Neuronal responses characterized by regular tuning curves are typically assumed to arise from structured synaptic connectivity. However, many responses exhibit both regular and irregular components. To address the relationship between tuning curve properties and underlying circuitry, we analyzed neuronal activity recorded from primary motor cortex (M1) of monkeys performing a 3D arm posture control task and compared the results with a neural network model. Posture control is well suited for examining M1 neuronal tuning because it avoids the dynamic complexity of time-varying movements. As a function of hand position, the neuronal responses have a linear component, as has previously been described, as well as heterogeneous and highly irregular nonlinearities. These nonlinear components involve high spatial frequencies and therefore do not support explicit encoding of movement parameters. Yet both the linear and nonlinear components contribute to the decoding of EMG of major muscles used in the task. Remarkably, despite the presence of a strong linear component, a feedforward neural network model with entirely random connectivity can replicate the data, including both the mean and distributions of the linear and nonlinear components as well as several other features of the neuronal responses. This result shows that smoothness provided by the regularity in the inputs to M1 can impose apparent structure on neural responses, in this case a strong linear (also known as cosine) tuning component, even in the absence of ordered synaptic connectivity.
directions are sampled unevenly and at a coarse resolution. Here we describe a Bayesian estimation procedure that improves the accuracy of curve-shape estimation, even when the curve is sampled unevenly and at a very coarse resolution. Using this approach we characterize the movement direction tuning curves in the supplementary motor area (SMA) of behaving monkeys. We compare the SMA tuning curves to tuning curves of neurons from the primary motor cortex (M1) of the same monkeys, showing that the tuning curves of the SMA neurons tend to be narrower and shallower. We also show that these characteristics do not depend on the specific location in each region.


Summary Neural oscillations in the low-gamma range (30?50 Hz) have been implicated in neuronal synchrony, computation, behavior, and cognition. Abnormal low-gamma activity, hypothesized to reflect impaired synchronization, has been evidenced in several brain disorders. Thus, understanding the relations between gamma oscillations, neuronal synchrony and behavior is a major research challenge. We used a brain-machine interface (BMI) to train monkeys to specifically increase low-gamma power in selected sites of motor cortex to move a cursor and obtain a reward. The monkeys learned to robustly generate oscillatory gamma waves, which were accompanied by a dramatic increase of spiking synchrony of highly precise spatiotemporal patterns. The findings link volitional control of LFP oscillations, neuronal synchrony, and the behavioral outcome. Subjects' ability to directly modulate specific patterns of neuronal synchrony provides a powerful approach for understanding neuronal processing in relation to behavior and for the use of BMIs in a clinical setting.

2012


Some motor tasks, if learned together, interfere with each other's consolidation and subsequent retention, whereas other tasks do not. Interfering tasks are said to employ the same internal model whereas noninterfering tasks use different models. The division of function among internal models, as well as their possible neural substrates, are not well understood. To investigate these questions, we compared responses of single cells in the primary motor cortex and premotor cortex of primates to interfering and noninterfering tasks. The interfering tasks were visuomotor rotation followed by opposing visuomotor rotation. The noninterfering tasks were visuomotor rotation followed by an arbitrary association task. Learning two noninterfering tasks led to the simultaneous formation of neural activity typical of both tasks, at the level of single neurons. In contrast, and in accordance with behavioral results, after learning two interfering tasks, only the second task was successfully reflected in motor cortical single cell activity. These results support the hypothesis that the representational capacity of motor cortical cells is the basis of behavioral interference and division between internal models.

2011

The brain has a remarkable ability to learn and adjust behavior. For instance, the brain can adjust muscle activation to cope with changes in the environment. However, the neuronal mechanisms behind this adaptation are not clear. To address this fundamental question, this study examines the neuronal basis of long-term sensorimotor learning by recording neuronal activity in the primary motor cortex of monkeys during a long-term adaptation to a force-field perturbation. For 5 consecutive days, the same perturbation was applied to the monkey's hand when reaching to a single target, whereas movements to all other targets were not perturbed. The gradual improvement in performance over these 5 days was correlated to the evolvement in the population neuronal signal, with two timescales of changes in single-cell activity. Specifically, one subgroup of cells showed a relatively fast increase in activity, whereas the other showed a gradual, slower decrease. These adapted patterns of neuronal activity did not involve changes in directional tuning of single cells, suggesting that adaptation was the result of adjustments of the required motor plan by a population of neurons rather than changes in single-cell properties. Furthermore, generalization was mostly expressed in the direction of the required compensatory force during adaptation. Altogether, the neuronal activity and its generalization accord with the adapted motor plan.


Continuous high-frequency deep brain stimulation (DBS) is a widely used therapy for advanced Parkinson's disease (PD) management. However, the mechanisms underlying DBS effects remain enigmatic and are the subject of an ongoing debate. Here, we present and test a closed-loop stimulation strategy for PD in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) primate model of PD. Application of pallidal closed-loop stimulation leads to dissociation between changes in basal ganglia (BG) discharge rates and patterns, providing insights into PD pathophysiology. Furthermore, cortico-pallidal closed-loop stimulation has a significantly greater effect on akinesia and on cortical and pallidal discharge patterns than standard open-loop DBS and matched control stimulation paradigms. Thus, closed-loop DBS paradigms, by modulating pathological oscillatory activity rather than the discharge rate of the BG-cortical networks, may afford more effective management of advanced PD. Such strategies have the potential to be effective in additional brain disorders in which a pathological neuronal discharge pattern can be recognized.


The human primary motor cortex (M1) is robustly activated during visually guided hand movements. M1 multivoxel patterns of functional MRI activation are more correlated during repeated hand movements to the same targets than to greatly differing ones, and therefore potentially contain information about movement direction. It is unclear, however, whether direction specificity is due to the motor command, as implicitly assumed, or to the visual aspects of the task, such as the target location and the direction of the cursor's trajectory. To disambiguate the visual and motor components, different visual-to-motor transformations were applied during an fMRI scan, in which participants made visually guided hand movements in various directions. The first run was the "baseline" (i.e., visual and motor mappings were matched); in the second run ("rotation"), the cursor movement was rotated by 45° with respect to the joystick movement. As expected, positive correlations were seen between the M1 multivoxel patterns
evoked by the baseline run and by the rotation run, when the two movements were matched in their movement direction but the visual aspects differed. Importantly, similar correlations were observed when the visual elements were matched but the direction of hand movement differed. This indicates that M1 is sensitive to both motor and visual components of the task. However, repeated observation of the cursor movement without concurrent joystick control did not elicit significant activation in M1 or any correlated patterns of activation. Thus, visual aspects of movement are encoded in M1 only when they are coupled with motor consequences.


Previous studies support the notion that sensorimotor learning involves multiple processes. We investigated the neuronal basis of these processes by recording single-unit activity in motor cortex of non-human primates (Macaca fascicularis), during adaptation to force-field perturbations. Perturbed trials (reaching to one direction) were practiced along with unperturbed trials (to other directions). The number of perturbed trials relative to the unperturbed ones was either low or high, in two separate practice schedules. Unsurprisingly, practice under high-rate resulted in faster learning with more pronounced generalization, as compared to the low-rate practice. However, generalization and retention of behavioral and neuronal effects following practice in high-rate were less stable; namely, the faster learning was forgotten faster. We examined two subgroups of cells and showed that, during learning, the changes in firing-rate in one subgroup depended on the number of practiced trials, but not on time. In contrast, changes in the second subgroup depended on time and practice; the changes in firing-rate, following the same number of perturbed trials, were larger under high-rate than low-rate learning. After learning, the neuronal changes gradually decayed. In the first subgroup, the decay pace did not depend on the practice rate, whereas in the second subgroup, the decay pace was greater following high-rate practice. This group shows neuronal representation that mirrors the behavioral performance, evolving faster but also decaying faster at learning under high-rate, as compared to low-rate. The results suggest that the stability of a new learned skill and its neuronal representation are affected by the acquisition schedule.


Sensory-motor learning is commonly considered as a mapping process, whereby sensory information is transformed into the motor commands that drive actions. However, this directional mapping, from inputs to outputs, is part of a loop; sensory stimuli cause actions and vice versa. Here, we explore whether actions affect the understanding of the sensory input that they cause. Using a visuo-motor task in humans, we demonstrate two types of learning-related behavioral effects. Stimulus-dependent effects reflect stimulus-response learning, while action-dependent effects reflect a distinct learning component, allowing the brain to predict the forthcoming sensory outcome of actions. Together, the stimulus-dependent and the action-dependent learning components allow the brain to construct a complete internal representation of the sensory-motor loop.


When faced with unpredictable environments, the human motor system has been shown to develop optimized adaptation strategies that allow for online adaptation during the control process. Such online adaptation is to be contrasted to slower over-trial learning that corresponds to a trial-by-trial update of the
movement plan. Here we investigate the interplay of both processes, i.e., online adaptation and over-trial learning, in a visuomotor experiment performed by macaques. We show that simple non-adaptive control schemes fail to perform in this task, but that a previously suggested adaptive optimal feedback control model can explain the observed behavior. We also show that over-trial learning as seen in learning and aftereffect curves can be explained by learning in a radial basis function network. Our results suggest that both the process of over-trial learning and the process of online adaptation are crucial to understand visuomotor learning.


In monkeys, neurons in the hand representation of the primary motor cortex (M1) are often tuned to the direction of hand movement, and there is evidence that these neurons are clustered according to their "preferred" direction of movement. However, this organizational principle has yet to be demonstrated in M1 of humans. We conducted a functional magnetic resonance imaging (fMRI) study in which participants used a joystick to move a cursor from a central origin to one of five equidistant targets. The fMRI signal of individual voxels was sensitive to the directional aspects of the reaching task and manifested direction-specific adaptation. Furthermore, the correlation between multivoxel patterns of responses for different movement directions depended on the angular distance between them. We conclude that M1 neurons are likely to be organized in clusters according to their preferred direction, since only such a coarse-grained representation can lead to directional selectivity of voxels, encompassing millions of neurons. A simple model that estimates cluster size suggests that the diameter of these clusters is on the order of a few hundred micrometers.


Activity of single neurons in the motor cortex has been shown to change during acquisition of motor skills. We previously reported that the combined activity of cell ensembles in the motor cortex of monkeys (Macaca fascicularis) evolves during adaptation to a novel force field perturbation to encode the direction of compensatory force when reaching to visual targets. We also showed that the population directional signal was altered by the available sensory feedback. Here, we examined whether traces of such activity would linger on to later constitute motor memories of the newly acquired skill and whether memory traces would differ depending on feedback. We found that motor-cortical cell ensembles retained features of their adaptive activity pattern in the absence of perturbation when reaching to both learned and unlearned targets. Moreover, the preferred directions of these cells rotated in the direction of force field while the entire population of cells produced no net rotation of preferred direction when returning to null-field reaches. Whereas the activity pattern and preferred direction rotations were comparable with and without visual feedback, changes in tuning amplitudes differed across feedback conditions. Last, savings in behavioral performance and neuronal activity during later reexposure to force field were apparent. Overall, the findings reflect a novel representation of motor memory by cell ensembles and indicate a putative role of the motor cortex in early acquisition of motor memory.
Learning motor skills entails adaptation of neural computations that can generate or modify associations between sensations and actions. Indeed, humans can use different strategies when adapting to dynamic loads depending on available sensory feedback. Here, we examined how neural activity in motor cortex was modified when monkeys made arm reaches to a visual target and locally adapted to curl force field with or without visual trajectory feedback. We found that firing rates of a large subpopulation of cells were consistently modulated depending on the distance of their preferred direction from the learned movement direction. The newly acquired activity followed a cosine-like function, with maximal increase in directions that opposed the perturbing force and decrease in opposite directions. As a result, the combined neuronal activity generated an adapted population vector. The results suggest that this could be achieved without changing the tuning properties of the cells. This population directional signal was however altered in the absence of visual feedback; while the cosine pattern of modulation was maintained, the population distributions of modulated cells differed across feedback consistent with the different trajectory shapes. Finally, we predicted generalization patterns of force-field learning based on the cosine-like modulation. These conformed to reported features of generalization in humans, suggesting that the generalization function was related to the observed rate modulations in the motor cortex. Overall, the findings suggest that the new combined activation of neuronal ensembles could underlie the change in the internal model of movement dynamics in a way that depends on available sensory feedback and chosen strategy.


Motor control and adaptation are multi-determinate processes with complex interactions. This is reflected for example in the ambiguous nature of interactions during sequential adaptation of reaching under kinematics and dynamics perturbations. It has been suggested that perturbations based on the same kinematic parameter interfere. Others posited that opposing motor adjustments underlie interference. Here, we examined the influence of discordances in task and in motor adjustments on sequential adaptations to visuomotor rotation and viscous force field perturbations. These two factors - perturbation direction and task discordance - have been examined separately by previous studies, thus the inherent difficulty to identify the roots of interference. Forty-eight human subjects adapted sequentially to one or two types of perturbations, of matched or conflicting directions. We found a gradient of interaction effects based on perturbation direction and task discordance. Perturbations of matched directions showed facilitation while perturbations of opposite directions, which required opposing motor adjustments, interfered with each other. Further, interaction effects increased with greater task discordance. We also found that force field and visuomotor rotation had mutual anterograde and retrograde effects. However, we found independence between anterograde and retrograde interferences between similar tasks. The results suggest that the newly acquired internal models of kinematic and dynamic perturbations are not independent but they share common neuronal resources and interact between them. Such overlap does not necessarily imply competition of resources. Rather, our results point to an additional principle of sensorimotor adaptation allowing the system to tap or harness common features across diverse sensory inputs and task contexts whenever available.
The study of complex information processing systems requires appropriate theoretical tools to help unravel their underlying design principles. Information theory is one such tool, and has been utilized extensively in the study of the neural code. Although much progress has been made in information theoretic methodology, there is still no satisfying answer to the question: "What is the information that a given property of the neural population activity (e.g., the responses of single cells within the population) carries about a set of stimuli?" Here, we answer such questions via the minimum mutual information (MinMI) principle. We quantify the information in any statistical property of the neural response by considering all hypothetical neuronal populations that have the given property and finding the one that contains the minimum information about the stimuli. All systems with higher information values necessarily contain additional information processing mechanisms and, thus, the minimum captures the information related to the given property alone. MinMI may be used to measure information in properties of the neural response, such as that conveyed by responses of small subsets of cells (e.g., singles or pairs) in a large population and cooperative effects between subunits in networks. We show how the framework can be used to study neural coding in large populations and to reveal properties that are not discovered by other information theoretic methods.

The basal ganglia network is divided into two functionally related subsystems: the neuromodulators and the main axis. It is assumed that neuromodulators adjust cortico-striatal coupling. This adjustment might depend on the response properties and temporal interactions between neuromodulators. We studied functional interactions between simultaneously recorded pairs of neurons in the basal ganglia while monkeys performed a classical conditioning task that included rewarding, neutral, and aversive events. Neurons that belong to a single neuromodulator group exhibited similar average responses, whereas main axis neurons responded in a highly diverse manner. Dopaminergic neuromodulators transiently increased trial-to-trial (noise) correlation following rewarding but not aversive events, whereas cholinergic neurons of the striatum decreased their trial-to-trial correlation. These changes in functional connectivity occurred at different epochs of the trial. Thus, the coding scheme of neuromodulators (but not main axis neurons) can be viewed as a single-dimensional code that is further enriched by dynamic neuronal interactions.

Previous studies have rarely tested whether the activity of high-frequency discharge (HFD) neurons of the basal ganglia (BG) is modulated by expectation, delivery, and omission of aversive events. Therefore the full value domain encoded by the BG network is still unknown. We studied the activity of HFD neurons of the globus pallidus external segment (GPe, n=310), internal segment (GPI, n=149), and substantia nigra pars reticulata (SNr, n=145) in two monkeys during a classical conditioning task with cues predicting the probability of food, neutral, or airpuff outcomes. The responses of BG (HFD) neurons were long-lasting and diverse with coincident increases and decreases in discharge rate. The population responses to reward-related events were larger than the responses to aversive and neutral-related events. The latter responses were similar, except for the responses to actual airpuff delivery. The fraction of responding cells was larger for reward-related events, with better discrimination between rewarding and
aversive trials in the responses with an increase rather than a decrease in discharge rate. \{GPe\} and \{GPi\} single units were more strongly modulated and better reflected the probability of reward- than aversive-related events. \{SNr\} neurons were less biased toward the encoding of the rewarding events, especially during the outcome epoch. Finally, the latency of \{SNr\} responses to all predictive cues was shorter than the latency of pallidal responses. These results suggest preferential activation of the \{BG\} \{HFD\} neurons by rewarding compared with aversive events.


Neurons in all brain areas exhibit variability in their spiking activity. Although part of this variability can be considered as noise that is detrimental to information processing, recent findings indicate that variability can also be beneficial. In particular, it was suggested that variability in the motor system allows for exploration of possible motor states and therefore can facilitate learning and adaptation to new environments. Here, we provide evidence to support this idea by analyzing the variability of neurons in the primary motor cortex \{(M1)\} and in the supplementary motor area \{(SMA-proper)\} of monkeys adapting to new rotational visuomotor tasks. We found that trial-to-trial variability increased during learning and exhibited four main characteristics: (1) modulation occurred preferentially during a delay period when the target of movement was already known, but before movement onset; (2) variability returned to its initial levels toward the end of learning; (3) the increase in variability was more apparent in cells with preferred movement directions close to those experienced during learning; and (4) the increase in variability emerged at early phases of learning in the \{SMA,\} whereas in M1 behavior reached plateau levels of performance. These results are highly consistent with previous findings that showed similar trends in variability across a population of neurons. Together, the results strengthen the idea that single-cell variability can be much more than mere noise and may be an integral part of the underlying mechanism of sensorimotor learning.


Computational models of motor control have often explained the straightness of horizontal planar reaching movements as a consequence of optimal control. Departure from rectilinearity is thus regarded as sub-optimal. Here we examine if subjects may instead select to make curved trajectories following adaptation to force fields and visuomotor rotations. Separate subjects adapted to force fields with or without visual feedback of their hand trajectory and were retested after 24 hours. Following adaptation, comparable accuracies were achieved in two ways: with visual feedback, adapted trajectories in force fields were straight whereas without it, they remained curved. The results suggest that trajectory shape is not always straight, but is also influenced by the calibration of available feedback signals for the state estimation required by the task. In a follow-up experiment, where additional subjects learned a visuomotor rotation immediately after force field, the trajectories learned in force fields (straight or curved) were transferred when directions of the perturbations were similar but not when directions were opposing. This demonstrates a strong bias by prior experience to keep using a recently acquired control policy that continues to produce successful performance inspite of differences in tasks and feedback conditions. On relearning of force fields on the second day, facilitation by intervening visuomotor rotations occurred only when required motor adjustments and calibration of feedback signals were similar in both tasks. These results suggest that both the available feedback signals and prior history of learning influence the choice and maintenance of control policy during adaptations.
The use of sensorimotor adaptation and learning paradigms in psychophysical and electrophysiological experiments can help to shed light on two fundamental questions. First, what are the computations that control sensorimotor behavior and, second, what are the neuronal mechanisms and representations underlying newly learned sensorimotor skills? We describe experiments that combined behavioral and electrophysiologic techniques and discuss implication of the results to three main questions: How do neuronal primitives of representation affect performance and learning? Do pre-motor and primary motor cortices form a hierarchy of computation, with different roles during learning and motor performance? How do these different cortical areas and the representations of movement change during the different stages of learning and memory formation?


Neurons in the motor areas of cortex play a key role in associating sensory instructions with movements. However, their ability to acquire and maintain representations of novel stimulus features, especially when these features are behaviorally relevant, remains unknown. We investigated neuronal changes in these areas during and after associative learning, by training monkeys on a novel reaching task that required associating target colors with movement directions. Before and after learning, the monkeys performed a well known center-out task. We found that during learning, up to 48% of the neurons developed learning-related responses, differentiating between the associative task and the center-out task, although movement kinematics were the same. After learning, on returning to the center-out task in which color was irrelevant, many of these neurons maintained their response to the associative task; they displayed novel sensitivity to the color of the target that was relevant during learning. These neuronal responses prevailed in both the primary motor cortex and the ventral and dorsal premotor cortices, without degrading the information that the neurons firing carried about movement direction. Our results show that motor cortical neurons can rapidly develop and maintain sensitivities to novel arbitrary sensory features such as color, when such features are behaviorally relevant.


Midbrain dopaminergic neurons \{DANs\} typically increase their discharge rate in response to appetitive predictive cues and outcomes, whereas striatal cholinergic tonically active interneurons \{TANs\} decrease their rate. This may indicate that the activity of \{TANs\} and \{DANs\} is negatively correlated and that \{TANs\}
can broaden the basal ganglia reinforcement teaching signal, for instance by encoding worse than predicted events. We studied the activity of 106 {DANs} and 180 {TANs} of two monkeys recorded during the performance of a classical conditioning task with cues predicting the probability of food, neutral, and air puff outcomes. {DANs} responded to all cues with elevations of discharge rate, whereas {TANs} depressed their discharge rate. Nevertheless, although dopaminergic responses to appetitive cues were larger than their responses to neutral or aversive cues, the {TAN} responses were more similar. Both {TANs} and {DANs} responded faster to an air puff than to a food outcome; however, {DANs} responded with a discharge elevation, whereas the {TAN} responses included major negative and positive deflections. Finally, food versus air puff omission was better encoded by {TANs}.} In terms of the activity of single neurons with distinct responses to the different behavioral events, both {DANs} and {TANs} were more strongly modulated by reward than by aversive related events and better reflected the probability of reward than aversive outcome. Thus, {TANs} and {DANs} encode the task episodes differentially. The {DANs} encode mainly the cue and outcome delivery, whereas the {TANs} mainly encode outcome delivery and omission at termination of the behavioral trial episode.


Oscillatory bursting activity is commonly found in the basal ganglia {(BG)} and the thalamus of the parkinsonian brain. The frequency of these oscillations is often similar to or higher than that of the parkinsonian tremor, but their relationship to the tremor and other parkinsonian symptoms is still under debate. We studied the frequency dependency of information transmission in the {cortex-BG} and cortex-periphery loops by recording simultaneously from multiple electrodes located in the arm-related primary motor cortex {(MI)} and in the globus pallidus {(GP)} of two vervet monkeys before and after 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine {(MPTP)} treatment and induction of parkinsonian symptoms. We mimicked the parkinsonian bursting oscillations by stimulating with 35 ms bursts given at different frequencies through microelectrodes located in {MI} or {GP} while recording the evoked neuronal and motor responses. In the normal state, microstimulation of {MI} or {GP} does not modulate the discharge rate in the other structure. However, the functional-connectivity between {MI} and {GP} is greatly enhanced after {MPTP} treatment. In the frequency domain, {GP} neurons usually responded equally to 1-15 Hz stimulation bursts in both states. In contrast, {MI} neurons demonstrated low-pass filter properties, with a cutoff frequency above 5 Hz for the {MI} stimulations, and below 5 Hz for the {GP} stimulations. Finally, muscle activation evoked by {MI} microstimulation was markedly attenuated at frequencies higher than 5 Hz. The low-pass properties of the pathways connecting {GP} to {MI} to muscles suggest that parkinsonian tremor is not directly driven by the {BG} 5-10 Hz burst oscillations despite their similar frequencies.
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