal and noise correlations (Lee et al., 1998) between pairs of neurons did not exhibit any change either. Onsets of response was calculated by identifying the response onset of each neuron by several methods e.g. cusum (Ellaway, 1977; Pauluis and Baker, 2000). Response shapes were identified by clustering (k-means, fuzzy c-means, hierarchical) of the original PSTHs (Fellous et al., 2004) in the time-domain and after applying principal component analysis (PCA) (Richmond and Optican, 1987). My hope was to find differences in the shapes or in cluster associations between pre- and post-learning; this study is ongoing.

Behavioral program

The behavioral program is a framework for designing and implementing behavioral paradigms. It was implemented in visual C++ on a Windows 98/2000/XP operating system. Below is a short description of its components together with few interface examples.

The software comprises three integrated components:

1) A tool for implementing trial-based behavioral paradigms.
2) A tool for real-time execution of the experiment and managing it.
3) A tool for communicating with the environment.
1) The paradigm tool has a layered design that enables simple modular composition of trial-based paradigms but has full flexibility. The layers are:

- A global parameter definition.
- A trial-flow definition, using a new computer language that allows for the use of: parameters, assignments, if statements, loops, and functions (built-in and external). The list of built-in functions can draw basic shapes (circles and rectangles), manage the display shown to the animal, manage the relationships between the manipulanda and the screen, send behavioral events, compute basic mathematical functions, etc.. External functions can be written by the experimenter and a battery of C++ functions is written to aid the implementation (examplified in a below).
- A trial list. Each trial-list is a trial-flow with a required assignment of parameters.
- A trial order. A list of groups of trials to be executed in a serial order during the experiment (examplified in b below).
- Each group is comprised of trials (from trial-list) that will be executed in a randomly shuffled manner (examplified in c below).
2) The real-time execution tool is comprised of:
   - A compiler that transforms the trials into an intrinsic structured executable format.
   - An interpreter that executes the compiled trials with continuous access to changes in parameters and the environment.
   - A control screen for the experimenter with continuous supervision and report of the on-going experiment (shown below)

![Image of control screen](image)

3) The communication tool is comprised of:
   - Continuous reading of the location of the manipulanda.
   - Continuous output to the screen and reward system.
   - Continuous output to the acquisition system providing it with information about the manipulanda, behavioral events and other control signals.
   - All parts have a modular design so that any new type of input/output can be easily replaced/added without affecting the other components of the system.
Acquisition and Generalization of Visuomotor Transformations
by Nonhuman Primates

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ABSTRACT
The kinematics of straight reaching movements can be specified vectorially by the direction of the movement and its extent. To explore the representation in the brain of these two properties, psychophysics studies have examined learning of visuomotor transformations of either rotation or gain and their generalization. However, the neuronal substrates of such complex learning are only beginning to be addressed. As an initial step in ensuring the validity of such investigations, it must be shown that monkeys indeed learn and generalize visuomotor transformations in the same manner as humans. Here, we analyze trajectories and velocities of movements as monkeys adapt to either rotational or gain transformations. We used rotations with different signs and magnitudes, and gains with different signs and analyzed transfer of learning to untrained movements. The results show that monkeys can adapt to both types of transformations with a time course that resembles human learning. Analysis of the aftereffects reveals that rotation is learned locally and generalizes poorly to untrained directions, whereas gain is learned more globally and can be transferred to other amplitudes. The results lend additional support to the hypothesis that reaching movements are learned locally but can be easily rescaled to other magnitudes by scaling the peak velocity. The findings also indicate that reaching movements in monkeys are planned and executed very similarly to humans. This validates the underlying presumption that neuronal recordings in primates can help elucidate the mechanisms of motor learning in particular and motor planning in general.
INTRODUCTION

To explore the neural mechanisms that underlie the planning and generation of reaching movements, psychophysical studies have investigated adaptation to different kinematical perturbations. By manipulating the relationship between the performed movement and the visual feedback and observing generalization of adaptation to previously untrained movements, one can learn about the formation of internal models that capture the new input-output relationships in the environment (Kawato, 1999; Wolpert and Ghahramani, 2000) and the shape of their neural primitives (Ghahramani et al., 1996; Sainburg et al., 1999; Donchin et al., 2003).

Recently, Krakauer et al (Krakauer et al., 2000; Pine et al., 1996) have used this methodology to lend additional support to the hypothesis that reaching movements are planned vectorially by separate specification of the movement direction and its extent (Bock, 1992; Gordon et al., 1994b; Georgopoulos, 1995; Vindras et al., 1998). They employed two types of visuomotor perturbations: direction–related perturbations, such as rotational transformations; and extent–related perturbations, such as gain transformations and investigated generalization of learning to untrained directions and extents. They report that learning of rotations is local in the sense that it generalizes very poorly to unvisited directions (Imamizu et al., 1995) but rather well to different movement amplitudes. In contrast, learning of gains is global in the sense that it generalizes reasonably well to untrained amplitudes or velocities (Vindras and Viviani, 2002) and even directions.

To identify neuronal substrates that underlie the planning and generation of movement it is necessary to observe neuronal activity during movement performance. Unfortunately, there are practically no opportunities to observe single cell properties in humans and the coarse spatio-temporal resolution of image studies is only sufficient to identify brain areas that take part in the process. The similarities in monkeys’ frontal cortex architecture and their ability to perform accurate reaching movements with properties that are highly comparable to those found in humans serve as a basis for their use in studies that record single-cell activity during movements (Kalaska et al., 1997; Scott, 2003). Recently, few studies have begun to explore the neuronal substrates that underlie learning (Wise et al., 1998; Li et al., 2001) and the generalization of new sensorimotor fields (Paz et al., 2003; Paz and
Vaadia, 2004). Whereas reaching movements are a fundamental aspect of primates’ behavior, learning of complex sensorimotor tasks is a human trait. To contribute to identifying the neural substrates that underlie internal representations of newly learned sensorimotor skills, the study described in this article was aimed at: (1), further verifying the validity of monkeys as an animal model for studies on motor control by showing that the vectorial representation hypothesis applies to them; and (2), conclusively demonstrating that monkeys also learn and generalize in the same way.

More specifically, we investigated whether monkeys adapt and generalize in the same way as humans do to different visuomotor transformations. We tested whether learning of rotational transformations generalizes to untrained directions and whether learning of gain transformations generalizes to untrained movement amplitudes. We also tested whether, as found in humans, adaptation time to rotational transformations increases with increased angle of visual rotation (Cunningham, 1989; Imamizu and Shimojo, 1995; Abeele and Bock, 2001).

A concise part of the directional data has appeared in a previous publication (Paz et al., 2003).

MATERIALS AND METHODS

Experimental design
Two female rhesus (Macaca mulatta) monkeys (~4.5 kg) were seated in a dark chamber and manipulated a frictionless two-joint manipulandum to control the movement of a cursor on a screen located 50 cm in front of their torso and eyes. The monkeys were constrained at their wrist, head and torso and performed the movements with their shoulder and elbow, which were not constrained to a specific plane. No visual sight of the arm or the manipulandum was available during the sessions, and constant visual feedback of the cursor was provided at all times. Animal care and surgical procedures complied with the NIH Guide for the Care and Use of Laboratory Animals (rev. 1996) and this specific study was pre-approved by the Hebrew University Institutional Committee for Animal Care and Use (approval # MD.48-12-99/3)

Monkeys moved the manipulandum to move the cursor from a starting point in the center of the screen (origin) to a visual target in a delayed go-signal paradigm; this
required the monkey to hold the cursor in the origin circle for a random 750-1500ms after the target onset, and the disappearance of the origin indicated the go-signal. Holding was imposed on-line by a velocity criterion (<0.5 cm/s) and a position criterion (the origin circle), and was verified off-line by visual inspection and a non-significant change in the distribution of velocities and muscle activity (surface EMG recorded from the following muscles: flexor carpi ulnaris and radialis, extensor carpi ulnaris and radialis, biceps brachii, triceps brachii, deltoid, trapezius, pectoralis major, latissimus dorsi, rhomboid, teres major and oblique abdominal extensors). Movement duration was limited to a maximum of 2 sec (no lower limitation was imposed) and the path was limited by an invisible “corridor” with the same width as the origin and target circles (0.8 cm). Any deviation from the requirements aborted the trial and the reward was not delivered. Reaction time was not specifically constrained but was calculated off-line to be 293 ± 89 ms and we discarded trials exceeding +2 standard deviations.

Each session (day) was made up of three consecutive (immediately occurring) epochs: (1) the control epoch, a standard, multiple-target task with one-to-one mapping between the movement of the manipulandum and the movement of the cursor on the screen (Fig. 1, first column); (2) the learning epoch, a transformed, one-target task where only one target was presented and a rotational/gain transformation was introduced between the cursor on the screen and the manipulandum (Fig. 1, second column); (3) the testing epoch, where the standard, multiple-target task was presented again (Fig. 1, third column). Monkeys learned and practiced the standard task for a few months, but were not exposed to transformations before testing sessions. Gain and rotation were presented in separate sessions, but the different types of transformations (four rotations and two gains, detailed below) were chosen pseudo-randomly.

Gain protocol
As illustrated in Fig. 1a, the two standard, multiple-target tasks (control and testing epochs, left and right columns) incorporated 4 different amplitudes (2, 4, 6 or 8 cm) presented randomly. Only one target was presented during the learning epoch; at 4 cm above the origin. In this case, the gain between the cursor and the manipulandum was modified to be either 2 or 0.66 for a given session. Note that the gain of 2 required the monkeys to move an extent of 2cm in order for the cursor to reach the
4cm target on the screen; similarly, the gain of 0.66 required the monkeys to move the manipulandum 6cm to achieve the same cursor movement as for 4cm. Between 8 and 15 movements were performed at each amplitude in the control and testing epochs (separately) and between 25 and 50 movements were performed in the learning epoch.

Rotation protocol
As illustrated in Fig. 1b, the two standard, multiple-target tasks (control and testing epochs, left and right columns) tested 8 different randomly presented directions. Directions were homogenously distributed on a 4cm radius circle labelled 0° to 315° anti-clockwise, starting from the right. Only one target located upwards at 90°, was presented during the learning epoch, and a rotational transformation of either 45°, 90°, -45° or -90° (in different sessions) was imposed. Note that each transformation required the monkey to learn to move in a different direction in order to bring the cursor upwards to the presented target. For the 45°, 90°, -45°, -90° transformations, the monkeys learned to move to 135°, 180°, 45° and 0° accordingly. At least 5 movements were performed in each direction in the control and testing epochs (separately) and at least 25 movements were performed in the learning epoch.

The number of sessions performed by each monkey and the transformations were as follows:

<table>
<thead>
<tr>
<th>Monkey</th>
<th>-45</th>
<th>-90</th>
<th>45</th>
<th>90</th>
<th>0.66</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monkey 1</td>
<td>9</td>
<td>5</td>
<td>9</td>
<td>8</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Monkey 2</td>
<td>6</td>
<td>4</td>
<td>3</td>
<td>12</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

Data Analysis
The manipulandum position (X and Y coordinates) was derived from the position of two rotational encoders located at the two joints of the manipulandum and the lengths of its physical segments and was sampled at 500Hz. Trajectories were smoothed offline with a Gaussian filter (lowpass with a cutoff at 100Hz).

We used three different performance measures to test different features of learning and aftereffects:

For amplitude/gain data, the peak of the velocity profile was used as the standard measure. To pool data from the two gains, we subtracted the mean peak velocity of
the standard movement to 4cm; i.e. the trained target, and reversed the sign of the gain 2 sessions. This is appropriate since the two gains produced linearly equal changes in the peak velocity (Fig 2a,b). For the rotational transformations, the deviation in degrees of the cursor movement from 90° (the trained target) was taken at peak velocity and divided by the transformation in the session; i.e. either 45,90,-45 or -90, to produce a normalized error measure. We used these normalized errors as specific measures of learning and aftereffects for gain and rotation data respectively.

Second, we correlated the full speed profile (Pearson correlation coefficient) for two compared movements to test for any temporal differences between them.

Finally, we used a figural distance measure (Conditt et al., 1997): the figural distance (FD) between two trajectories, A and B, is based on the repeated measure of the Euclidean distance between each point in one trajectory and all the points in the other. If trajectory A has n points, [A(1), A(2), . . . , A(n)], and trajectory B has m points, [B(1), B(2), . . . , B(m)], then one may derive an n-dimensional vector:

$$\text{dist}_{A-B}(i) = \min_j \| A(i) - B(j) \| [1 <= i <= n]$$

and an m-dimensional vector

$$\text{dist}_{B-A}(j) = \min_i \| A(i) - B(j) \| [1 <= j <= n]$$

The vector $\text{dist}_{A-B}$ contains the distances between trajectory B and each point in A, whereas the vector $\text{dist}_{B-A}$ contains the distances between trajectory A and each point in B. The figural distance between A and B is defined as:

$$\varepsilon(A,B) = \left( \sum_{i=1}^{n} \text{dist}_{A-B}(i) + \sum_{j=1}^{m} \text{dist}_{B-A}(j) \right) / (m+n)$$

Therefore, the FD is insensitive to differences in speed and captures the difference in the shapes of the respective paths of the two trajectories.

To assess aftereffects, we compared single-trial trajectories from the post-learning in each session to the average trajectory before learning in the same session.

To compare learning and washout rates, we fitted the data from all sessions to the exponent

$$y = a + b \cdot e^{\frac{x}{\mu}} \quad \text{or} \quad y = a + b \cdot (1 - e^{\frac{x}{\mu}})$$

where x is an index of the learning trials and \( \mu \) is the learning rate measure. The higher the \( \mu \), the longer it took the monkeys to learn a transformation. We generated distributions by sampling with
replacements (bootstrap), each time fitting an exponent, and then compared the generated \( \mu \) distributions with a standard t-test or ANOVA.

We collapsed the data from the two monkeys and all sessions with the same transformation after verifying that learning and aftereffects were the same during the whole experimental period. To do so, we divided the data in each transformation into three equal consecutive periods of recording days (for example, monkey 1 had 9 days with a transformation of -45; the three periods were therefore constructed of days 1-3, 4-6 and 7-9) and a separate ANOVA was run on these three groups for normalized errors during the last 10 learning trials and in the first 3 trials of the testing epoch (aftereffects). In all cases, the derived \( p \) values were greater than 0.1 (Paz et al., 2003).

**RESULTS**

*Learning of gain transformations*

Movements to the four different target amplitudes displayed similar velocity shapes (Fig 2a, solid lines), but with a linear scaling of the peak velocity. Fig 2b shows the linear relationship between movement extent and peak velocity (slope=1.1, \( p=0.004 \)). Learning of new gains resulted in scaling the peak velocity and this corresponded to the performed movement amplitude (which, under the gain condition, was different from the observed cursor movement). Because the learning epoch consisted of only one target, at 4cm, monkeys had to move only 2cm in the gain 2 condition and 6cm in the gain 0.66 condition to make the cursor reach the target. We averaged velocity profiles on the last 10 movements in the learning epoch and compared the velocity profiles (Fig 2a, dashed lines) to the corresponding ones before training (solid lines). Fig 2b shows that the peak velocity at the end of learning was indeed very similar, both for the gain 2 condition as compared to the 2cm amplitude before learning (paired t-test over days, comparing averaged peak velocities from before training to the averaged last 10 trials in the learning epoch, \( p=0.32 \)) and for the gain 0.66 condition as compared to the 6cm amplitude (\( p=0.06 \)).

To quantify the learning rate of gain transformations, we plotted peak velocities for all days on the first 20 trials of the learning epoch (Fig 2c,d). An exponent was fitted to the learning curves and we compared learning rates by
calculating distributions and confidence intervals for the decay/rise parameter of the exponent (μ) (see methods). Learning a gain of 2 was slower than learning a gain of 0.66 (Fig 8a, μ = 4.02 ± 0.43 and μ = 2.29 ± 0.10 respectively, t-test < 0.001).

Transfer of learning to other movement amplitudes

To test for generalization of the learned gain to other untrained movement amplitudes during learning, we compared trajectories and peak velocities when the monkeys were returned to the standard, 4-amplitude task. These aftereffects revealed that the monkeys generalized the learned gain to the other amplitudes as well. Figs 3a,b depict the velocity profile for the first two movements in the testing epoch and the averaged movement in the control epoch (all aligned on their peak and averaged over days), shown are amplitudes 2, 4 and 6cm (1-3) for gain 2 sessions (a) and gain 0.66 sessions (b). The aftereffects match the learned gain for all 3 amplitudes (see figure legend). In contrast to the learning rate, the washout rate was similar for the two learned gains (Fig 8c, μ = 1.37 for gain 2 and 1.55 for gain 0.66, t-test=0.1); Fig 3c shows the washout curve combined for the two gains.

Quantifying aftereffects by normalized peak velocities (Fig 4a) showed that all 4 movement amplitudes exhibited aftereffects; in other words, learning was transferred to the three other amplitudes. In a full 2-way ANOVA, only the movement number was found to be significant whereas the amplitude factor and the interaction were not (p=0.001, p=0.4, p=0.3 respectively). A similar result was obtained when using velocity correlations (Fig 4b); A 2-way ANOVA found p=0.0007 for movement number and p=0.001 for the amplitude factor. This means that with this measure, there are differences between amplitudes; however, they are not due to the locality of learning relative to the trained target, as can be seen by the shape of the aftereffects function (Fig 4b), because the aftereffects decreased as a function of movement amplitude and not as a function of distance from the trained target. The figural-distance (FD) measure showed no difference for any factor (Fig 4c, ANOVA, p=0.65 and p=0.27). Namely, aftereffects were not observed at all for this measure. Since the FD only measures differences in the spatial path and is not affected by temporal differences (e.g. velocity profile) this strengthens the assumption that learning of gains only takes place via scaling of peak velocity and did not prompt alterations in the movement path.
Learning of rotational transformations

Fig 5a depicts the average movement paths to eight directions performed by the 2 monkeys in the standard, control epoch (solid lines). Overlaid in dashed lines are the paths for the four possible rotational transformation sessions; paths are averaged over the last 10 trials of the learning epoch for each rotation separately. Fig 5b shows that velocity profiles were similar during the control, learning and testing epochs (ANOVA comparing daily averages of peak velocities, p>0.1).

Learning curves for all four rotational transformations are shown in Fig 5c-f. It depicts the actual (not normalized) direction taken at peak velocity as a function of trials in the learning epoch, for all days. Movements started at 90° and gradually rotated as required by the transformation in the session. Comparing the learning rates by comparing the exponential factor $\mu$ (Fig 8b), suggests that the bigger the rotation, the longer it takes to learn it. Rotations of 45° (Fig 5c) and 90° (5d) were matched by $\mu$’s of 2.70 ± 0.14 and 4.50 ± 0.20 respectively (t-test, p<0.001); and -45° (5e) and -90° (5f) by $\mu$’s of 1.53 ± 0.13 and 3.23 ± 0.3 respectively (t-test, p<0.001). A full 2-way ANOVA for magnitude (45 and 90) and sign (clockwise and anti-clockwise) revealed that both factors were significant (p<0.01 for both) but the interaction was not. Thus, learning an anti-clockwise rotation took longer than learning a clockwise one; however, we believe a specific study is required to address the source of this difference.

Transfer of learning to other movement directions

To observe aftereffects, we compared the first two movements in the testing epoch to the averaged movement in the control epoch for the four different sessions (Fig 6a-d). It can be seen that the first two movements deviate towards the direction of the learned transformation in that session. More specifically, when required to move to the same target as presented in the learning epoch, monkeys tended to perform the same movement as in the learning epoch; i.e. as required by the transformation. The deviation is largest for the trained target during learning (upward, 90°) and decreases as a function of angular distance from this target (no aftereffects were observed on movements for any other direction, 225-315°, not shown in the figure). The washout
curve for all four transformations (normalized to the transformation, see methods) is presented in Fig 6e. In contrast to the learning rate, the washout rate (Fig 8d) was similar at different magnitudes (45° and 90°, t-test, p=0.4; -45° and -90°, t-test, p=0.5); but similar to learning, washout took longer for anti-clockwise than for clockwise (although there was higher variability, Fig 8d, 2-way ANOVA, p=0.05 for sign factor, p>0.1 for magnitude and interaction).

To quantify the locality of learning, Fig 7 shows the aftereffects on all eight movement directions. Both the measure of normalized directional deviation taken at peak velocity (Fig 7a) and the figural distance (Fig 7c), show that aftereffects are observed mainly on the trained direction and decrease as a function of angular distance from it. An ANOVA indicates that direction and movement number were significant (p<0.005 for both measures and both factors). Velocity correlations (Fig 7b) were not significantly different (ANOVA, p=0.37 and p=0.48 for movement number and direction).

**DISCUSSION**

Our results show that non-human primates, or at least rhesus monkeys, adapt to visuomotor transformations of rotation and gain and generalize them in a manner that is highly similar to that of humans. Our monkeys a) scaled the peak velocity when learning new gain transformations (Ojakangas and Ebner, 1991;Bock and Burghoff, 1997) and b) generalized it to other untrained movement amplitudes (Pine et al., 1996;Krakauer et al., 2000;Vindras and Viviani, 2002). In contrast and as observed in humans, c) they learned rotational transformations only locally and had poor generalization to other directions (Imamizu et al., 1995;Pine et al., 1996;Krakauer et al., 2000); d) longer adaptation was required for larger angle of rotations (Cunningham, 1989;Imamizu and Shimojo, 1995;Abeele and Bock, 2001). Finally, e) longer adaptation was required for shorter movements (as in gain 2). This could have been due to the very short trajectories (2cm) that were required either from the proportionately higher variability in movement extent (Gordon et al., 1994b) and higher variability in producing accurate small accelerating forces (Gordon and Ghez, 1987), or from the fewer points that were available for information about the nature of the error.
Because the learning of new sensorimotor tasks and its transfer to other untrained locations in the workspace is extensively used in human studies to characterize representations of internal models in the brain (Kawato, 1999; Wolpert and Ghahramani, 2000), our results validate the use of monkeys in such experiments. Experiments that include recordings of neuronal activity and can elucidate mechanisms of learning and representation of new sensorimotor environments (Wise et al., 1998; Li et al., 2001; Gribble and Scott, 2002; Paz et al., 2003; Paz and Vaadia, 2004).

Did our monkeys acquire a new internal model during learning that represented the new visuo-motor relationships in the environment? Arguably they could have learned a one-to-one relationship for each individual movement (i.e. a lookup table) or used continuous error correction from visual and proprioceptive feedback. The fact that they generalized the learning of gain to other amplitudes and some generalization of rotation was observed for neighboring directions make the use of a lookup table unlikely (Imamizu et al., 1995). The fact that they performed the movements quite smoothly with a bell shaped velocity profile and a stable movement onset and duration during all task phases argues against using only constant feedback correction. Additionally, although the monkeys may have realized that the standard task had returned and could have switched to standard, default mapping of hand to cursor, aftereffects were observed for ~3 movements of every parameter value, amounting to 3*4 amplitudes or 3*8 directions. This further attests to the formation of an internal representation of the learned transformation. The fact that aftereffects matched the transformation in both peak velocity for gain or directional deviations for rotations further confirms that the monkeys did not only use increased viscoelasticity stabilization to produce the correct movement during learning but actually learned the transformation.

Four limitations to our study call for further testing. First, we did not dissociate spatial (amplitude) and temporal (speed) factors. Since different amplitudes are naturally coupled with linearly scaled matching velocities (in humans and monkeys), we did not investigate which factor determines the generalization pattern. Second, we did not test generalization of rotations to other amplitudes or gain to other directions. A few human studies have shown that adapting to directional errors can be well generalized to other amplitudes and velocities (Goodbody and Wolpert, 1998; Krakauer et al., 2000) and that adaptation to gain generalizes to other directions.
The third caveat is related to the continuous visual feedback that was available at all times and allowed movement corrections to take place before the peak velocity as well as after it. Thus, the estimates of adaptive changes in feedforward control could be contaminated by feedback corrections, and conclusions regarding generalization which refer to the underlying inverse model governing the response could be affected. More studies are needed to confirm that monkeys use delayed visual feedback as humans do. For example, a recent prism study showed that monkeys can adapt to delayed visual feedback but require less delay than humans (Kitazawa and Yin, 2002). Finally, our experiment was performed in a local region in space and was not constrained to a specific posture, joint or muscle combination. Therefore, we cannot conclude that locality and specificity of learning rotations are related to external direction of movement (see (Gordon et al., 1994b;Ghahramani et al., 1996;Krakauer et al., 2000) for further discussion). Our results may be consistent with other reference frames as well.

Our results are consistent with previous neuronal findings. Cortical neurons are broadly tuned to the direction of movement (Georgopoulos et al., 1982) with speed acting as a gain factor on their activity (Moran and Schwartz, 1999a). Although the origin of this tuning is still hotly debated (Mussa-Ivaldi, 1988;Scott and Kalaska, 1997;Kakei et al., 1999;Todorov, 2000a;Moran and Schwartz, 2000;Scott et al., 2001) the implications here are the same. In the case of directional data, the learned transformation is probably coded by a population of neurons with directional selectivity for the trained direction (Paz et al., 2003) and therefore learning is not transferred to other directions (because other populations with different directional selectivity are still “naïve”). These ideas are in line with psychophysical studies (Ghahramani et al., 1996;Shadmehr and Moussavi, 2000), suggesting that transfer of learning is determined by the shape of the underlying neuronal primitives (Donchin et al., 2003). In contrast, only one direction was used in the case of amplitude/velocity, and therefore the same population of neurons that participated in the learning process could have been utilized in the testing process as well.

To conclude, monkeys apparently not only perform well-trained reaching movements as humans do, but also learn and generalize them in the same manner. This suggests that the planning of the movement itself, the internal representation and the transformations from sensory to motor are carried out by the same rules of
computation, which thus validates neuronal recordings on primates used to elucidate these mechanisms.
Figure 1. Schematic of Behavioral paradigm

a, Learning gain transformations. Each session (day) started with a multiple (4)-target task (control epoch) where one out of four possible targets (linearly spaced amplitudes: 2, 4, 6, 8cm) was randomly chosen and a standard, one-to-one mapping was imposed between the movement of the manipulandum and the cursor (first column). Next, a one-target task (learning epoch) was presented, where only one target (at 4cm) appeared and a gain transformation was imposed on the relationship between the movement of the manipulandum and that of the cursor. The transformation was chosen randomly out of two possible ones (0.66 and 2) at the beginning of a session and remained constant for that session (middle column). For example, a gain transformation of 2 required a movement of 2cm in order for the cursor to travel 4cm. Finally, the multiple-target task appeared again (testing epoch, right column). This is where movements were tested for aftereffects attributed to learning. The trajectories of the hand (solid) and the cursor (dashed) are shown schematically.

b, Learning rotational transformations. A multiple (8)-target task where targets could appear at one of eight randomly chosen targets, linearly spaced on a circle. In the one-target task, the target always appeared upwards, at 90° and a rotational transformation of either -45°, -90°, 45°, or 90° was imposed (middle column). Finally, the multiple-target task appeared again (right column).
Figure 2. Learning gain transformations

**a**, Averaged velocity profiles for the four different amplitudes in the standard task (solid lines), overlaid with the two averaged velocity profiles for the last 10 trials of the learning epoch (dashed lines). Averages include all trials from all days for the two monkeys and profiles were first aligned on their peak. Movements in the learning epoch were all to the target at 4cm but the hand movement was scaled according to the matching gain (2 or 0.66) and so was the peak velocity.

**b**, A linear relationship between the peak velocity and the movement amplitude during the standard task (circles) and the two peak velocities in the last 10 learning trials for the two gain transformations (square-0.66 and diamond-2).

**c,d**, learning curves for the two gain transformations, 2 (c) and 0.66 (d). Shown are the peak velocities in the first 20 trials of the learning epoch for all days with a fitted exponent.
Figure 3. Aftereffects and washout for gain transformations

a1-3,b1-3, Aftereffects as revealed by velocity profiles (aligned on their peak and averaged over all days for the two monkeys). Each plot compares the first (dash) and second (dash-dot) movements in the testing epoch to the averaged movement in the control epoch (solid), for 3 amplitudes (2cm, 4cm, 6cm). Aftereffects matched the learned gain: for gain 0.66 (a), the first 2 movements in the testing epoch (dash and dash-dot lines) are faster; i.e. have higher peak velocity than the control (solid line); and for gain 2 (b), the first 2 movements are slower; i.e. show lower peak velocity than the control. The similarity of aftereffects for the trained target at 4cm (middle column) with the targets at distance of 2cm (left column) and 6cm (right column) indicates that learning was transferred.

c, "washout" curve as revealed by peak velocities for the target at 4cm in the testing epoch. We combined the two gain transformations by subtracting the peak velocity for the target at 4cm and reversing the sign for the 0.66 gain, after verifying that washout rates were the same (Fig 8c). Gain 2 – diamonds, gain 0.66 – circles.
Figure 4. Transfer of gain learning to untrained amplitudes

a, Aftereffects as revealed by normalized peak velocities. 1st movement (blue) in the testing epoch exhibited the largest error for almost all movement amplitudes, followed by the 2nd (green), and the 3rd (red). Note that for all movement amplitudes error exists and decreases as a function of trials.

b, Aftereffects as revealed by correlations of speed profiles. The 1st movement in the testing has the lowest correlation with the averaged movement in the control (blue) for all movement amplitudes, followed by the 2nd and the 3rd. The lower correlation for shorter movements may be due to higher variability in the performance of these movements (note that the variability across days is indeed higher in movements to 2 and 4 cm than to 6 and 8 cm).

c, No differences were found in the shape of trajectories, measured by figural distance (FD).
Figure 5. Learning of rotational transformations

a, average movements to eight directions during the control, standard epoch (solid lines), overlaid by movements from the four rotational transformations (dashed lines, averaged over the last 10 trials of the learning epoch). Averages include all trials from all days of the two monkeys and standard deviations at 3 points along each movement path are shown for the control.

b, Averaged velocity profiles from the three epochs: control (solid), last 10 trials of the learning epoch (dashed) and testing (dash-dot).

c-f, learning curves for the four rotational transformations: 45° (c), 90° (d), -45° (e) and -90° (f), shown is the actual direction (not normalized) taken at peak velocity as a function of trials in the learning epoch.
Figure 6. Aftereffects and washout for rotational transformations

a-d, aftereffects for the first two movements in the testing epoch as compared to the control (averaged over days). Shown are movements to the upper half of the screen for all four transformation sessions (a:45°, b:90°, c:-45°, d:-90°). No aftereffects were observed for the lower half of the screen (not shown). Note that: a. all aftereffects are in the direction of the transformation; b. decrease as movement number advances; and c. are observed mainly for the upper target (the one trained during the learning epoch).

e, "washout" rate for the upward target (90°), all directional deviations were normalized to the transformation in their session (methods) and were combined after verifying that washout rates were the same (Fig 8d). Transformation of 45° – circles, 90° – diamonds, -45° – asterisks, -90° – squares.
Figure 7. Poor transfer of learning rotations to untrained directions. 

a, c, poor generalization to the other, untrained directions. Aftereffects as revealed by directional deviation (a) and figural distance (c) were observed mainly for trained (upward – 90°) target and rapidly decreased with angular distance from it. 

b, no differences were found for speed correlations.
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**Figure 8.** Learning and washout rates
All figures show the mean exponential factor $\mu \pm S.D$ as obtained by sampling with replacement (bootstrap).

**a,** Learning of gain 2 took longer than learning of gain 0.66 (t-test, $p<0.001$), presumably because fewer points were available for information about the nature of the error in gain 2 (shorter movements of 2cm as compared to 6cm under gain 0.66 condition).

**b,** Learning of rotational transformations: Larger transformations took longer to learn (45, 90, t-test, $p<0.001$ and -45, -90, t-test, $p<0.001$). A full 2-way ANOVA revealed that not only the magnitude factor was significant ($p<0.01$) but also the sign ($p<0.01$ for both). Thus, although not investigated specifically here, learning of anti-clockwise rotations appears to have taken longer.

**c,d,** Washout rates were very similar for gain transformations (c) (t-test, $p=0.1$) and rotational transformations (2-way ANOVA, $p>0.1$ for magnitude factor; although a small, significant increase was observed for anti-clockwise rotations, $p=0.05$ for sign factor).

The similar washout rates could be due to the fact that in all cases, washout requires returning to the same type of mapping (one-to-one) and the fact that this mapping is a default, extensively trained one.
Preparatory activity in motor cortex reflects learning of local visuomotor skills

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In humans, learning to produce correct visually guided movements to adapt to new sensorimotor conditions requires the formation of an internal model that represents the new transformation between visual input and the required motor command. When the new environment requires adaptation to directional errors, learning generalizes poorly to untrained locations and directions, indicating that such learning is local. Here we replicated these behavioral findings in thrsus monkeys using a visuomotor rotation task and simultaneously recorded neuronal activity. Specific changes in activity were observed only in a subpopulation of cells in the motor cortex with directional properties corresponding to the locally learned rotation. These changes adhered to the dynamics of behavior during learning and persisted between learning and rehearsing of the same rotation. These findings suggest a neural mechanism for the locality of newly acquired sensorimotor tasks and provide electrophysiological evidence for their retention in working memory.

During performance of visually guided movements, the brain transforms visuospatial information into appropriate motor commands (i.e., visuomotor transformation)15,16. Psychophysical studies suggest that when humans learn a new visuomotor transformation, an internal model of limb dynamics and kinematics is modified. Such a process would allow the motor system to achieve the desired outcome—reaching toward a visible goal—under the new conditions8,16. The learning of a new motor skill that requires adaptation to directional errors generalizes poorly across movement directions,8,16, workspace15, and posture16. This suggests a reliance on neural elements with localized spatial fields8,15,19, analogous to receptive fields in sensory systems. Such elements are common in many parts of the motor system, including the primary motor cortex where the majority of cells show directional tuning15,17. A few studies have investigated cortical activity while monkeys adapted to generalized novel dynamic14,16 or kinematic20 fields, but none have addressed the issue of learning a specific, local field. We reasoned that such learning would induce a specific and local neuronal change.

Evidence that the primary motor cortex (MI) is involved in motor learning14 comes from both cellular15,19 and human studies. Evidence for MI involvement during the initial phases of learning a new motor skill comes from studies using functional neuroimaging15,19,22 and transcranial magnetic stimulation (TMS)20. Further, behavioral and imaging studies show that consolidation occurs after learning a new motor skill, a process where the newly learned behavior shifts from an unstable to a stable state21,22. The early phases of consolidation were recently linked to the human primary motor cortex17, suggesting its involvement in retaining the information in working memory until it is further redistributed for long-term memory storage. These results suggest that both during and immediately after motor learning, activity in motor cortex should reflect recent learning and support the retention of the learned behavior.

To search for electrophysiological evidence of learning and retention of local visuomotor skills, we recorded neuronal activity in motor cortex before, during and immediately after monkeys learned a rotational mapping to one target in space. Our behavioral results indicate that monkeys, as humans, show poor generalization of the learned transformation to other directions of space. Exploring the related neuronal changes, we found that the tuning curve of neurons with preferred direction close to the learned direction was altered during the course of learning. These cells showed a relative increase in their firing rate, and did so only when the monkeys moved toward the learned direction and mainly during the preparation for movement. According to behavioral measures, the monkeys retained the learned task in working memory for at least one hour, and the altered tuning curves were indeed sustained during that time.

RESULTS
We devised a task to address several points of interest in motor learning. To test for local learning, we used only one target location (90°) during the learning epoch. We also used visuomotor rotational transformations, proposing that the directional tuning found in motor cortex can be linked to kinematic perturbations that introduce directional errors. To achieve learning on a daily basis during the whole recording period (rather than switching among pre-learned behaviors), a different rotational transformation was randomly chosen for each day from a set of four possible transformations (90°, 45°, 45°, 90°). To observe systematic change in the activity of neurons, the same transformation was repeated (at least four repetitions for each transformation and each monkey, on different days). To compare
Neuronal changes in a controlled motor behavior (eliminating the possibility that changes result from differences in kinematics or dynamics), we performed a default, eight-target task (with a one-to-one mapping between cursor and hand movement) both before and after learning, and compared neuronal activity for movements with the same kinematics. Finally, to test for retention of the newly learned motor skill, we introduced the same transformation again at the end of each session (“re-learning”).

Behavioral findings
To determine whether learning was indeed local, we compared directional deviations of trajectories, taken at peak velocity and normalized to the transformation (signed normalized deviation, SND; see Methods). When the monkeys were returned to the default eight-target task after the learning epoch, their hand movement trajectories deviated from the learned movement direction (that is, the hand movement required to move the cursor from the origin to the target during the transformation learning epoch). These deviations represent kinematic ‘aftereffects,’ demonstrating that an internal model has been modified during visuomotor remapping. The deviations were largest for the target used in the learning epoch (i.e., the target at 90°). Trajectories deviated to a lesser extent as a function of angular distance from this target and as a function of trial number after learning (Fig. 2a). Thus, the aftereffects show limited generalization across the workspace, a finding that supports the notion of a local internal model and is concordant with human psychophysics.⁹

During the learning epoch itself, more than ten trials on average were required to reach a behavioral plateau with only small and stable errors (Fig. 2b). As in other studies,⁷,learning consisted of two phases: a transient phase during the first trials followed by a slower phase. To test for retention of learning, we compared the behavior in this first learning epoch (Fig. 2b, black line) to the re-learning epoch (gray line) where the same transformation was introduced in the same session but after the post-learning epoch. Improvement of performance in this re-learning epoch was immediate and reached a plateau after 1–3 trials, indicating that the newly learned transformation was retained for at least 1–2 h, the duration of the post-learning epoch. The next day, however, no aftereffects were observed, indicating that learning was lost overnight. We calculated the deviation of the trajectories in the first and second trials of the pre-learning epoch (the beginning of the session) as a function of the learned transformation on the previous day (Fig. 2c). To further verify that learning occurred on a daily basis, we divided the recording period into early and late segments (Fig. 2d–f). Similar learning occurred in all segments (Fig. 2d) as well as similar aftereffects (Fig. 2e, f). The analyses in Fig. 2c–f thus show that the monkeys did not consolidate the newly learned transformation, allowing us to observe newly formed neuronal changes on a daily basis and pool neurons across recording days.

To verify that behavior was indeed the same on the two default, eight-target tasks (before and after the learning epoch) we compared movement kinematics in the two epochs. We excluded the first three trials in the post-learning epoch, which showed significant aftereffects; note that trials 4 and 5 also showed small and non-significant aftereffects but only on upward (90°) direction trials. The remaining trajectories were similar in the pre- and post-learning epochs (Fig. 3a). Comparison of averaged velocity profiles (Fig. 3b) shows that although the peak velocity was slightly higher in the pre-learning
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Figure 2. Movement kinematics during and after learning. (a) Aftereffects on standard movements in the post-learning epoch indicate the formation of a local internal model. The aftereffects are shown as signed normalized deviations (s.n.d.; see Methods). Note that aftereffects decrease as a function of angular distance from the learned target and as a function of trial number after learning. The performance expressed in s.n.d. with two-trial moving average is shown as a function of trial number during the learning and re-learning epochs. The shaded area around the lines shows 0.95 confidence limits. Note the different temporal pattern of improvement in performance in the two epochs. During the learning epoch, performance improved slowly and reached a plateau after more than ten trials, whereas in the re-learning epoch, it improved immediately, indicating retention of the learned transformation. (c-f) Learning was washed out over night and similar learning occurred during the whole recording period. (c) Aftereffects on the first (black) and second (gray) trials in the pre-learning epoch normalized to the previous day learned transformation. Note the lack of aftereffects. (d) The same analysis and format as in (b) but calculated separately for three session groups. Each line represents a different set of ten recording days (early, mid, late). Note the similar learning curves. (e,f) The same analysis as in (a), but calculated separately on the first half of recording days (e) and the second half (f). Note that similar aftereffects occurred in the two groups.

compared to the post-learning epoch (t-test, P = 0.05), no significant change existed between learned and non-learned directions. Additional analyses showed that reaction times (pre-learning, 298 ± 93 ms; post-learning, 296 ± 97 ms) and movement times (pre-learning, 1,087 ± 219 ms; post-learning, 1,130 ± 249 ms) were similar before and after the learning epoch (t-test, performed separately for the two monkeys). Thus, the monkeys exhibited the same kinematics during the two identical tasks.

Neuronal findings

We analyzed neuronal activity during two time intervals: (i) preparatory activity (PA), which was measured during the 600 ms after target onset but during a hold period and (ii) movement-related activity (MRA), which was measured during the 600 ms after the go signal. We analyzed the preparatory activity of 129 motor cortex cells (38 in monkey X and 91 in monkey W) and the movement-related activity of 239 cells (104 and 155, respectively). Only cells that were recorded reliably before, during and after learning were included in the sample, to enable direct comparisons of changes in single cell activity.

Figure 4 shows the activity of one cell during the learning epoch. The firing rate of this cell increased as learning progressed (PA, left), but only after a relatively steady phase of about ten trials. Immediately following the go signal, no activity change was evident (MRA, right). The observed increase in preparatory activity could reflect the actual movement direction that gradually changes during learning. One finding that argues against this is the different temporal pattern behavior improves during the first trials and reaches a plateau after 10–15 trials (Fig. 2b), whereas the increase in this cell's activity begins only after about ten trials. For this reason, we compared the population averaged activity during learning to the expected activity. The expected activity was calculated from the tuning curve of each cell in the pre-learning epoch and from the actual movement direction in a specific trial of the learning epoch. Whereas all neurons pooled together did not show any significant change in activity, only cells with a preferred direction within 30° of the learned movement direction showed a significant deviation from their expected activity (paired t-test for at least three consecutive trials). In contrast, cells with other preferred directions did not show such change. For the population of neurons with pre-
Figure 3: Similar behavior before and after learning. (a) Example of actual trajectories for one day (monkey W). Left, pre-learning; right, post-learning. Red trajectories are in the learned-movement direction in that session. (b) Averaged velocities for all recording days (monkey W), comparing pre-learning to post-learning, and learned-movement direction on the other non-learned directions. No significant difference was found between learned and non-learned directions. (c) Electrographic activity confirms that monkeys did not begin movement during the hold period. Shown in EMG activity from 600 ms before to 600 ms after target onset (but before the go signal), pre- (blue) and post- (red) learning.

Figure 4: Increase in preparatory activity (PA) during learning trials, but not in movement-related activity (MRA). The figure shows activity of one motor cortex cell during the learning epoch. Left, raster plot and matching spike count in the 750 ms following the target onset (PA). Right, the same for the 750 ms following the go signal (MRA). A gradual increase in firing rate is evident (bottom to top) for PA only.

Figure 5: Temporal pattern of changes in neuronal and muscular activity during learning. (a) Preparatory activity (n = 17) and movement-related activity (n = 37) of cells with preferred direction within 30° of the learned-movement direction, comparing average expected activity (X ± SEM). Expected activity was calculated as the activity from the pre-learning tuning curve in the actual movement direction during the learning trial. The dashed line represents behavioral performance, as expressed by s.d., during the learning epoch (same as in Fig. 2 but scaled to allow for comparison of temporal pattern). Notice that for this group of cells, with PDs near the required movement direction, the expected activity increases as performance improves, and trajectories become closer to the required movement direction. However, the observed preparatory activity clearly exceeds the expected as learning progresses. (b) Reduction in muscle activation correlates with improvement in performance. Muscle activation (total r.m.s. normalized to each muscle's maximal activity and averaged over muscles) is shown in black and the number of significant positive correlations between muscle pairs is shown in gray. The performance function (s.d.) is the same as in a, but all graphs are scaled to allow for comparison of temporal pattern.

These are expressed by co-contraction and higher muscle activity. Later, as learning progresses and the contribution of the internal model increases, the role of viscoelasticity decreases. In accord with these findings, the level of EMG activity and inter-muscle correlations decreased in the same temporal pattern as the error in behavior (Fig. 2b) and contrasts with that of the neural activity during learning.

To further establish that neuronal changes occurred only in preparation for movement and only in a specific subpopulation of cells (i.e., those with preferred direction near that of the learned-movement direction), we compared tuning curves from the pre-learning epoch with those from the post-learning epoch. We did not find any systematic or significant changes in the neurons’ preferred direction (bootstrap procedure), and preferred directions were uniformly distributed (Rayleigh test). Then we compared the actual tuning curves of single cells (Fig. 6a,b) and found that for cells with
preferred direction near the learned-movement direction, enhancement in firing rate was centered on this direction.

This specific elevation of the tuning curve is reflected at the population level, as illustrated in Fig. 7, which depicts the PA at the learned-movement direction of all cells as a function of the angle between each cell's PD and the learned-movement direction. Comparing the population activity before and after learning, indicates that only cells with a PD near the learned-movement direction showed an increase in firing rate after learning. Comparing with the same finding during learning (Fig. 5a), a significant difference was found between pre- and post-learning epochs only for cells with PDs within 30° of the learned-movement direction (2-way ANOVA and post-hoc analysis). To verify that these cells change their activity mainly in the neighborhood of their PD, we aligned each cell tuning curve around its PD and found that the averaged PD aligned tuning curve also showed increased activity only around its center. We also extended the database of cells by removing the criterion of cosine 8a, which added 46 directionally tuned cells for a total of 177 cells. For this extended population of cells as well, almost all cells with PD within 30° from the learned-movement direction show elevated activity at this direction (Fig. 8a–c).

As a control, we conducted the same analysis for non-learned directions (Fig. 8d). When the distances between the PD and movement direction are relative to an arbitrarily selected direction, no change is present. None of the seven other movement directions was associated with a change in tuning. We further tested whether learning-induced changes were observed only in the PA by performing the same analyses as in Fig. 7, this time for MRA. No change was observed in movement-related activity (Fig. 8e, diamonds).

Previous studies have shown that excessive training can induce changes in representation maps of motor cortex11,20. This raises the possibility that the observed effect in our study results from the mere repetition of a given movement during the learning epoch. To control for this possibility, we conducted sessions with a repetitive, control condition, which entailed a one-target task without angular transformations. Here, the target direction was either 180° or 90°, in separate sessions. Cells recorded in these sessions did not show
changes in their activity (Fig. 5c, squares and circles). We therefore conclude that the change of tuning in the post-learning epoch was caused by the learning of new visuomotor transformations during the learning epoch. Two of the aforementioned findings support this conclusion: first, the change was not observed during movement-related activity and second, the kinematics and dynamics of movements were similar after learning.

In line with the retention of behavioral improvement (faster learning in the re-learning epoch, Fig. 2b), we did not observe any washout of changes in activity in the post-learning epoch. Although only a small number of trials (6–9) was available for statistics, the two examples in Fig. 6a show that the cells’ enhanced activity remained the same during the whole post-learning epoch. To test this at the population level, we divided the post-learning trials into two groups: early (the first three trials) and late (the last three trials). The same trend of change was apparent in both phases (Fig. 7a, inset). We verified it using a bootstrap method, sampling with replacement of trials and cells and comparing the obtained distribution of differences to the ‘true’ difference between early and late (P = 0.3, n.s.). The sustained pattern of activity might serve in retention of the newly acquired skill until it can be further consolidated. However, no traces of the learned transformation were found the following day (Fig. 7c–f), indicating that consolidation was never complete. In parallel, we found that the neuronal effect observed during and after learning was not observed on the following day (Fig. 7d).

DISCUSSION

The present results demonstrate a modification in the activity and spatial tuning functions of neurons in the motor cortex as a result of learning a local visuomotor skill. This altered activity reflects learning and retention of the newly acquired internal model, one that converts visuospatial cues into the motor commands required for hand movements and/or joint rotations to achieve the goal. The finding that only cells with FIDs near the learned-movement direction modified their activity reflects the specificity of the elements comprising the local internal model, as suggested by recent theoretical work53–55, psychophysical findings51,56, and electrophysiological evidence from altered load conditions57–59. This finding provides a possible neuronal basis for the psychophysical finding that the learning of a sensorimotor mapping, one that introduces directional error, is local53–55. A possible explanation for the elevation of the activity of cells with FIDs near the direction of the required hand movement is that such elevation can serve to ‘win’ over the default choice (i.e., to move the hand in the direction of the target).

Neuronal changes were observed only in advanced phases of learning and lasted for the remaining of the learning epoch when behavior was stable, muscle activity was reduced and inter-muscle correlations decreased. These findings are consistent with studies showing that neuronal changes during movement preparation lag behavioral changes47–49. It is also consistent with the notion that early in learning new dynamics, visuomotor properties are used to help produce the correct movement and that only in later phases an internal model is formed to represent the newly learned environment49,50. Our findings suggest that the motor system may also use similar mechanisms (co-contraction) for enhanced motor control at early stages of learning new kinematics.

The changes we observed persisted when the monkeys returned to performance of the default task, even after the behavioral aftereffects disappeared, and were sustained until the re-learning of the same transformation. This finding is congruent with the retention of behavioral improvement found in the re-learning epoch and suggests that the primary motor cortex stores the newly acquired skill in working memory50. The neuronal changes were washed out over...
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Figure 8: Learning-induced changes were specific and were not observed for mere repetition of movement, for non-learned directions, or for movement-related activity. (a–c) To further verify the learning-induced changes, we used an extended database of cells by removing the criterion for zone size (n = 177). Histograms of changes in firing rate in the learned direction (post minus pre-learning) for cells with a preferred direction within 30° of the learned direction (a) and for the rest of the cells (b). The small horizontal bar below the histograms designates the 95% confidence interval for the population mean. (c) Same analysis as in Fig. 7a, but on this extended database (d). Averaged preparatory activity of cells when aligned to an arbitrary, non-learned direction. The absolute shows the cells’ PD distance from that direction (same format as in Fig. 7). Activities were similar for pre- and post-learning epochs, indicating that learning a specific direction did not affect other directions. (e) Cells did not change their movement-related activity (diamonds), nor was there an effect after mere repetition of movement (squares, preparatory activity; circles, movement-related activity). The absolute shows the absolute PD distance from the learned movement direction or from the repeated movement direction.

night, reinforcing the finding that no aftereffects were observed on the next day and that similar learning behavior occurred during the whole recording period. The lack of behavioral aftereffects and improvement in skill performance from day to day implies that the learned skill did not undergo consolidation, where a newly learned skill is transferred for longer-term memory storage. This absence of consolidation can be attributed to two factors. First, the four different randomly chosen transformations were an incentive not to consolidate, as learning the previous day could interfere with learning of the current transformation. Second, consolidation might require a sufficient number of training trials. For example, prim adaptation studies have shown that 50 trials are sufficient to induce immediate aftereffects, but over 250 trials are required for longer (24 h) consolidation.

METHODS

Animals, recordings and behavioral tasks: Two female rhesus monkeys (Macaca mulatta, ~4.5 kg) were implanted with recording chambers (27 × 27 mm) above both the right and left hemispheres. Animal care and surgical procedures complied with the NIH Guidelines for the Care and Use of Laboratory Animals (1996) and with guidelines supervised by the Institutional Committees for Animal Care and Use at Hebrew University. The monkeys were seated in a dark chamber, and eight microelectrodes were lowered into each hemisphere. The electrode signals were amplified, filtered and sorted (PC-PHIS, MDU, Alpha-Omega), and all spike shapes were sampled at 24 kHz. The monkeys operated two × y-manipulanda to control two cursors (+ for the right hand; × for the left) on a video screen 50 cm away. Wrist cuffs minimized distal movements. As illustrated in Fig. 1a, each trial began when the monkey centered both cursors on the target (central circle) for at least 1 s. One of the cursors then turned green, indicating the hand to be used in the trial (lateral one). After a variable hold period of 1.0–3.4 s, a target (circle of 0.8 cm diameter) appeared at one of eight possible positions 4 cm from the origin (Fig. 1a, middle column). After an additional 1.0–1.5 s hold period, the origin disappeared (go signal), prompting the monkey to move the green cursor in a straight trajectory (limited by an invisible virtual corridor 0.5 cm in width) to reach the target in less than 2 s. After another hold of 750 ms, a liquid reward was delivered.

In each session, the monkey performed a default eight-target task before (pre-learning epoch) and after (post-learning epoch) a transformed one-target task (learning epoch), and then repeated the transformed one-target
task (re-learning epoch). This re-learning epoch was used to assess retention of the learned motor skill. In the default task (Fig. 1a, first and third rows), the target was chosen randomly in each trial from among the eight possible positions. In the transformed one-target task (Fig. 1a, second and fourth rows), the upward target (designated 90°) was presented on every trial, and an angular transformation was applied to the relation between hand movement and the direction of cursor movement on the video screen. The transformation was the same during both epochs of a given session but randomly chosen out of four possibilities (-90°, 45°, 45° or 0°) at the beginning of each day. Note that during the learning epochs for the angular transform illustrated (-90°), a hand movement at an angle of 0° (i.e., a rightward hand movement) was required to move the cursor from the origin to the target at 90° (i.e., an upward cursor movement). The phrase ‘learned-movement direction’ refers to the direction of hand movement needed to bring the cursor to the target for these visuomotor remapping tasks. There were four possible learned-movement directions in this study: 0°, 45°, 90°, and 180°, associated with the -90°, 45°, 45° and -90° transforms, respectively. Monkeys were trained for several months with the default eight-target task but did not see the transformations before the recordings.

Surface electromyography (EMG) recordings were taken from the following muscle: flexor carpi ulnaris and radialis, extensor carpi ulnaris and radialis, biceps brachii, triceps brachii, deltoid, trapezius, pectoralis major, latissimus dorsi, rhomboideus major and minor, trapezius, and subscapularis (several of these shown in Fig. 3c).

Penetration locations were verified by magnetic resonance imaging (MRI; Biospec Bruker, 4.7 T). At the end of each session, we examined the activity of neurons evoked by passive manipulation of the limbs and applied autoregressive time-domain analysis (ICM; 50 ms of 206 μm cathodal pulses at 50 Hz) to evoke movements. To monkey X, we also selected anatomical observations to verify the accuracy of penetration sites relative to the central sulcus.

Data analysis. We selected single neurons for analysis on the basis of several inclusion criteria: (i) ability to elicit their spikes; (ii) penetration sites where ICM evoked single-joint shoulder or elbow movements at 540 μA; (iii) at least five trials in each direction both pre- and post-learning; (iv) the lack of significant change in activity in the first hold period for the pre-learning epoch vs. the post-learning epoch (Manly-Whitney U-test); (v) the results of a one-way ANOVA showing a significant effect for direction; and (vi) a criterion that exceeded t = 0.5. For comparing pre-learning and post-learning population activities (as in Fig. 7), we normalized each cell’s firing rate by its baseline and depth of modulation:

\[ \text{r_{normalized}} = \frac{r - a}{b - a} \]

where d is the movement direction, and a and b are the baseline and modulation depth, respectively, as calculated by a cosine fit \( r(d) = a + b \cos d \). We verified that these criteria were based on ANOVA statistics did not bias our results by replacing the criteria (i) with a unit-modality test. We studied cells that were activated during contralateral and ipsilateral movements, and after verifying that each of the two populations produced similar results, we pooled all the cells together.

The deviation from axiomatic was assessed by a signed normalised deviation (s.d.), calculated as a directional deviation—the required hand direction minus the actual hand direction (taken at peak velocity), normalised by the transformation in the session (45°, 90°, -45° or 0°). Note that both the denominator and numerator are signed; thus a positive number only occurs when both deviation and transformation have the same sign, indicating that improvement in performance matched the transformation in sign and magnitude (Fig. 2b). A negative number results when the deviation and the transformation have opposite signs, showing that aftereffects matched the transformation.

The statistical significance throughout this report is accepted at the P < 0.01 level, unless otherwise mentioned. We used both parametric (t-test and ANOVA) and non-parametric (Mann-Whitney and Kolmogorov-Smirnov) tests for all statistical tests.

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CONFLICTING INTERESTS STATEMENT

The authors declare that they have no competing financial interests.

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ARTICLES


Learning-Induced Improvement in Encoding and Decoding of Specific Movement Directions by Neurons in the Primary Motor Cortex

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Many recent studies describe learning-related changes in sensory and motor areas, but few have directly probed for improvement in neuronal coding after learning. We used information theory to analyze single-cell activity from the primary motor cortex of monkeys, before and after learning a local rotational visuomotor task. We show that after learning, neurons in the primary motor cortex conveyed more information about the direction of movement and did so with relation to their directional sensitivity. Similar to recent findings in sensory systems, this specific improvement in encoding is correlated with an increase in the slope of the neurons' tuning curve. We further demonstrate that the improved information after learning enables a more accurate reconstruction of movement direction from neuronal populations. Our results suggest that similar mechanisms govern learning in sensory and motor areas and provide further evidence for a tight relationship between the locality of learning and the properties of neurons; namely, cells only show plasticity if their preferred direction is near the training one. The results also suggest that simple learning tasks can enhance the performance of brain-machine interfaces.

Introduction

Practice can induce behavioral improvement that is often specific to the situation experienced during the practice sessions (or "training"). Such findings suggest that changes occur in neurons with fine selectivity (or "tuning") for the stimuli experienced or the movements made during training. In the visual system, for example, behavioral improvement is specific to the trained stimulus, such as the orientation of a light bar (Fiorentini and Berardi 1989; Crist et al. 1997), and is paralleled by specific changes in neurons that are tuned to the orientation of a light bar (Schoups et al. 2003) or, in other experiments, the direction of visual motion (Zohary et al. 1994). In the auditory system, changes in response properties of single neurons and cochlearotopic maps are specific to the parameters characterizing the sound (Suga et al. 2002). In the motor system, skill acquisition induces expansion in the cortical representation of the used forelimb (Nudo et al. 1996) and enhance synaptic connections in the trained contralateral hemisphere (Rizzolatti and others 1990). A line of studies found that when monkeys perform reaching movements and adapt to directional errors induced by force fields, primary motor cortex (M1) cells shift their preferred direction (PD) in the same way as for the muscle activity needed to perform the task (Gandolfo et al. 2000; Li et al. 2001; Padoa-Schioppa and others 2002). We have recently shown that learning a local rotational visuomotor task can induce an elevation in the activity of single neurons in M1 (Paz et al. 2003) and that these changes are observed only in a specific subpopulation of neurons, those with a PD close to the movement direction used during the learning.

Whereas many studies indicate that learning can induce specific changes in brain activity, this finding does not necessarily imply that newly learned skills are "better" represented in the brain. The crucial question is this: Do neurons encode task parameters, such as movement direction, any better after learning? In the motor system, such improved encoding (Chen and Wise 1997) can be used for decoding by downstream areas and as an efficient copy for further computation (Wolpert and Ghahramani 2000; Sommer and Wurtz 2002). It can also be used by an external observer to allow for more accurate prediction of behavior (Landach et al. 2000). In this paper, we examine two questions. First, do learning-induced changes in firing rates provide more information on the task? And, second, what aspect of the cell's activity contributes mostly to this improvement?

To address the first question, we employed an information-theory analysis (Cover and Thomas 1991; Rieke et al. 1997) to calculate the mutual information (MI) (see Figure 2) between cells' activity and direction of movement. Informational measures have two relevant advantages. First, they use the full distribution (estimated from the data) of neuronal activity and do not assume any specific shape of the tuning curve or noise distribution. This allows for a more fine-tuned examination of learning-related changes. Second, they provide a measure as to how well different directions can be differentiated, based on neuronal activity. To address the second question, we examined two features of the neuronal

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Abbreviations: DL: information per direction; M1: primary motor cortex; JVM: maximum a posteriori; AJV: mutual information; PA: preparatory activity; PD: preferred direction; PV: population vector.

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response that could contribute to the increase in information: response variability and the slope of the tuning curve. Finally, to demonstrate that the observed increase in information can be extracted, we use the neuronal activity to decode the actual movement direction.

**Results**

Monkeys adapted to visuomotor rotations on a daily basis by altering the relationship between the visual feedback (cursor) and the hand movement (Figure 1). Learning was confined to only one target in space, i.e., learning that is local in direction. We tested neuronal sensitivity to direction by comparing the information content conveyed in the firing rate of single cells during the pre- and post-learning epochs (identical task of standard movements to eight directions spanning the two-dimensional working surface; only differentiated by a learning epoch). We specifically looked for a change in representation that was related selectively to the learned direction, i.e., the hand direction that was used to bring the cursor to the target during the transformation. Activity was measured from the hold period that immediately follows the target appearance, but before the go-signal, and was therefore termed preparatory activity (PA). There were three reasons for this choice. First, such PA has been reported in many motor cortices and is thought to participate in movement planning and in computing visuomotor transformations (Kurata and Wise 1988; Alexander and Crutcher 1990; Kalaska et al. 1997; Shen and Alexander 1997; Zhang et al. 1997; Kakei et al. 2001). Second, as previously found in this experimental paradigm, learning-related changes have only been reported for this period (Paz et al. 2003). Third, as a means of eliminating any kinematic-related changes (Wise et al. 1998), we further verified that movements shared similar kinematics before and after learning (see Materials and Methods; Figure 1).

**Mutual Information**

The MI between one-cell activity and direction of movement is exemplified in Figure 2. We compared the MI between pre- and post-learning (Figure 3A). The figure depicts the distributions of MI between direction and spike count for all cells (Figure 3A, corrected for bias) for pre-learning (dashed line) and post-learning (solid line). No difference was found between the MI on the population level, either by comparing the distributions (Kolmogorov-Smirnov, p = 0.3) or by comparing their means (paired t-test, p = 0.53). We further tested the average information about
Results III

Figure 2. Mux between Neuronal Activity and Direction of Movement
The example shows a simulation of the activity of one cell during 64 movements to evenly spaced eight directions, presented in a random order (eight trials per direction). Each dot in the scatter plots a and b describes the spike count of the cell in a specific trial. Without prior knowledge about the direction of movement (A), a large uncertainty exists about the responses of the neuron. However, ordering the trials according to the movement direction (B) reveals a large reduction in the uncertainty about the cell responses. The probability p(d) of observing a trial with direction d and spike count r is shown in (C), along with a specific conditional distribution h(r|d = 30).

The entropy
\[ H(D) = -\sum p(d) \log p(d) \]

is a measure of the uncertainty about movement direction. H(D) = log(8) = 3 bits, in the case that all eight directions have equal probability to occur. The conditional entropy is defined as
\[ H(D|R) = \sum p(R|D) H(R) \]

and describes the mean uncertainty about direction given the cell response.

Learning Improves Information in M1

Learning improves information in M1.

Direction conveyed by each spike by normalizing each cell’s information by its firing rate and again found no significant difference (test in Figure 3A: Kolmogorov-Smirnov, p = 0.25, paired t-test, p = 0.7).

Although the population as a whole did not change significantly, single neurons could still increase or decrease their information about direction. To explore this, we probed each neuron individually for changes in Mux. Using a bootstrap method, we shuffled trials from pre- and post-learning and randomly selected two different groups of trials, we then calculated the Mux for each group and the difference between the two Mux. The procedure was repeated 1,000 times to produce a distribution of Mux differences. The actual Mux (difference between the pre- and post-learning) was compared to this distribution to obtain a p-value. A high p-value means that the Mux in the post-learning epoch was significantly higher than the Mux in the pre-learning epoch. Figure 3B plots the histogram of the p-values for all cells. A significant number of cells showed an increase in Mux with a p-value larger than 0.95 (black in Figure 3B; n = 37 out of 177, p < 0.01, \( \chi^2 \)); a nearly significant number of cells showed a decrease in Mux with a p-value lower than 0.05 (white in Figure 3B; n = 18, p = 0.06), while the rest did not (gray in Figure 3B). We also examined the actual change in information content for all cells (Figure 3C, upper) and specifically for the cells that had a significant change (Figure 3C, lower).

Following the rationale explained in the Introduction, the association between the learned parameter (direction) in local rotational transformations and the sensitivity of many cells to direction, we probed for a relation between cells’ PD and the learned direction. Figure 3D plots a circular histogram of PDs of cells that exhibited a significant increase in their Mux. For the plot, we normalized each cell’s PD to the average direction in its recording session, and this revealed a bimodal distribution (Rayleigh test, p < 0.05) with its center on the learned direction. In contrast, the PD distributions of the whole population (Figure 3D, upper inset) and of cells that significantly decrease their information content (Figure 3D, lower inset) did not exhibit this trend and seemed homogenous.

To test that this change in information is indeed owing to the learning of visuomotor transformations and not owing to the mere repetition of a single movement during the learning epoch, we conducted the same analysis for control, repetition sessions. Only a nonsignificant (p > 0.1, \( \chi^2 \)) number of cells (eight out of 126) had a p-value greater than 0.95 (Figure 4A). Further, this population did not exhibit any specific distribution of PDs (Figure 4B, Rayleigh test, p > 0.1).

Individual Information per Direction

The Mux represents the information that a cell’s spike count conveys about all the eight tested directions. We further investigated how much information a cell conveys about one direction in particular, which is termed the individual information per direction (I|D) (Rolls et al. 1997; Buracas et al. 1998) and is measured as the reduction in uncertainty about the spike counts, given a specific direction.

We calculated the DI of each cell for each of the eight possible directions, pre- and post-learning. The distribution

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of the differences between the post-learning DI and pre-learning DI for the learned direction was significantly above zero (Figure 5A, "Learned"). This indicates that after learning, cells' firing rates conveyed more information about the learned direction. Figure 5A also shows that information about other non-learned directions did not change. As with the Mu, to probe for the directional tuning of the cells, we plotted the circular histogram of PDs of cells that increased their information about the learned direction (a positive post-learning minus pre-learning). Again, a unimodal distribution (Rayleigh test, \( p < 0.01 \)) was found with its peak on the learned direction (Figure 5B).

**Possible Origins for Improvement in Information**

Information theory makes use of the complete (estimated from data) stimulus-response distribution and thus does not tell us what feature in cell activity primarily contributed to the increase in information content. However, we found that the increase in information is specific to a single-learned direction and that cells with a PD close to the learned direction mainly contributed to this increase. We have previously reported that cells with PD close to the learned direction increased their firing rate after learning when movement was to the learned direction (Paz et al. 2003). We therefore explored more closely this elevation in firing rates and its relationship to the increase in information content.

Figure 6A histograms the net changes in activity (post-minus pre-learning) at the cells' PDs for the whole population. Figure 6B shows the same net changes for cells that significantly increased their information about direction, where a significant positive trend was found (by fitting a

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**Figure 3.** Comparing Mu of Single Cells Pre- and Post-Learning

(A) Distributions of single-cell information about direction of movement pre-learning (dashed) and post-learning (solid). No significant difference was found between the distributions (Kolmogorov-Smirnov, \( p = 0.5 \)). The inset shows the Mu per spike, calculated by dividing the information per cell by the cell's firing rate (Kolmogorov-Smirnov, \( p = 0.25 \)).

(B) Improvement in information of individual cells. Histogram of PDs for all cells: a significant \( p < 0.01 \) number of cells (\( n = 37 \)) had a PD greater than 0.95, representing cells that significantly increased their information content about direction after learning. 18 cells had a PD value lower than 0.95, representing cells that decreased their information content, but this was found to be only marginally significant (\( p = 0.06 \), \( \chi^2 \)).

(C) Histograms of difference in information, post minus pre-learning, for all cells (upper) and only for cells that increase \( p > 0.95 \) or decrease \( p < 0.05 \) their information content significantly (lower).

(D) Circular histogram for PD of cells that significantly increased their information. The cells' PDs were normalized to the learned direction in each cell recording session, revealing a unimodal distribution (Rayleigh test, \( p < 0.05 \)). The upper inset shows the circular histogram for all cells and lower inset shows the circular histogram for cells that decreased their information, in both cases, the distributions seem homogenous (Rayleigh test, \( p > 0.1 \)).

**Figure 4.** Changes Were Not Observed after Mere Repetition of Movement to One Direction

Same as in Figure 3B and 3D, but for control sessions that included the mere repetition of standard, nontransformed movement to one target during the learning epoch. The number of cells that exhibited an increase in their information content was not significant (4A right bar, eight out of 126), and their distribution was homogenous and showed no specific relation to the direction of the repeated movement (B).

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normal distribution; see legend to Figure 6B). We further aligned each cell tuning curve on the cell’s PD and calculated the average tuning curve. This revealed that this group of cells indeed elevated their activity mainly around their PD (Figure 6C).

Two natural features of a cell’s tuning curve can contribute to the improvement in information content. First, a cell can increase the slope of the tuning curve just near the learned direction, and thus small changes in direction can lead to a larger difference in the cell’s response, providing a better differentiation of direction based on the neuronal activity (illustrated in Figure 7A). Second, cells can reduce the variability of their response near the learned direction. This is also termed “reliability,” because when variability is low, each single report made by the cell is more reliable (illustrated in Figure 7B). A standard method for characterizing this is the Fano factor (Berry et al. 1997), calculated as the variance of the response divided by its mean. We correlated the net change in information content (post-learning minus pre-learning) to these two factors: change in slope near the learned direction (Figure 7C1–C3) and change in the Fano factor (Figure 7D1–D3). Figure 7 shows that whereas no systematic change in the corresponding factor was found for the whole population (Figure 7C for slope and Figure 7D1 for FF), a significant positive trend was observed for the population of neurons that significantly increased their information after learning (Figure 7C2 and also, but to a much lesser extent, for the Fano factor (Figure 7D2). Figure 7C3 and 7D3 extends this relation and shows the correlation between the corresponding factor and the increase in information. A significant positive correlation was only found for the slope factor and only for cells that significantly increased their information (Figure 7C3, black asterisks and line). No correlation was observed between the change in slope and the change in information for the rest of the cells (Figure 7C3, gray dots) or between the change in Fano factor and the change in information, either for the whole population (Figure 7D3, gray dots) or for those that significantly increased their information (Figure 7D3, black asterisks). Further, the increase in the slope of the tuning curve near the learned direction was specific to this direction only and to cells that significantly increased their information content (Figure 8).

These results suggest that cells increased the slope of their tuning curve near the learned direction and improve the information content in their activity. Cells can use several strategies to do so and we considered three possibilities: first, by shifting their tuning curve and positioning the learned direction at a better “slope-wise” location on the tuning curve (illustrated in Figure 9A), second, by narrowing the tuning curve (Figure 9B); and, third, by local changes increasing or decreasing specific points near the desired (learned) location (Figure 9C). Although the three possibilities are not mutually exclusive and might be interrelated, we attempted to distinguish among them by correlating the change in information to each one. Figure 9A–9F shows that the increase in information was correlated with the increased firing rate at the learned direction (Figure 9F1–9F5), but not with shifts in PD (Figure 9D1–9D3) or with the narrowing of
tuning curves (Figure 9E1-9E5). We therefore suggest that cells locally increased their firing rate to increase the slope of their tuning curve at the learned direction.

Decoding Movement Direction

We hypothesized that the improved information regarding movements in the learned-movement direction would lead to an improved ability to reconstruct movements from population activity. To test this assumption, we applied two reconstruction methods: the population vector (PV) approach, a widely used decoding scheme for M1 activity (Georgopoulos et al. 1988; Moran and Schwartz 1999), and a maximum a posteriori (MAP) estimator (Sanger 1996).

For the PV analysis, we selected 129 of the 177 cells, only including cells that exhibited directional tuning by a cosine fit. Neurons were pooled according to the learned-movement direction in their recording session, and we computed the PV from the pre-learning and post-learning activity. Figure 10A shows the deviation of the PV direction, i.e., the difference between the PV prediction and the actual movement direction for the four possible learned-movement directions. A marked and statistically significant improvement was observed in the predicted direction ($p < 0.05$ for all four learned directions, bootstrap and $t$-test). We verified that this improvement was due to learning in two ways: first, by shuffling trials from the pre-learning and the post-learning epochs, and second, by shuffling cells from days with different transformations. In both cases, the mean of the distribution of improvements was not significantly different from zero. Furthermore, the improvement in the PV prediction was specific to the learned-movement direction. Figure 10B shows the signal-to-noise ratio (mean/SD) of improvements in PV accuracy (the difference between the accuracy of the pre-learning prediction and the post-learning prediction). We normalized each session directions to the learned direction in the session. A statistically significant improvement was found only for the learned-movement direction ($\chi^2, p < 0.01$). This improvement in the PV prediction can be accounted for by the enhanced firing of cells with a PD near the learned-movement direction, as shown above (see Figure 6). Cells with
their PD close to the learned-movement direction made a larger contribution to the PV, but mostly when the movement was in that direction. Because each cell contributes a weighted vector in the direction of its own PD, only the learned-movement directions showed improvement in PV accuracy. This improvement in prediction due to altered directional tuning is reminiscent of studies that examined learning of visuomotor associations in frontal eye fields (Chen and Wise 1996, 1997) and of studies showing evolution of directional tuning in M1 when monkeys received real-time visual feedback of brain-controlled trajectories (Taylor et al. 2002).

The PV method includes several assumptions about the coding and the decoding of the M1 population activity and is not guaranteed to be optimal (Sanger 1994; Snippe 1996; Pouget et al. 2000; Scott et al. 2001). Therefore, we also tested the performance of a probabilistic approach. Using a MAP estimator, we predicted the movement direction for all possible directions, including the learned-movement direction pooled and normalized from all sessions. Figure 10C depicts the success rate for 100 repetitions (by cross-validation) for each direction. Figure 10D shows the same, but in the post-learning epoch. A higher success rate of correctly predicting the movement direction can be observed for learned direction only in the post-learning epoch ($\chi^2$, $p < 0.01$, chance level is at 0.125; dashed line in Figure 10D). This indicates that after learning and by using this decoding method, we could better predict the actual movement direction from neuronal activity.

**Discussion**

This report describes improved encoding and decoding of specific directions by neurons in M1 of monkeys after learning a visuomotor skill that requires learning only for one direction in space. Our results suggest a close link between properties of neurons, such as directional tuning of cells, and learning a skill that is local in the same parameter, in this case direction, a finding that is concordant with ideas and findings in sensory systems (Zohary et al. 1994; Suga et al. 2002; Sharma et al. 2005). The fact that the increased information we found was associated with an increased slope of the tuning curve, as also reported in a recent visual study (Schoups et al. 2001), further suggests that similar mechanisms may govern neuronal interactions and learning throughout the central nervous system.

The fact that improved information in neuronal activity was evident mainly for the learned direction is in accordance with studies showing confined generalization of learning a sensorimotor skill, one that requires adaptation to directional errors. The width of the behavioral generalization function (i.e., the angular distance from the learned direction where aftereffects could still be observed) was similar for our monkeys (Paz et al. 2003) and in human studies, ranging from 45° (Gandolfo et al. 1996; Krakauer et al. 2000) to 90° (Imamizu et al. 1995; Thoroughman and Shadlen 2000). The neuronal changes we previously observed occurred mainly for cells with PD within 30° of the learned direction, and the change in slope observed in this study was sharply focused and not seen for directions 45° away from the learned direction (see Figure 8; note, however, that changes in firing rate were wider [see Figure 6]). While narrower primitives reasonably lead to narrower generalization function (Donchin et al. 2003), the exact generalization width depends not only on the primitives' width, but also on the connectivity and the specific model used. These are still largely unknown.

An intriguing result in this study is that learning-related changes were observed and persistent in the post-learning epoch, when performing a standard task that required no transformation. Further, measured kinematics was the same as in the pre-learning epoch. If the improved information can be used, why isn't it? First, our monkeys were trained on a task that did not require improved performance in the standard task after learning, but did encourage them to reserve learning for future use of the same visuomotor task. This is in agreement with our previous report, showing that the monkeys retained the task until the performance of the relearning epoch (i.e., they exhibited immediate recall rather than learning in this second learning epoch), and suggests that the neuronal change should persist but somehow gated. Indeed, everyday behavior shows that we can learn new tasks without interfering with the performance of existing ones. An alternative possibility is that we did not measure the appropriate kinematic variable that was altered and improved due to the neuronal changes. For example, a task that would demand finer directional sensitivity (i.e., angular distance of less than 45°) might show a change in performance after learning.

It is also worth noting that our experiment was performed in a local region in space and was not constrained to a specific posture (Scott and Kaelkens 1997) or joint or muscle combination (Scott et al. 2001). Therefore, we cannot conclude that locality and specificity of change in information content are related to external direction of movement. Our results may be consistent with other reference frames as well (Massa-Ivaldi 1988; Todoron 2000).

One important question is what kind of learning can induce such an increase in information content. Although
psychophysics studies have shown that adapting to new kinematics and/or dynamic environments results in the formation of internal representations in the brain (reviewed by Kawato 1999; Wolpert and Ghahramani 2000), changes were also observed after extensive training and mere repetition (Nudo et al. 1996). Moreover, many sensory systems exhibit stimulus-related adaptations (Dragoi et al. 2009; Suga et al. 2002), where repeated presentations of a stimulus induce a change in activity of neurons. To control for this possibility, we conducted sessions with a repetition condition, which entailed a one-target task without angular transformations. Cells recorded in these sessions did not exhibit a change in their information content, and PV analysis produced similar results before and after repetition. An alternative explanation could be attention-related modulations (Spitzer et al. 1988). We discuss elsewhere why this is an unlikely source for the changes we observed (Paz et al. 2005), yet we cannot rule out the possibility that increased attention might lead to similar improvement in information.

Mut measures are more often used in sensory research, describing the information that neurons convey about a presented stimulus, and only few papers have applied such measures to the motor system (e.g., Hatopoulos et al. 1998). We believe this stems from the fact that in sensory systems, neurons respond to the stimulus, whereas in the motor system, neurons "cause" the movement. In this study, we treated direction of movement as a stimulus to which the neuron responds. This can be justified because M1 is a symmetric measure and the point of view can be reversed; e.g., we can interpret the results as neuronal activity → movement, rather than movement → neuronal activity. More importantly, frontal motor fields, M1 included, are only part of the brain's learning system and project to many brain areas that take part in processing an upcoming movement, such as the basal ganglia and cerebellum (Middleton and Strick 2000).
Therefore, M1 activity may be decoded by those areas involved in coplaning of the movement. Moreover, an efference copy of the planned motor command is probably used for error estimation and correction (Wolpert and Ghahramani 2000; Sommer and Wurtz 2002). Indeed, we are aware of our movements before they have actually started (Haggard and Magno 1999). This suggests that when learning new sensorimotor tasks, activity in M1 should not only produce the correct behavior, but also change in a way that enables other brain areas a better readout of the motor command. This will allow more efficient computation and better control of the forthcoming movement.

Although higher information content implies better encoding by neurons, it does not entail better decoding; this is highly dependent on the algorithm used and on the error function introduced. Since our task involved manipulation of movement direction and since real-time prediction of movement trajectory has taken on major interest in recent years (Wessberg et al. 2000; Taylor et al. 2002), we used the discrepancy between the actual movement direction and the predicted one from neuronal activity as the error signal (either categorical, for the MAP, or continuous, for the PV).

The MAP method (Sanger 1996; Zhang et al. 1998) is theoretically optimal (Seung and Sompolinsky 1993) and requires fewer assumptions on the tuning-curve shapes and distribution of PDs (Sanger 1994), but requires larger amounts of data to estimate the true distributions (Pouget et al. 2000). The PV method has been shown to be robust in many scenarios (Georgopoulos et al. 1988; Moran and Schwartz 1999) and very useful in predicting hand movement in real time (Taylor et al. 2002). In our experiment, both methods yielded a better prediction of the learned-movement direction during its planning stages and long before its initiation (see also Laubach et al. 2000). Although we cannot determine whether neurons further downstream use this improved information to decode a previous layer of neurons, we believe it is possible. Further, our findings could lead to improved strategies for recovering trajectory information from populations of M1 cells (Wessberg et al. 2000; Serruya et al. 2002; Taylor et al. 2002). The specificity of the learning is of high importance here. The large number of degrees of freedom, the complexity of movements, and the technical difficulties of recording many neurons simultaneously are only starting to be addressed, and a plausible strategy might require learning and practicing specific and essential movements. Our results suggest that this would modify brain activity in a way that would enable earlier and better readout of brain activity from fewer neurons.

Materials and Methods

The experimental setup and data acquisition procedures are described in detail in Paz et al. (2002). The sampled cells were taken from the same database.

Physiological procedures. Two female rhesus (Macaca mulatta) monkeys (approximately 4.5 kg) were implanted with recording chambers (27 × 27 mm) above both the right and left hemispheres. Animal care and surgical procedures complied with the National Institutes of Health Guide for the Care and Use of Laboratory Animals (rev. 1996) and with the Hebrew University guidelines supervised by the Institutional Committee for Animal Care and Use. The monkeys were seated in a dark chamber, and eight microelectrodes were introduced into each hemisphere. The electrode signals were amplified, filtered, and sorted (MCP-PLUS, Alpha-Omega, Nazareth, Israel), and all spike shapes were sampled at 24 KHz. We used a template-based method for real-time isolation of spike shapes (MSD, Alpha-Omega).

Penetration locations were verified by MRI (Biopac Bioreseker 1.7 Tesla, Bruker BioSciences, Billerica, Massachusetts, United States) before recordings. At the end of each session, we examined the activities of neurons evoked by passive manipulation of the limb and applied intracortical microstimulation (50 μs at 200 μs cathodal pulse at 300 Hz) to evoke movements. Only penetration sites that evoked single-joint shoulder or elbow movement at thresholds of
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lesser than or equal to 40 µA were used in this study. In one monkey, we also made anatomical observations, to verify the accurate penetration rates relative to the central sulcus.

Behavioral paradigm: Monkeys moved a manipulandum to control the movement of a cursor on a video screen located 50 cm from their eyes. The goal was to move the cursor as far as possible away from a starting point at the center of the screen (ignoring a virtual target in a delayed go-signal paradigm); this required the monkey to hold (as verified by hand velocity and EMG) the cursor in the origin circle for a random 750-1,500 ms after the target onset. The disappearance of the origin indicated the go-signal. In each session (day), four consecutive epochs were presented: (1) pre-learning epoch (more than 10 trials), a transformed standard, eight-target task in which the target direction was randomized; (2) learning epoch (more than 30 trials), a transformed, one-target task in which only one target (upward, 90°) was presented; (3) a rotational transformation was introduced between the cursor on the screen and the manipulandum; (4) post-learning epoch (more than 100 trials), where the default eight-target task was presented again; and (4) relearning epoch, same as the learning epoch. Rotations were 90°, 45°, -45°, or -90° and were chosen randomly for each session, but fixed for the duration of the learning epoch in a session. Note that learning here is local in direction since only one target direction was introduced during the learning epoch. The term "learning" refers to the direction of hand movement needed to bring the cursor to the target for these rotations (thus, there were four possible learned-movement directions in this study: 90°, 45°, 135°, and 180°, 0°, 45°, -45°, and -90° transformations, respectively). Monkeys were trained for several months with the standard eight-target task, but did not see the transformations before the recordings. To achieve learning on a daily basis during the whole recording period (rather than switching between pre- and post-learned behaviors), a different rotational transformation was randomly chosen for each day from the set of four possible transformations. To observe systematic change in the activity of neurons, the learning epoch was repeated several times (equal to or greater than four repetitions) for each transformation and each monkey, on different days.

Note that in this paradigm, the monkeys learn the visuomotor rotation by repeating performance of a single movement (to the learned direction). To test whether the repetition could be responsible for the improvement, we conducted control sessions. These sessions (labeled "replication" sessions) consisted of a one-target task without any visuomotor transformation (namely, a standard task to one direction only). We performed 16 such sessions (ten with repeated movements to 90° and six with movements to 180°).

Data analysis: Psychophysical studies have shown that immediately after learning, humans exhibit aftereffects, which is evidence for the formation of an internal representation of the newly acquired skill (Lachner and Dziio 1994; Sashin and Musio-Isvidi 1994; Kawato 1989). This has been observed in monkeys as well (Paz et al. 1995). To compare neuronal activities for movements with same kinematics, we excluded the first trials (three to five) in the post-learning epoch that exhibited significant aftereffects (measured as the directional deviation at peak velocity from a straight movement and compared to the distribution of deviations before learning). For the remaining trials, we compared velocity profiles, including direction and direction of motion, at different points in time and actual trajectories to verify that there were similar to the trajectories in the pre-learning epoch (see Figure 1B-1D). We also performed replication sessions where monkeys were asked to perform at least two more pre-learning trials and the difference between the values of the post-learning and before-learning was obtained.

In all three groups (p < 0.1), we also verified that learning was the same during the whole recording period. We divided the recording period into two to three consecutive segments and compared (1) learning rates in the learning epochs and (2) aftereffect magnitudes and washout rates in the post-learning epoch (Paz et al. 1995).

In order to avoid changes in activity that result from any kinematic or dynamic differences, and since learning-related changes were only observed in activity taken from preparations for movement (before the go-signal), here we only report neuronal activity from this period, i.e., activity during the 600 ms following the target appearance but before the go-signal. We isolated 172 cells (113 from monkey W4 and 61 from monkey X) based on (1) the lack of significant change in activity during the first-leg period during which no information was available about the impending task for the pre-learning epoch versus the post-learning epoch (by Mann-Whitney U tests); (2) the results of a one-way ANOVA showing a significant effect for direction; (3) more than five trials per condition both pre- and post-learning. We calculated spike counts in the 600-ms range following the target onset, referred to as the PA. Examining the neurons for changes in PA did not reveal any systematic or significant changes (bootstrap-test, three of 172 showed a significant change) and PAs were uniformly distributed (Rayleigh tests).

A correlation between the direction of the movement and each cell response was calculated by standard methods (Cover and Thomas 1991) using the formula

\[ I = - \sum \frac{P_r(\theta) \log P_r(\theta)}{P(\theta)} + \sum \frac{P(\theta) \log P(\theta)}{P(\theta)} \]

where \( d \) is the direction of movement and \( r \) is the number of spikes (see Figure 2). We used either the direct method for calculating \( P(\theta) \) or assuming a Poisson distribution with the mean taken from all trials. We compensated for the limited number of trials (bias correction) by applying either analytical correction (Panzeri and Treves 1996) or by shuffling trials between directions to obtain mean baselines and standard deviations. We performed the following formula (Sanes 1996) to obtain the most likely direction:

\[ \hat{d} = \arg \max_i \left[ \frac{1}{N} \sum \log P_r(\hat{d}) \right] + \frac{1}{2} \log \frac{1 - \sum \log P_r(\hat{d})}{1 - \sum \log P_r(d)} \]

where \( \hat{d} \) denotes the mean firing rate of cell i in directions \( d \) and \( \theta \) is the rate in the randomly drawn trial. For ease of computation, we took the log of the probability and did not calculate \( N \) the normalization factor. The process was repeated 100 times and performed separately for the pre-learning and post-learning phase.

(2) PV analysis (Georgopoulos et al. 1988; Schwartz 1995). One hundred twenty-nine cells (91 from monkey X and 38 from monkey W4) were characterized as directionally tuned by fitting a cosine function (\( r^2 > 0.5 \)). The cells' PAs were homogeneously distributed both pre- and post-learning (Kuo test, pre-learning, \( p = 0.4 \), post-learning, \( p = 0.5 \)). We performed two bootstrap tests for significance. First, we shuffled trials from pre- and post-learning and calculated the difference between the deviations of the PV pre-learning to that of the post-learning was repeated 1,000 times to obtain confidence intervals. Second, we shuffled cells from days in which different preparations were learned and again obtained confidence intervals. This process tests whether the improvement in prediction was indeed related to the specific direction learned in the session.

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Analysis of learning-related changes: additional controls and simulations.

In this section I address two sources of evidence that further support the relationship between observed neuronal changes and observed behavioral changes ascribed to learning. The first describes various aspects in neuronal activity that were not altered as a result of learning and hence provide further support that the specific elevated activity described in the second section is the main change due to learning. The second comes from simulations of learning-related changes and population vectors showing that the improvement in prediction (section III) can be explained exclusively on the basis of the observed specific elevation of activity (section II).

Additional controls

Several studies have described learning-related shifts in the tuning curves of cells (Paz R et al., 2004), both in studies of perceptual (Dragoi et al., 2000; Schuett et al., 2001; Suga et al., 2002; Godde et al., 2002) and motor learning (Wise et al., 1998; Li et al., 2001; Padoa-Schioppa et al., 2002). However, several studies in both fields have failed to find such shifts (Schoups et al., 2001; Gribble and Scott, 2002; Paz et al., 2003). I therefore examined more carefully whether learning induced shifts in the preferred directions of cells in my study, and whether such shifts are related to the parameters of learning.

Bootstrap methods were used to shuffle trials between before and after learning and obtain confidence limits for possible changes in preferred direction. The actual difference was then compared to test for a significant change. Only one cell in the preparatory activity indicated a significant change. However, 22 cells (out of 197) showed significant changes in PD during the movement-related activity. I therefore examined whether these changes were somehow related to the transformation performed in each cell's session, and correlated the change to the trained direction. Figure 1 summarizes the results and shows that shifts in preferred direction could not
be linked to the learning. In sum, the cells did not exhibit any shifts in their tuning curve that can be attributed to the learning.

Other factors that were explored are:

- A few studies have linked behavioral improvement with improvement in the directional tuning of cells, both in perceptual (Zohary et al., 1994; Dragoi et al., 2002) and in motor studies (Chen and Wise, 1996; Taylor et al., 2002).
- Theoretical and modeling studies have examined the importance of the width of the tuning curve to the overall sensitivity of the population (Pouget et al., 1999; Zhang and Sejnowski, 1999) and several perceptual studies have described learning induced narrowing of tuning curves (Recanzone et al., 1993; Muller et al., 1999; Sur et al., 2002).
- A few studies have found a reduction in the signal-to-noise ratio after learning (Poggio et al., 1992; Muller et al., 1999), thus improving reliability and accuracy of the neural code (Dayan and Abbott, 2001).
- Basic properties such as depth of modulation and baseline rate could hypothetically contribute to the learning-related improvement if they exhibit a relationship to the trained direction.

To examine these changes, Figure 2 shows the above-mentioned factors for all cells in the population as a function of their preferred direction distance from the trained direction. No systematic phenomena could be observed and statistical analysis (paired t-test for post-learning vs. pre-learning) was not significant for any factor. In sum, the only factors that exhibited a relationship to the learning of visuomotor rotational transformation were the elevated activity near the center of the tuning curve of cells with PD near the trained direction (sections II, III) and the slope of their tuning curve near the trained direction (section III).
Simulations

In all electrophysiology studies (and in general, in most scientific studies), the experimenter correlates the observed changes in activity to a controlled aspect of the experiment (e.g. behavior). However, correlation is not causation. There is always a likelihood that the observed changes are merely an artifact/outcome/reflection of another process in the brain, one that is the main factor underlying the behavioral change. To address this issue, several studies have used lesions to identify a tighter relationship between a certain brain area and a given behavior. In studies of neuronal activity, it is useful to show that observed changes can theoretically cause the observed change in behavior. This would provide further evidence that changes are most likely to be the relevant factor. Here, I used simulations to show that the observed modulations in neuronal activity could be the sole cause of the improvement in accuracy of prediction (section III).

The database consisted of two sets of 1000 cells, each cell with a cosine tuning curve (Georgopoulos et al., 1982). Baselines and depth of modulation were taken from a Gaussian distribution with mean and standard deviation as calculated from the database of real cells, and preferred directions were homogenously distributed (Schwartz et al., 1988). To simulate the learning-related modulations in one of the two sets, a Gaussian-shaped hill of activity was added to 90% of the cells with preferred direction ±30° from the 180° direction. For each of the cells in this sub-population, the added “Gaussian” had two parameters: its standard deviation (i.e. its width), and a weighting coefficient (i.e. its height). Both parameters were taken from two standard distributions whose parameters (2*mean 2*s.t.d) were obtained to mimic the real effect observed in the results as closely as possible. This was done using a least-square curve fit (using ‘lsqcurvefit’, Matlab), by performing the same analysis used to describe the learning-related changes for the real data (the analysis reported in section II, shown in figure 7a which calculates the change in activity as a function of the cells’ PD from the trained direction) and comparing its results on the simulated population to that of the real population. Another way of simulating learning effects is to use variations of the Von-Mises functions which control the flatness/sharpness of its peak (Batschelet, 1981; Amirikian and Georgopoulos, 2000), this was also tried and produced similar results.
I then performed a population vector (PV) calculation (Georgopoulos et al., 1988) on the two sets of simulated cells, one with the learning effects and one without. Figure 3b,c show that the PV analysis for the set with learning-related changes yielded higher accuracy when compared to the PV analysis for the set without these changes. The magnitude of the improvement was comparable to the comparison between post-learning and pre-learning for the real data (see figure 3a, which shows the same results as in section III, figure 10a,b but with extended controls). Further, the specificity of the improvement was confined to the “trained” direction in the simulation (i.e. 180°) but was negligible for direction 45° away from it (figure 3c). Figure 3b also shows the relationship between the number of cells used for the prediction and its accuracy. After learning, fewer cells are needed to achieve a given degree of accuracy, providing more support to the supposition that simple learning tasks can aid the performance of brain-driven artificial devices (section III).

These results show that the learning-related changes observed in real cells; i.e. the specific elevation of activity, are sufficient to induce the improvement in accuracy of prediction after learning.
**Figure 1.** Cells did not shift their preferred direction (PD) as a result of learning.

**a,** An example of one cell that did shift its tuning curve as a result of learning. Shown is the cell firing rate for each direction in the standard task pre-learning (blue) and in the standard task post-learning (red). The learned direction in this cell’s session is shown by an arrow (135°, i.e. a rotation of 45°). However, the overall population of cells did not exhibit any consistent change in their tuning curves and/or preferred directions.

**b,** The histograms depicts the change in PD of cells (post-learning minus pre-learning), for the actual data (solid) and for bootstrapped data (dashed). Bootstrap was calculated for each cell by shuffling trials from post- and pre-learning, randomly dividing them into two groups of pseudo-post and pseudo-pre-learning, and calculating the change in PD. The process was repeated 100 times for each cell and the mean of the changes is presented here for all cells. The two distributions (real and bootstrap) were not significantly different (kolmogorov-smirnoff, p>0.1). However, 22/197 cells showed a significant change in their PD, obtained from comparing the actual difference to the distribution of 100 differences obtained from the bootstrap process.

**c,** Distribution of PDs in the pre-learning (left, blue) and in the post-learning (right, red). PDs were aligned to the learned direction in each cell’s session. Both distributions were homogenously distributed (Rayleigh test, p>0.1). This shows that cells did not shift their PD towards the learned direction (or away from it).

**d,** To verify that cells did not shift their PD with some relation to the learned direction, the figure shows the distance of each cell’s PD from the learned direction in the post- vs. in the pre-learning. Red dots denote the cells that were found to have a significant change in their PD (b).

**e,** To further examine if cells shifted their PD as a function of the transformation (e.g. sign, magnitude) in their session, the figure plots the change in PD (post minus pre) for each transformation separately. No systematic change was found.
**Figure 2.** No change was observed in any other factor of the tuning curve. Shown is the value of the examined factor (y-axis) for all cells in the post-learning (red) and in the pre-learning (blue). Cells are ordered on the x-axis according to their PD distance from the learned direction in their session. Tuning width (a), depth of modulation (b), tuning quality measured by the $R^2$ for the cosine fit (c), baseline (d), and signal to noise ratio (e), were not significantly altered (5 paired t-tests for each factor, all p>0.1).
Figure 3. The accuracy of population vector (PV) prediction is increased for real data and for simulated data.

\(a\), The same data as in section III, figure 10; showing the improvement in PV prediction. A bootstrap method was used to achieve a distribution of improvements in the prediction. A large signal to noise (SN) ratio of this distribution (y-axis) results from a large mean and a small variance, a small SN can result from either a small mean (i.e. no improvement) or a large variance (i.e. not a reliable/significant improvement). A significant and reliable improvement can be seen only for the learned direction in the visuomotor session and when using the preparatory activity (see section III for details); and not for any arbitrary direction or for the repetition control experiments or when using movement-related activity. \(a1\) shows the error (deviation) in PV prediction for each transformation separately, using the preparatory activity; An improvement was observed for all four transformation types. \(b1\) shows the same using movement-related activity.

\(b,c\), Simulation results (see text for details). Shown is the deviation in prediction (right y-axis) of the PV in the simulated population for the pre-learning (dashed blue) and for post-learning (dashed red), as a function of number of cells used for the prediction (b) or as a function of the predicted direction (c, 180° is the simulated ‘learned’ direction). Also shown in black is the difference between the two curves i.e. the improvement in prediction (left y-axis). The improvement in these results can be matched for the improvement obtained from the real data (a), both in magnitude (b) and in specificity for direction (c).
Viewing and doing: similar cortical mechanisms for perceptual and motor learning

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Historically, different groups of researchers have investigated the mechanisms of perceptual learning and motor learning. For sensory cortex, neurophysiological and psychophysical findings have linked changes in perception with altered neuronal tuning properties. However, less information has been forthcoming from motor cortex. This review compares recent findings on perceptual and motor learning, and suggests that similar mechanisms govern both. These mechanisms involve changes in both the center of neuronal tuning functions and their width or slope. The former reflects the values of the sensory or motor parameters that a neuron encodes, and the latter adjusts the encoding sensitivity. These similarities suggest that specific unifying principles for neural coding and computation exist across sensory and motor domains.

Pity the plight of baseball batters: sometimes a pitch flies straight and fast, but other times it approaches on a slow curve. Batters must develop the motor skills needed to hit both pitches and choose between them as the ball travels toward them at 35–45 m s\textsuperscript{-1}. Accordingly, they must learn to recognize which pitch is which, pronto. Time does not permit the batter to weigh the pros and cons, the evidence for one pitch or the other, or the need for one motor skill or the other. The relevant knowledge is all implicit; the memories procedural. Rapidly rotating balls curve in flight, and so — to identify the pitch — batters detect the pattern made by the red stitches in the ball as it spins. That skill requires perceptual learning; the crucial batting skills require motor learning. Yet the brain of a batter must acquire both kinds of skill, and, if it cannot do so, that brain needs to find a different occupation.

In trying to understand both perceptual and motor learning, neuroscientists have adopted a 'divide-and-conquer' strategy, in which different researchers approach various parts of a problem. The 'conquer' part requires a synthesis of findings. David Marr's distinctions of levels of understanding brain function \cite{1} might help us do that. He distinguished the level of a 'computational theory', which clarifies the problem to be solved, from the levels of 'algorithm' and 'implementation', which involve solving the problem. Because sensory and motor systems use similar 'hardware' — neurons and synapses — they must have close analogies at the level of implementation. However, the issue is whether those similarities extend to the algorithmic level. Such similarities would simplify the interaction between sensory and motor systems, but have neuroscientists obtained any empirical evidence to support this idea?

At one level, sensory and motor systems resemble each other closely: almost all brain areas have neurons with 'activity fields', also known as receptive fields, motor fields or tuning curves (Figure 1). A population of neurons with different activity fields can provide the basis for representing sensory or motor parameters, and as such they can serve as the 'primitives' — the fundamental components — of a neural representation. The nature of these primitives and their locations in the brain can sometimes be inferred by measuring how learned skills transfer to situations other than those experienced previously. Take a simple perceptual skill, for example, the ability to discern the difference between bars of light oriented at slightly different angles. Imagine that learning this skill for one set of orientations at one place in the visual field does not generalize (or transfer) to other orientations or to other places in the visual field. In that case, such learning probably depends on narrowly tuned primitives at the level of the primary visual cortex (V1), where any given neuron responds to a small range of locations and orientations \cite{2}. Ahissar and Hochstein \cite{3} extended this idea and suggested that difficult visual skills depend on learning mediated by 'lower' visual areas, where narrow tuning leads to poor generalization, whereas easy skills depend on 'higher' visual areas, which have the opposite properties.

The same principles apply to the motor system. The concept of neuronal primitives suggests that specific computational principles exist for sensorimotor transformations \cite{4,5} and imposes constraints on the learning of those transforms \cite{6,7}. As with perceptual learning, examination of how motor skills transfer reveals something about the primitives underlying motor learning. For example, the extensive generalization of learning seen for smooth-pursuit eye movements of different speeds suggests broadly tuned primitives \cite{8}, and studies of
Learning-related changes in tuning values

The description of neuronal activity is commonly reduced from an equation specifying the full tuning curve (Figure 1) to a single "tuning value", which commonly corresponds to the greatest discharge rate and is referred to as the 'preferred' or 'best' value. For example, A1 neurons have a best frequency (BF) for responding to tones, V1 cells have a preferred orientation (PO) for responding to lines and bars, and M1 cells have a preferred direction (PD) for reaching movements. This compact description of neuronal tuning is useful in many coding schemes, for example, the population vector, in which the PD of M1 cells and their instantaneous activity estimate movement direction.

Learning sometimes induces shifts in the 'tuning value', which can be described as either attractive (a change towards some parameter) or depressive (a change away from some parameter). As an example of depressive changes, after adapting to a grating of one orientation, neurons in V1 of cats and monkeys shift their PO away from that orientation [11]. As an example of attractive changes, after applying intracortical microstimulation (ICMS) to a subpopulation of neurons with tuning to one orientation, adjacent neurons shift their PO towards that of the stimulated ones [12]. Another attractive tuning change occurs in V1 after pairing an orientated line stimulus with ICMS [13]. In the auditory system, attractive BF shifts follow auditory fear conditioning at a given frequency, acoustic discrimination learning, frequency adaptation and application of ICMS to a subpopulation of neurons with tuning to one frequency [14,15]. Depressive shifts occur only rarely [16].

The results from sensory systems have some recently discovered correlates in the motor system. Skill acquisition affects the PDs of single cells in M1 [16–19], as does adaptation to directional errors induced by force fields [20,21]. In the latter experiments, monkeys practiced reaching movements while holding a robotic arm that imposed a complex pattern of forces. For example, one pattern of force was proportional to the velocity of the hand in both dimensions of a two-dimensional workspace. When monkeys learned to reach in this new environment, M1 cells shifted their PDs in about the same way as the muscles did. Moreover, a population of cells maintained their new PDs (and altered activity levels) after the monkeys readapted to moving without the imposed forces. Interestingly, adapting to local visuomotor transformations [22] and to viscous loads [23] did not induce consistent shifts in the PDs of M1 cells, so changes in the tuning value have not been universally observed in studies of motor learning.

Further, albeit indirect, evidence for changes in the tuning value in M1 comes from the work of Classen et al. [24]. They had subjects move their thumb repeatedly in one direction and, after this training, applied transcranial magnetic stimulation (TMS) to M1. In this condition, the elicited movements systematically shifted towards the training direction — an attractive plasticity. This result could have come from a shift in the PDs of M1 cells, although this hypothesis remains to be tested. Nevertheless, the occurrence of PD shifts in these instances
suggests fundamental similarities in sensory and motor plasticity at the cortical level.

Which neurons change?

Another aspect of learning involves the selection of a subpopulation of neurons involved in a change in tuning properties. In V1, observed shifts in PO after adaptation to one orientation occur only in cells with nearby PO's. Moreover, the larger the difference between the PO of a cell and the training orientation, the smaller the shift (Figure 2a) [25]. In the auditory system, the situation is similar: maximal shifts in BF were observed for cells with BFs close to the training BF (but not for those 'too close') [26].

In the motor system, Paz et al. [22] recorded the activity in M1 before, during, and after monkeys adapted to visual-motor transformations commonly called 'rotation'. In the baseline condition, the monkey moved a cursor on a video monitor in a straightforward manner, similar to the mouse–cursor relationship on a computer. For example, when the monkey moved its hand forward, the cursor moved upwards (90° when 0° is to the right). During the learning condition, the movement of the cursor was 'rotated' so that a hand movement in some other direction moved the cursor upwards. For example, a -45° rotation required the monkey to learn that a hand movement forward and to the left led to upward cursor movement, and movements of the hand in any other direction also caused the cursor to move at a rotational transformation of -45°. In the experiment, the monkeys learned a different 'rotation' each day, but saw only one target during the training period. Before and after training, the monkey moved the cursor to targets in eight directions from a central location in the baseline condition. In agreement with studies in humans involving similar transforms [27], the monkeys showed limited generalization of learning for movement directions other than the training direction. There was some generalization for movements within ± 45° of the training direction, but virtually none for movements in more distant directions (Figure 2b). That is, the motor learning was largely local. Paralleling these behavioral findings, changes in activity were observed only in neurons with BFs close to the training direction (Figure 2c).

This specificity in the way that the representational primitives of M1 change during motor learning could explain the limited spatial generalization observed. Only a selective subpopulation of cells, those with tuning values in or near the training direction, participated in the learning process. Movement in many different directions, however, requires participation of neurons with a wide range of tuning values. But neurons tuned to directions far from the training direction did not change. Hence, as in the sensory system [2], learning did not automatically transfer from a training place or direction to distant ones.

Shape of the tuning curve and implications for improved coding

Learning in sensory systems might affect the shape of tuning curves. For example, the slope of the curve might change at a particular point along the curve, even without a significant change in the tuning value (the center or peak of the curve) or the amplitude of the peak. This possibility, which is illustrated in Figure 1b, has several implications for neural coding. In one view, neuronal tuning curves encode the value of a stimulus by signaling their preferred value and the population serves as a set of basis functions. According to this idea, decoding can occur through function approximation [28] - that is, approximating stimulus value from the activity of a population of neurons with diverse tuning values and tuning-curve widths [30]. Viewed from a somewhat different perspective, tuning

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Figure 2: Learning-related changes occur in a selected subpopulation of cells. (a) In the task used to generate these data, brief presentations of a grating stimulus (alternating dark and bright bars) caused adaptation to a new orientation. For cells in the primary visual cortex (V1), shifts in their preferred orientation (PO) depended on the angular distance of their original PO from the presented orientation (black represents significant shifts). The closer their original PO to the one presented, the more their PO shifted. Negative values indicate an attractive shift (i.e., shifts towards the experienced orientation). This finding indicates that changes in activity occurred most prominently in a selected subpopulation of neurons. Adapted, with permission, from Ref. [25]. (b) Monkeys adapted to a daily basis to rotational transformations that required them to move their hand in an angle relative to the direction of a cursor. During training, only one target appeared (indicated as 0°). The plot shows the after-effects of training for movements in eight directions. All tested after-adaptation but with no 'rotation' (the baseline condition). After-effects were most pronounced for the training direction (0°) and decreased as a function of angular distance from it (and as a function of number of trials, shown by the different colors). Indicating poor generalization and showing that adaptation is local with respect to movement direction. Adapted, with permission, from Ref. [22]. (c) For primary motor cortex (M1), neuronal activity was recorded before, during and after the learning shown in (b). Each value on the x-axis represents a range of angular deviations from the preferred direction (0°) of the cells. The notations describe a range of PO differences between the value at the top and the value at the bottom, separated by a colon. Cells increased their activity in a delay period preceding movement, but only for movements in or near the training direction and only for cells with POs near that direction. This shows that changes occur in a selected subpopulation of neurons and could explain the poor generalization observed in (b). Adapted, with permission, from Ref. [22].
curves represent a probability distribution through which neurons encode stimulus intensity with a degree of uncertainty included [29]. Decoding could occur through a Bayesian-inference process, which estimates the probability of a specific stimulus based on neuronal firing rates. Two factors have special importance in this process: the signal-to-noise ratio and the slope of the tuning curve. Lower noise allows a clearer estimate of the veridical stimulus value by each single observation and thus leads to more reliable read-outs. Steeper tuning curves provide more distinguishable firing rates at adjacent points along the curve, increasing the veridicality of a neuron to stimulus values encoded on its flanks (Figure 1b).

Supporting these ideas, several studies have reported increased neuronal sensitivity [25,31] and decreased variability [31] in V1 neurons to gratings of one orientation (Figure 2a). A1 neurons also exhibit sharpening of their tuning curve after focal electrical stimulation [32] and following training on a frequency discrimination task [33]. Recently, Schoups et al. [34] have studied changes in the slope of V1 tuning curves after monkeys mastered a fine-grained, orientation identification task. They found that the flanks of tuning curve for the orientation of a bar-like stimulus have a higher slope than before the perceptual learning (Figure 3b). Thus, in sensory systems, learning-related changes in the width of a tuning curve could be secondary to an increase in the slope of its flanks.

Until lately, evidence of this kind was unavailable for the motor system. Recent studies, however, show that cells change the strength of their directional preference during the course of learning [16,18,19] and that this plasticity can aid in predicting planned and performed movements [16,19,53,56] (Figure 3c). As in sensory systems, probability-based and cortical approaches show promise [37]. For example, under certain conditions, better decoding of movement direction can be achieved by using a Bayesian estimator than by using a population vector [37].

Figure 3. Learning-related changes in the shape of tuning curves. (a) After a brief period of adaptation, the tuning curve of this primary-visual cortex (V1) cell sharpened (gray) relative to its tuning before that training (black). Sharpening of the tuning curve would increase the sensitivity of the neural code. The cell responded to a narrower spectrum of stimulus values, its response encoded more specifically the actual stimulus value. Adapted, with permission, from Ref. [35]. (b) In a different study of V1 cells, monkeys were trained to identify the orientation of a small grating and showed improved performance that was specific for both stimulus location and orientation. The graph shows the mean of the flanks of the tuning curves for a population of V1 neurons, as a function of the amount of training. A1 neurons also exhibit sharpening of their tuning curve after focal electrical stimulation [32] and following training on a frequency discrimination task [33]. Recently, Schoups et al. [34] have studied changes in the slope of V1 tuning curves after monkeys mastered a fine-grained, orientation identification task. They found that the flanks of tuning curve for the orientation of a bar-like stimulus have a higher slope than before the perceptual learning (Figure 3b). Thus, in sensory systems, learning-related changes in the width of a tuning curve could be secondary to an increase in the slope of its flanks.

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Evidence that the encoding process can also support probabilistic approaches was recently revealed by a close examination of neuronal activity after learning visuomotor 'rotations' of the sort already described. Paz and Vaadia [38] demonstrated that M1 neurons contained more information about direction of movement after learning than before, and that this increase in information content correlated with an increase in the slope of the tuning curve (Figure 3d). Furthermore, this slope increase was specific to the part of the tuning curve near the training direction (Figure 3d, inset).

Why would M1 transmit more information about the executed movement and allow improved decoding? According to the traditional view, better information promotes efficiencies in spinal computations, leading to enhanced performance in terms of success in achieving goals within task constraints. In addition, however, the motor system also transmits an internal signal, termed efference copy or corollary discharge [39], which informs other computational networks about the generated movement. This signal can help plan subsequent action. More importantly, it can generate a prediction about the potential outcome of a movement in time to provide corrections before a movement has ended, a computation called a forward model [40,41]. Accordingly, improved encoding of information provides as much benefit for the motor system as for sensory systems, perhaps because, as for sensory areas, other brain areas need to use the signals generated by motor areas.

Perceptual learning is thought to result from an expanded representation of the trained stimulus dimensions [42], and similar concepts have been suggested for motor learning [24]. Results such as those discussed in this section suggest that instead of thinking about expanded representations in terms of the number of cells encoding a given stimulus dimension, it may be more productive to consider subtle change in the way that cells encode stimuli, which is reflected in tuning-curve adjustments, could account for both perceptual and motor learning.

Contextual specificity and complexity of responses

Although many neurons in sensory areas are tuned to the types of low-level stimulus features discussed so far, they can also be tuned to complex interactions of low-level features that cannot be predicted from their linear combinations, including specific visual objects [43] and natural, complex acoustic signals [44,45]. In the motor system, an example of this phenomenon comes from studies of binocular arm movements. The responses of M1 neurons cannot be explained as a linear combination of their responses during performance of the separate unimanual movements that compose them [46,47]. Interestingly, similar observations have been made for binocular interactions: many A1 neurons exhibit complex interactions, responding maximally to specific combinations of sound levels in the two ears [48].

Learning can also be specific to the context of skill acquisition. This principle has long been established for the sensory system [2]. For example, Crist et al. observed limited transfer of perceptual learning between a spatial bisection task and a Vernier task (Figure 4a, left), despite the fact that both require enhanced acuity for the spatial separation between lines [49]. Similarly, V1 cells exhibit contextual modulation in the bisection task [50]. A line outside their receptive field affected their response to a parallel line inside it, but only when the animal performed the bisection task (Figure 4a, lower right), not when it performed a fixation task (Figure 4a, upper right).

Another example of context dependency comes from the auditory system. Ulanovsky et al. [51] recorded the activity of single cells in A1 while cats heard sequences of two frequencies (close to the BF of the cell). When the first frequency was rare, cells responded more strongly to it than to the second frequency. However, when the first frequency was common, cells responded less strongly to it that to the other frequency (Figure 4b). Thus, neurons in A1 adapted in a specific contextual way; they modulated their activity in response to the statistics of stimulus occurrence (rare versus common), rather than exclusively to tone frequency.

Similarly, learning new motor tasks can be context dependent [52]. For example, evidence for dependency of motor learning on visual context was provided by Cohn et al. [53], who trained people to adapt to Coriolis forces in an environment in which their whole bodies rotated. When the participants experienced a visual-rotation illusion, which mimicked the context of Coriolis forces, they compensated for reaching movements as if they were under the influence of that force.

Can people learn two motor skills in parallel, but in different contexts? If so, then it seems likely that the motor system uses multiple controllers that can be selected and switched according to task context [54,55]. In some situations, learning multiple skills in parallel seems to be difficult. For example, sometimes when people try to learn a second skill before they have fully consolidated the first, practice on the second skill can impair performance on the first. In these experiments, people learn to overcome errors in movements that are induced experimentally. The difficulty in learning two skills in quick succession occurs both when the induced errors depend on limb dynamics (forces) [56] and when they depend on kinematics (position and its derivatives) [57]. However, when errors in one direction (e.g., clockwise errors) depend on dynamics, whereas those in the other direction (e.g., counter-clockwise errors) depend on kinematics, parallel learning can occur [57]. This finding suggests that, at least in the same conditions [58], people learn dynamics and kinematics in different contexts and depend on at least partially different neural systems [59]. Furthermore, even within the domains of kinematics and dynamics, parallel context-dependent learning is possible. For kinematics, consolidation is not disrupted when people experience opposing rotations while performing two different tasks (e.g., a continuous drawing task versus a reaching task) [60]. For dynamics, when two opposing force fields are presented at different hand positions, people can simultaneously learn both skills and switch between them [61]. Adapting to two force fields that are based on contextual cues takes extensive practice, and might be impossible under some circumstances [62]. In other situations, however, such as when random and frequent switching of context occurs, people
can learn to react accurately in two opposing, dynamics-dependent force fields, instructed only by nonspatial auditory and color cues [63].

Context effects can also be observed in the activity of M1 cells [64]. For example, Taylor et al. [18] trained monkeys to control the movement of a cursor in a three-dimensional virtual-reality environment, either by the movement of their hand or via a brain-machine interface that translated M1 activity into cursor movement. They found that many cells acquired different PIs for the two similar, yet contextually different, tasks, and that this difference evolved systematically over many days (Figure 4c). In a similar task, monkeys controlled a brain-machine interface and performed reach and grasp movements [19]. Changes in the strength of directional tuning, distribution of preferred directions and strength of correlations were evident upon switching between brain-controlled and hand-controlled tasks. Thus, for both perceptual and motor learning, neuronal activity reflects not only the physical properties of the stimulus or movement, but also information about the relevant context.

Concluding remarks

William of Ockham (c. 1285–1349), the medieval philosopher famous for formulating the principle of parsimony ('Ockham's razor'), would have wanted a unified account of perceptual and motor learning. The brain must solve problems within the constraints of its hardware: neurons and plastic synapses. It should not be surprising, therefore, that the solutions it has found for perceptual and motor learning resemble each other at Marr's level of implementation. The similarities discussed here for the algorithmic level are more intriguing, and they also reflect a basic fact about the brain: like the baseball batter described in the opening paragraph, we have but one brain, which must both do and view.

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References

Doctoral Thesis, Rony Paz

Results V


Discussion

In this dissertation I have examined the learning of new sensorimotor skills and their representation in the primary motor cortex of behaving primates. Learning is of prime interest in contemporary science because it is the most complex behavior in animals and enables adaptation to a continuously changing environment. It is a hallmark of human nature; our flexible behavior is perhaps the major reason for our relative evolutionary success. Learning is also a very useful scientific tool of investigation in itself. One can regard learning as a perturbation study, observing behavior during and after diverse perturbation types can reveal properties of the underlying mechanisms. I have used learning in both senses, as a perturbation paradigm to reveal properties of the neuronal mechanisms underlying sensorimotor behavior, and as the process that generates and modifies the neuronal representation of behavior to adjust to a changing environment. First, I would like to summarize briefly the important novel findings of my study and then discuss them comprehensively.

1. Monkeys learn and generalize visuomotor transformations in the same manner that humans do. This suggests that the planning of the movement itself, the internal representation and the transformations from sensory to motor are carried out by the same rules of computation.

2. Learning to compensate for directional errors in one direction did not transfer (generalize) to movements in other directions. In other words, learning is spatially local.

3. The findings explain the confined generalization of learning via relevant adjustments in the primitives of representation. Specifically, only cells with a preferred direction near the trained direction during learning modified their activity and did so only for movements to this direction.

4. The modification of activity was persistent between learning and subsequent performance of the transformations, suggesting a neuronal
correlate of working-memory; i.e., activity that supports the maintenance of the newly acquired internal representation for use in the near future.

5. This new internal representation was observed in a primary cortical area (MI). The novelty of this finding stems from the traditional role of primary areas in general and MI in particular. Specifically, MI was treated as an “upper motor neuron”. Several recent studies have shown its relation to more complex motor tasks; its involvement in learning, however, was only recently and indirectly shown and only for simple motor tasks.

6. Neuronal activity conveyed more information about direction of movement after learning than it did before it. Information was mainly gained for the direction experienced during learning.

7. The increase in information came about by an increase in the slope of neurons' tuning curves (increased sensitivity), rather than by a reduction in the variability (increased precision/reliability).

8. After learning, an external observer (the experimenter) could predict more accurately the actual direction of movement based on neuronal activity. Again, this improvement was specific to the trained direction.

9. In both the representational and algorithmic level, recent findings suggest that similar rules govern sensory and motor systems. These unifying principles facilitate the transformation from sensory to motor and provide further scientific confirmation for their correctness.

In sum, the experiments provide a framework for investigating how new sensorimotor transformations are acquired and represented in the primate brain. The findings show how primitives of representation determine properties of behavior and learning; provide insight into how sensorimotor transformations are carried out from both ends of the computation; and show ways in which learning paradigms can be used for scientific and clinical applications.
Learning and sensorimotor transformations are mediated by the primitives of representation

It is commonly accepted that neurons at both ends of the sensorimotor system serve as primitives of representation of simple physical features. Cells in the retina respond to light intensity in a specific area of the visual field and motor neurons in the spinal cord activate directly a specific set of muscles. We also know that the transformation from retinal coordinates to muscle coordinates can take place, because primates can perform accurate movements that are based on visual information, and studies have shown that the brain transforms visuospatial information into the appropriate motor commands (Soechting and Flanders, 1989; Kalaska et al., 1997; Buneo et al., 2002). These transformations between retinal and skeletomuscular reference frames are performed in several stages in a cascade of cortical areas, starting from the so-called "dorsal stream" of visual processing and then to frontal motor areas (Goodale and Milner, 1992); very abstractly the complete pathway is comprised of: retina/thalamus -> primary and higher visual areas in the occipital lobe -> areas in the parietal lobe -> high motor areas in the frontal lobe -> primary motor area -> spinal cord / muscles. In each area, a slightly different level of representation is implemented; changes can vary from the reference frame itself (i.e. coding of the object relative to eye/head/body/shoulder etc.), the width of the primitives (i.e. the width of the tuning functions) and their inter-connectivity.

It is worth dividing the transformations into two major types: extrinsic reference frames and intrinsic ones; together they form the complete sensorimotor transformation of coordinates. The extrinsic reference frames are those which concern the external coordinates: the transformation from retinal or eye-centered coordinates to the arm configuration (relative to the body / shoulder) that is needed to bring the hand to the target; this is also termed the inverse kinematic problem. The intrinsic reference frames are those which compute the needed muscle activations to achieve the required hand trajectory. This is also termed the inverse dynamic problem. Because neurons in MI modulate their activity as a function of hand direction in Cartesian coordinates (Georgopoulos et al., 1982; Moran and Schwartz, 1999a; Kakei et al., 1999), but also as a function of posture (Scott and Kalaska, 1995; Kakei et al., 1999), joint power (Scott et al., 2001) and muscles activity (Kakei et al., 1999); it is
highly likely that MI participates in both transformations to some extent. I will briefly describe how my results can be interpreted in a general computational framework, first for kinematics and then for dynamics; and then suggest a more specific interpretation.

A computational framework recently suggested for kinematic transformations relies on basis functions (Pouget and Snyder, 2000); a theory from nonlinear function approximation. Consider the transformation from eye-centered to joint-centered coordinates. This is a nonlinear function that takes as input the location of the object (target) on the retina together with the posture of the eye and computes the joint-centered configuration of the arm. It is possible to compute any function with an intermediate layer of neurons that serve as a basis functions; informally, they must span all possible inputs, and cannot be a linear combination of the inputs or of themselves (see (Pouget and Snyder, 2000)). A simple linear weighted summation of their input responses can approximate any nonlinear function; further, the different functions can be learned and implemented by altering the weights. For example, such an intermediate level of representation (“the basis function”) can possess Gaussian tuning curves to the object location on the eye, and be modulated by a sigmoid function of the eye position; i.e. gain-modulated. In Parietal areas, many neurons code the object location in eye-centered coordinates and are gain-modulated by the position of the eye, head, body and limb position (Cohen and Andersen, 2002); suggesting that this network of cortical areas participates in the transformation from visual input to several required reference frames (Pouget and Sejnowski, 1997) for different effectors (e.g. saccades, reaching, kicking) (Buneo et al., 2002; Scherberger et al., 2003).

For reaching movements, frontal motor areas should transform the reference frame used in parietal areas to a reference frame suitable for moving the arm; e.g. shoulder-based and joint-based. Accordingly, neurons in pre-motor and motor areas were found to be gain-modulated by posture signal (Caminiti et al., 1990; Boussaoud et al., 1993; Scott and Kalaska, 1997) and could suggest the transformation of coordinates (Ajemian et al., 2001). A possible explanation for my findings, therefore, is that the modulation observed during learning is actually a gain modulation. Before learning, when movements are tested to eight directions in space with the visual signal aligned with the direction of movement (standard mapping), a tuning curve is obtained for each neuron as a function of external direction. During learning, a third
parameter is manipulated and therefore the tuning curve can now be examined as a function of two parameters, hence the observed gain modulation. For example this third parameter can be, as suggested by parietal studies, the posture of the eyes. In standard reaching, the eyes follow the movement of the hand whereas in visuomotor rotational transformations the eyes follow the cursor which moves differently than the hand. From the point of view of reference frames, eye-dissociation-from-hand is a promising candidate for gain-modulating the tuning curve.

For the dynamics problem; i.e. the transformation from extrinsic to intrinsic coordinates, several families of models have been suggested: inverse and forward models; optimal controller e.g. minimum jerk/torque models and minimum variance; the equilibrium-point hypothesis and more (Kawato, 1999; Wolpert and Ghahramani, 2000; Flash and Sejnowski, 2001). To determine whether MI participates in these computations, the activity of its neurons must correlate (at least to some extent) with both extrinsic parameters; e.g. direction of movement and its speed and intrinsic ones; e.g. muscle activity, joint power. Indeed, many studies have correlated the activity with a plethora of variables and debated the reference frame in MI. In a recent experiment specifically designed to test this, Kakei et al (Kakei et al., 1999) found that neurons in pre-motor (PMv) are more sensitive to the external direction of movement (Kakei et al., 2001), while neurons in MI can be divided into three equally distributed populations: extrinsic-like (i.e. correlate with the external direction of movement, muscle-like (i.e. correlate with muscle activity – an intrinsic property), and 'gain modulated extrinsic-like', cells that are extrinsic-like but gain-modulated with different arm postures.

Following several modeling studies (Salinas and Abbott, 1995; Pouget and Snyder, 2000; Baraduc et al., 2001; Ajemian et al., 2001) this group has suggested that the gain modulated extrinsic-like cells could play a part in the coordination transformation network (Kakei et al., 2003). In such a scenario, pure extrinsic-like neurons that code for the external direction of movement project to extrinsic-like neurons that also receive input from a different system (e.g. one that is sensitive monotonically to the posture of the hand); this second level of neurons projects to the next level with a simple linear summation, resulting in neurons that are muscle-like. Thus, this network can transform extrinsic-like coordinates into intrinsic-like ones, via an intermediate network of gain-modulated extrinsic-like neurons (actually, this transformation can be implemented in the general framework of the previously
described basis function algorithm. However, several problems arise mainly because of the non-uniqueness of the solution and the existence of 'impossible' solutions i.e. it is an ill-posed problem, see (Jordan and Rumelhart, 1990; Pouget and Snyder, 2000; Wolpert and Ghahramani, 2000)).

The elevated firing rate I observed in MI after learning the visuomotor transformation could reflect a gain-modulation of extrinsic-like neurons. The same network that transforms the required end-point in space to required muscle activations now transforms it into different muscle activations as required by the rotation. During learning, the gain modulators projecting onto the proposed network alter their activity to produce the correct gain-modulation in the extrinsic-like cells. In turn, their linear summation will result in the correct activation of muscle-like cells. The correct gain activity can be learned via simple learning algorithms (e.g. delta-rules). This raises an interesting question of where these gain-modulators reside. They could be located either in 'higher' frontal areas that participate in learning, sub-cortical areas; e.g. basal-ganglia or even in pre-motor areas and MI itself. This question remains open.

The above mentioned interpretations concern gain-modulation of tuning curves. The first was based on the basis-functions approach and addressed kinematic transformations; the second was a more specific implementation of dynamic transformations. However, several limitations hinder adopting them completely: First, only cells with a preferred direction near the trained direction modulated their activity; second, I have found that almost all of these cells elevated their activity after learning and not only a third or so of them, as expected from the ratios described and suggested by the network configuration (Kakei et al., 2003); third, almost all cells elevated their activity and almost none decreased it; fourth, cells did not shift their preferred direction, as could be expected from muscle-like cells when dissociating between direction of movement in space and direction in some intrinsic reference frame (Kakei et al., 1999). Thus, although the aforementioned mechanisms use gain-modulation, it is hard to reconcile my findings with them. Instead, my results, with emphasis on the specificity of the sub-population of neurons that changed during learning, suggest a simpler, more straightforward interpretation.

Let us consider a network of neurons in MI that code for the direction of movement and is able to produce the correct movement. We do not care whether the actual code is for the external direction of movement (Schwartz and Moran, 2000; Georgopoulos and Ashe, 2000; Moran and Schwartz, 2000) and is only later
transformed into muscle activations or whether it is already in force / muscle / joint coordinates (Mussa-Ivaldi, 1988; Todorov, 2000a; Todorov, 2000b; Scott et al., 2001). This network consists of populations of cells with different preferred directions that span the space (in a continuum, a homogenous manner). The executed movement direction is calculated via a weighted sum of their activity. In the standard/default mapping, the strongly activated cells have a PD near the direction of the visual target, and will therefore result in movement in that direction. This default coupling between visual stimulus and movement direction could be due to pre-natal evolutionary programmed wiring that favors this visual-motor coupling, or due to everyday experience and development based associations (e.g. LTP) between a similar direction in the visual and motor levels.

When learning new rotational transformations, the brain learns that the observed visual target requires a different direction of movement. It therefore needs to produce this direction by altering the activity in the network of MI cells. There are three ways to do so:

(a) Shift the PDs of neurons in MI with PD near the visual target to that of the required hand direction. We can rule out this option because we did not observe any shift of PDs during and after learning (section IV). Interestingly, a study that examined adaptation to viscous force-fields in a specific joint configuration did not find shifts in PDs either (Gribble and Scott, 2002); whereas a study that examined adaptation to velocity-based force-fields for all directions did find such shifts (Li et al., 2001; Padoa-Schioppa et al., 2002). The difference could result from the confined learning to a small part of the space. Whereas global learning enables a rotation of all PDs so that the distribution remains homogenous and all directions are represented equally, rotating PDs only for a confined part of the space results in uneven representation of directions. This can harm most algorithms that rely on directional primitives (Deneve and Pouget, 2003) and result in a distorted directional performance (Scott et al., 2001).

(b) Rewire the input that comes from neurons with visual PD near the visual target direction (e.g. neurons from parietal and pre-motor areas) to cells in MI with PD near the required hand direction. In fact, while the mechanism is different, this option will appear as a PD shift when examined in the current experimental conditions. Thus we can rule it out as well. Moreover, this option has a major caveat. Rewiring is a type of plasticity that is very consuming biologically, usually demands a
longer time-course, and its extent in the adult brain is still debated (Buonomano and Merzenich, 1998). Further, the default mapping should still be available on demand – it is not wise to abandon it so easily to a different, experienced-once environment. Indeed, the very short time it takes to return to standard performance confirms this (i.e. aftereffects were evident only for 3-5 trials, section II). In other words, default and rotated mapping do not have an equal value -- the former is permanent and the latter is probably temporary.

(c) The third option is again, a gain modulation type of change, but a specific one. If the network sums the activity of the neurons in MI linearly to compute the final hand direction, then the network must now somehow "overcome" the default mapping. The suggestion is then that the higher activity for cells with PD near the required hand direction is intended to dominate the default activity produced by the cells with PD near the direction of the visual target – a competition between populations. This can come about either by external gain modulators that are activated during learning or by strengthening of synapses on specific cells, both easily reversible mechanisms. The fact that the modulation occurs only in preparation for movement and not during the movement itself provides further support for this idea, because it suggests that the role of this activity is only in determining the required direction prior to execution, whereas the movement itself is produced via the same pattern of muscle activations as in standard conditions.

Is this suggestion biologically plausible and can it occur in natural conditions? The simulations described in section IV (Paz R et al., 2002) provide some evidence that this is indeed the case. The simulations use the population vector algorithm which is a simple, biologically plausible algorithm that is a simplified version of a population code (Georgopoulos et al., 1988; Seung and Sompolinsky, 1993; Salinas and Abbott, 1994); and show that the elevated firing rate in a specific sub-population of neurons can account for the observed improvement in prediction after learning. Therefore, the neuronal changes we observed are sufficient to induce learning-mediated changes in behavior. Preliminary analysis and similar results from other studies (Georgopoulos et al., 1989; Cisek and Scott, 1999) show that the population vector can rotate under similar conditions until it reaches the required direction. Naturally, this just shows the plausibility of the interpretation, we cannot conclude that the brain actually uses a similar algorithm to the one used by the population vector approach.
Time course and location of the impact of learning

My finding that learning-related changes did occur in the primary motor cortex is somewhat surprising (sections II, III, V). Traditionally, the primary motor cortex was regarded as an “upper motor neuron”, meaning it only sends simple activation signals to the spinal cord and muscles. This strict characterization now seems obsolete because many studies have found a variety of tasks and parameters that correlate with MI activity; e.g. the aforementioned extrinsic parameters of movement (Moran and Schwartz, 1999a; Kakei et al., 2003), serial order tasks (Carpenter et al., 1999), bimanual movements (Donchin et al., 1998; Steinberg et al., 2002), context related activity (Ben Shaul et al., 2004), mental rotation (Georgopoulos et al., 1989), and more (Georgopoulos, 1991; Scott, 2003). These studies suggest a role for MI which is far more complex than originally thought. Learning was thought to take place either in sub-cortical areas such as the cerebellum and the basal-ganglia, or in higher cortical areas; but recent indirect evidence suggests that it can also be mediated by MI (Jenkins et al., 1994; Karni et al., 1995; Sanes and Donoghue, 2000; Muellbacher et al., 2001). The question then is: can the role of MI be extended even beyond the complex tasks recently described into actual participation in learning? Or are the changes we observed a mere reflection of inputs from other areas that are traditionally involved in learning? To answer that we should consider what possible role a primary area could have in learning.

From the viewpoint of a computational machine, the brain can be seen either as: (a) a cluster of areas with different functional roles and a hierarchical design; here the transformation of input to output is structured and can be conceptually described as: sensory input -> primary sensory areas -> higher areas -> primary motor areas -> motor output; and each area in the sequence has a distinctive function. Or as: (b) one complete network with no real segregation between areas. In this view all the brain functions in parallel to perform the input-output processing. This extreme point of view leaves no room for discussing what role a primary area should have in learning, because all areas function in the same way inside a large network and do all the tasks together. In other words, there are no primary areas in this scenario. As is always the case in real life, the correct answer lies somewhere in between these two extreme points of view. The above mentioned findings about the more complex role for MI in all aspects of behavior and movement shows that the pure hierarchical view might be
too extreme, because even primary areas participate in the network of higher brain functions. Nevertheless, it is still commonly accepted that the traditional hierarchical view mostly holds and primary areas are anatomically and physiologically at the end of the computation; this can be seen from their response properties to stimuli/movement and from the anatomical connections they have with the thalamus (for sensory) and spinal cord (for motor) responses.

From the standpoint of an area that is at the end of the hierarchy, a primary area is likely to have two roles in the course of learning: first, it can serve at the early phases of learning to supply more information and control on the task; and second, it may possess an “internal representation” of the learned task at the final phases of learning.

Primary areas are very suitable for the first role because they have direct knowledge about the external world and its features, whether it is the input in sensory or the output in motor. For example, the properties of feature search in a visual scene, e.g. the set-size effect on speed and the elementary nature of the features that were found to pop-out; led to the suggestion that this search mode (Treisman and Gelade, 1980) is mediated directly by low-level processing stages i.e. primary visual areas (Sagi and Julesz, 1987; Kastner et al., 1997; Nothdurft et al., 1999) (but see (Hochstein and Ahissar, 2002) for further discussion). Moreover, attention mechanisms that are required for initial stages of perceptual learning and memory (Shiu and Pashler, 1992; Ahissar and Hochstein, 1993; Morrone et al., 2002) were recently shown to modulate activity in primary visual areas (Ito and Gilbert, 1999; Crist et al., 2001).

From the motor perspective, when learning new environments, humans (and animals) use a strategy of stabilization (Thoroughman and Shadmehr, 1999; Osu et al., 2002), they use increased viscoelasticity to stabilize their movements so that unexpected perturbations will not disrupt their movements completely. That means that MI is likely to participate by generating the movement continuously (rather than “send and forget” the motor command), with more muscles participating and higher co-contraction. This is indeed what we observed (section II), in the early phases of learning: activity in MI was higher during the execution of the movement and it was matched with higher muscle activation and co-contraction. The increased attention at early phases of learning could also contribute to the increased activity, mediated perhaps by other cortical areas (Rowe et al., 2002).
The primary areas are also very suitable for the second role, possessing an “internal representation” of the learned task. By “internal representation” I refer to a neuronal mechanism that represents a complex scenario. At the beginning of learning, the correct response is produced via increased control, complex computation, attention, and feedback correction mechanisms. As learning progresses, a specific “internal representation” of the new task is formed in the brain for quicker and safer re-production on demand. A primary area that sits at the end of the computational hierarchy and is sensitive to the small details (primitives) of the environment can process a newly learned sensory skill faster and earlier, or can produce a newly learned motor skill faster and with less computation.

Consistent with this view, studies of perceptual learning have suggested that the initial stage of learning typically occurs in high-level areas and might involve perceiving the "gist" of the task; but as learning progresses, subsequent modifications occur at lower-level (primary) areas (Karni and Sagi, 1993; Ahissar, 2001; Gilbert et al., 2001). The final location of the internal representation of the learned skill depends on several factors, such as task difficulty and training procedure (Ahissar and Hochstein, 1997; Liu, 1999) and suggests that visual perception advances in the reverse hierarchical direction (Hochstein and Ahissar, 2002). Evidence that perceptual skills are finally learned at primary areas comes from psychophysical and physiological studies (Gilbert et al., 2001). Behavioral studies test the generalization of learning and use its specificity as indicative of the learning site (Ahissar, 2001). For example, characteristics of learning to search visually a novel complex stimuli may reflect a shift in the cortical representation of complex features toward earlier stages in the visual pathway (Sigman and Gilbert, 2000). Physiological studies probe primary areas for changes in activity. For example, in the primary visual area (V1), neurons modulate their activity in a way that correlates with the acquisition of an internal representation of stimulus location on the basis of previous knowledge (Sharma et al., 2003); and overall activity is increased selectively for the trained stimuli (Furmanski et al., 2004). The similarities between sensory and motor learning (section V) (Paz R et al., 2004) suggest that similar processing can occur in the motor hierarchy and that MI is a good candidate for holding a representation of a newly learned motor skill.

In particular, in the case of sensorimotor tasks an “internal representation” is a neuronal mechanism that reflects the input-output relationship in the new environment
An industry analogy would be a bunch of smart people sitting in a factory; each time an order comes in, they all assemble it together with great care and thinking. Suddenly one of them notices that all the orders are alike and shouts “let us build a machine that by pressing a button produces exactly the required order”. This machine would be the “internal representation” in the factory of the new input-output relationship. In this study, the internal representation reflects a rotated arm movement in response to a presented target. In line with the suggestion that the representation is formed in a primary area, we found that the specific change in the activity of MI occurred only in later phases of learning and even paralleled the behavioral plateau (i.e. when performance was as required). Moreover, these changes occurred in a period of time just before movement execution; several studies have suggested that activity in motor cortices at this period reflects movement preparation and planning (Kurata and Wise, 1988; Alexander and Crutcher, 1990; Shen and Alexander, 1997; Johnson et al., 1999; Padoa-Schioppa et al., 2002).

For emphasis, let us contrast the two types of change: the first was an increase in activity that occurred during the movement execution in the early phases of learning and therefore reflects a strategy to control and stabilize performance at the initial stage of learning. The second is a specific change (only in sub-populations of neurons with properties matching the learned task, see the previous section of the discussion) that occurs in preparation for movement (remember the “send and forget” command that the brain uses for highly trained movements) and is evident only at later phases of learning when behavioral performance is complete. This could reflect the internal representation of the new input-output relationship in the environment.

Finally, the new representation of the learned skill must be kept in memory for future use. A demonstration that the newly learned skill is indeed kept in working memory for 1-2 hours is shown by the immediate re-learning of the transformation (section II). However, if it is to be saved for longer time-scale, the memory must undergo a consolidation process where memories are transferred from a fragile state into a stable state of long-term memory (McGaugh, 2000); and motor skills undergo a consolidation process as well (Brashers-Krug et al., 1996). Taking into consideration the aforementioned argument – why internal representation should be kept in primary areas – then it is better that the long-term memory would also reside in these areas. There is some evidence supporting this claim (Karni et al., 1998) but others that challenge it (Shadmehr and Holcomb, 1997). However, it was recently shown that the
early phases of consolidation require MI (Muellbacher et al., 2002). In my study, we found that the specific changes observed were persistent between the learning and re-performance of the transformation. This can be interpreted as a direct demonstration that the internal representation is kept in MI until it can be further consolidated, either to other brain areas or back and forth to MI itself. However, as my study was not specifically designed to test for consolidation, I cannot conclude that this activity is indeed the early stages of consolidation. Rather, it is some sort of working memory that lasts while the animal needs it; i.e. during the experiment.

My study leaves one puzzle unsolved. In the previous section I claimed that the observed learning-related changes can account for correct performance under the visuomotor transformation; i.e. generating the required rotated hand movement. In other words, I have argued that the complex modulation is the internal representation of the learned skill. In this section I have described the persistence of these changes and their hypothesized role in working-memory. In other words, the internal representation is maintained in working-memory to be utilized in near future use of this skill. However, that means that the internal representation of the visuomotor transformation was present while the monkeys performed under the standard mapping conditions. How can they perform accurately on the standard task when the nonstandard representation still resides in MI? One possibility is that just as in the beginning of learning a strategy of increased control and viscoelasticity is used to produce the movement; the same strategy applies immediately after learning and therefore overrides the active internal representation until it "washes out". Unfortunately, we did not record enough standard trials after learning to see when exactly this activity returned to normal (section II shows indirectly that a full night did the job). Support for the notion that neuronal activity might be delayed in returning to normal in relation to behavior comes from studies of learning new visuomotor associations. These studies have shown that learning-related changes in neuronal activity lag behind behavioral performance in several trials (Mitz et al., 1991; Brasted and Wise, 2004); the reason for this lag is still unknown. An alternative explanation could be a gating mechanism further downstream that can inhibit the output of these neurons in the standard mapping that comes immediately after learning. Such mechanisms were observed in other systems (Seidemann et al., 1998) but we did not directly test or identify them in the current experiment.
Using the effects of learning

A recent line of studies suggest a pragmatic – clinical application for motor research. If external parameters of the movement (e.g. direction and extent) are represented by neuronal activity in motor areas, then one can deduce the actual movement just by looking at the neuronal activity. Whereas predicting the movement from neuronal activity was demonstrated a few decades ago (Georgopoulos et al., 1988) and was considered a support for the characterization of MI’s role in producing the movement, only recently was it used as a goal in itself. The idea is to design and implement a neural prosthesis, a robot-hand that is controlled directly by brain activity and can be a substitute for amputees and paraplegics (Chapin, 2000; Donoghue, 2002; Taylor et al., 2002; Nicolelis, 2003). In general, this seems like an engineering goal rather than a scientific one and it is not clear what line of investigation is best. On one hand, a complete understanding of the motor system and what cells code for will allow for the accurate design of algorithms that predict the movement based on brain activity (Schwartz et al., 2001; Sanger, 2003). On the other hand, science can benefit from the engineering approach because it accelerates advances in technology (Nicolelis et al., 2003; Obeid et al., 2004); and answers scientific questions along the way (Chapin et al., 1999; Wessberg et al., 2000; Taylor et al., 2002; Serruya et al., 2003).

My study provides two ways in which a scientific enquiry can aid this clinical engineering problem: first, by identifying an important parameter of the neural code. As detailed in section III, I have found that neurons increase the slope of their tuning curve rather than decrease the noise (variability) at the trained direction and this was correlated with an increase in information content. Because neurons did so as a result of learning, it suggests that this is an important feature of the neural code. Thus, it makes sense to design algorithms that rely heavily on the slope of the tuning curve (i.e. the sensitivity of the averaged activity between proximal directions) as their main contributor parameter. In other words, if we have found a factor that interests the neurons themselves, because they alter it during learning; it is better to utilize it for our external calculations. The learning is of high importance here; one could find many correlations between aspects of neuronal activity and movement parameters but
the learning provides additional clues as to which of these parameters is the real “intention” of the system – to be used further downstream. Note though that other aspects of the neural code could be of importance as well. For example, correlation between pairs of neurons (Hatsopoulos et al., 1998); however, a preliminary examination of cross-correlations and noise-correlations did not reveal any promising results.

The second way adopts a "utilitarian" approach, which is based on my findings. Section III shows that neuronal activity conveyed more information about movement direction after learning than it did before it. An important finding was that this increased information was evident exclusively for the trained direction, while information on other arbitrary directions remained more or less the same. To complement this finding, I showed that using two standard algorithms (Population vector and Maximum a posteriori predictor) we could predict the movement direction more accurately after learning than before it. Again, better results were obtained only for the trained direction and not for others. This specificity of improvement in encoding and decoding can be of use when designing and implementing neural prostheses because of the natural complexity of our arm movements. Arm movements are performed in 3 dimensions (6, if one takes into account the end-point rotation coordinates) and an arm has >7 degrees of freedom. Moreover, many times the whole path of the movement is important, as well as the configuration of the whole arm, and not only the end-point location. Because humans perform a wide variety of complex voluntary arm movements and the current line of studies focuses on recording and reconstructing natural movements in 3-D, it seems hard to believe that a complete recovery of motor function will be available in the near future. This is supplemented by technological difficulties (implanting the electrodes, number of channels, transmitting the signal, computation power, real-time computation etc.).

My results suggest that if an animal learns to perform a specific set of movements then we can enable recording from fewer neurons to gain more information and reconstruct this specific set of movements better (section III,IV). This is supported indirectly by other studies that show that training indeed improves reconstruction performance in such scenarios (Taylor et al., 2002;Helms Tillery et al., 2003;Carmena et al., 2003). Whereas the long-term vision is somewhat unclear, the clinical implications are now feasible: a pre-defined set of useful movements is a big improvement for an amputee or paraplegic.
Critical issues have yet to be addressed in further research. For example, does learning induced improvement works for a bigger set of movements? Does it work for more complex movements? What areas are necessary and sufficient to record from? How can we train an amputee / paraplegic? In this sense, this study exposes only the tip of the iceberg by demonstrating the plausibility of the idea that learning may help developing brain-driven applications.
Bibliography


