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Cortical Plasticity: A View from Nonhuman Primates

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Neocortex · Feedforward · Feedback · Perceptual learning · Adaptation · Decoding · Hand grasping

Abstract
The primate's large brain-to-body weight ratio and high complexity are unusual in the animal kingdom. There is compelling evidence that it is an evolutionary adaptation that allows its owner to live a long life because of its competence in solving a wide range of problems. How primates use their brain to achieve such competence is of course of central interest to us. Here we review some key aspects of the neocortex that can be explored in nonhuman primates. Studies of the cortical circuits in the visual cortex reveal that the two major types of pathways, called feedforward and feedback, involve a very small fraction of the total synapses that any area contains. Nevertheless these pathways may be critical for some important forms of cortical plasticity, like perceptual learning and tasks involving perception and action.

Introduction

Why should an animal need a modifiable brain at all? Why does the nervous system need to be plastic? Brains can be hardwired so that they elaborate a complex sequence of actions, like foraging, eating, drinking, and reproduction, without the need for learning. Such pre-programmed brains do, however, require that the environment in which its owner lives is predictable. Thus, animals such as insects, which live brief lives in a constant environment, can be preprogrammed to perform a wide range of essential behaviors that do not require learning. All animals use their brains to make predictions about the future, but the longer an animal lives, the more likely it is that conditions will change. If the future becomes less predictable, animals with brains that are able to generate well-adapted behaviors will have the best chances for survival. These animals possess a quality we call intelligence. Adaptation means that the brain has the capacity to change the neural representation of a particular brain area either qualitatively or quantitatively. This capacity is called 'plasticity' and it may be the main reason why large brains and long lives go together.

Primates have large brains for their size [1], are also long-lived and slow to reach sexual maturity. They are intelligent and well-equipped to respond adaptively to possible changes in future conditions. This flexibility in behavior extends not just over time but also over space. Because they tend to forage over wide areas, they also encounter a wide variety of conditions to which they also have to respond appropriately. Since there is a positive correlation between the relative size of the brain and the range of problems animals can solve [2], it is not surprising that there is also a positive correlation between the relative size of a primate's brain and the size of the territory over which it ranges [3].

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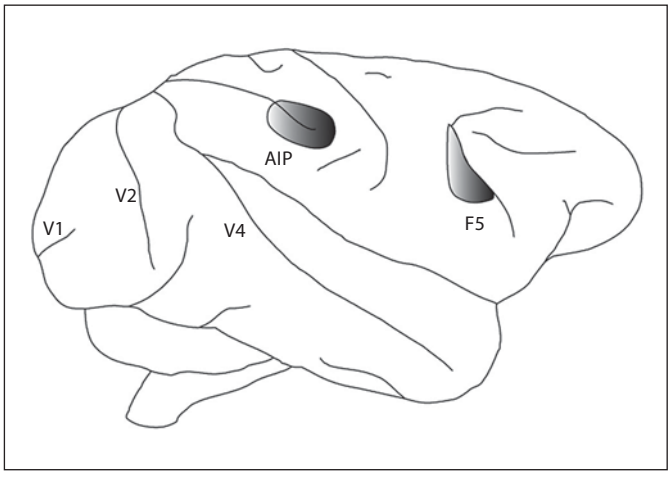

Fig. 1. Lateral view of a macaque brain. Labels indicate the visual areas: V1, V2, and V4. Shaded areas indicate AIP and premotor area F5.

In the following, we review key aspects of cortical connectivity and then give two examples of primate cortical research that raise particularly interesting questions in relation to cortical plasticity: perceptual learning and tasks involving perception and action. As we will see, cortical plasticity plays a central role in both of these topics while its mechanisms and neural implementation still await to be discovered.

Primate Neocortex

Although mammalian brains do have a similar 'bauplan', the primate brain is not simply an expanded rat or cat brain, because the rule that relates the volume of the neocortex to the volume of the whole brain is different for rodents, carnivores, and primates. The primate brain has proportionately more neocortex than the carnivore and even more than the rodent [2]. If the ratio of brain to body weight of an average mammal is expressed as an 'encephalization quotient' [1], then it is evident that the insectivores and rodents have small brains for their weight, the ungulates and prosimians have brains of moderate size, and the monkeys and apes have large brains. The change in brain size is largely due to an increase in the size of the neocortex. In carnivores the neocortex forms about 40% of the brain, whereas in primates it can vary from 53% in a cebus monkey to over 80% in the human brain. Other primates, like us, typically have brains that are large for their body weight compared to other animals. The significance of this for adaptive behavior is that brain size correlates with the animal's performance when faced with standardized problems. For example, in a set of 1,800 problems in visual discrimination learning, three species of primates (rhesus monkey, squirrel monkey and marmoset) outperformed cat, gerbil, rat and squirrel. The old world monkey outperformed by a considerable margin the new world primates [2]. This and other comparative evidence indicates that the old world primate in particular provides us with an important model for exploring the mechanisms of cortical plasticity in the human. The areas of neocortex that we will discuss here are shown in figure 1.

Cortical Circuits

Plasticity in brain circuits means that the effective connectivity between neurons is changed. These changes in effective connectivity may occur through many different mechanisms, from a change in the strength of a synapse to the growth of new connections. Thus, knowledge of the physical circuit is fundamental to understanding the changes in function that they produce during cortical plasticity. In the human, surprisingly, detailed maps of brain circuits do not exist. Our best knowledge of these circuits is indirect and comes mainly from studies of the brain circuits of macaques. Crick and Jones [4] have referred to this state of affairs as 'shameful', but unfortunately, it is not easy to remedy. Although new techniques of studying fiber tracts in humans are being developed (e.g., diffusion tensor imaging [5]), it seems likely that in vivo studies will always bump against the limits of spatial resolution. This means that for the foreseeable future, much of our understanding of the circuits of the human brain will come from studying brains of nonhuman primates and drawing analogies. However, even here there are caveats. Most of the detailed circuits from the macaque monkey are based on qualitative tract tracing analyzed at the light microscope level. Such studies show the existence of a connection between two structures, identity of the neurons of origin and, in association with other techniques, can identify target neurons as well. There are remarkably few quantitative studies of the brain circuits, particularly studies of the connections of the neocortex. Only through painstaking quantitative studies can we hope to go beyond the simple binary picture (i.e. connected, not connected) of cortical hierarchy, which has been the standard view for the past two decades.

Synaptic Connections of the Macaque Visual Cortex

Our own interest in cortical circuits has been at the level of a major site of plasticity: the synaptic connections between nerve cells. We made quantitative studies of the synaptic connections to the cortical visual areas in the macaque monkey. The visual system is organized in a bidirectional hierarchy: projections from the retina to the thalamus and onto the ascending levels of the visual cortex are defined as 'feedforward', whereas the descending projections are defined as 'feedback'. In short, V1 receives direct input from, and sends signals back to the thalamus. V1 is connected to area V2, which exchanges signals with a multitude of other extrastriate visual cortical areas, many of them also sending signals back to the thalamus. Most extrastriate cortical areas are thought to have a more specialized function than V1 or V2. Areas V3A and MT, for example, are thought to play an important role in depth and motion perception, while V4 is known to be important for form and color vision. We examined a number of feedforward projections in the macaque (summarized in fig. 2). These include the thalamic input to area 17 (V1) [6], the projections from V1 to areas V2 and MT [7; Anderson and Martin, in preparation], and from V2 to area V3A [8] and V2 to MT [9]. We also examined the feedback projections from V4 to V2 [10] and from V2 to V1 [Anderson and Martin, in preparation]. Remarkably, all these various projections show consistent patterns of synaptic connections. The ultrastructural appearance of their synapses is typical of excitatory glutamatergic synapses. Spiny (excitatory) neurons are the major targets (about 80% of targets) of these interareal projections, with about 20% of targets being smooth (inhibitory) neurons. All of these interareal projections and the projection from the thalamus to the primary visual cortex involve surprisingly few synapses. In all cases, only a few percent of the synapses formed with the dendritic tree of a single neuron actually come from a feedforward or a feedback. Neighboring excitatory neurons are the source of most of the remaining synapses [11].

The main differences between these two projection types, feedforward and feedback, are in the layers that they innervate. Feedforward projections between cortical areas resemble the thalamic input to the primary visual cortex in that the middle layers of the cortex (layers 3 and 4) are the major targets of innervation. In contrast, the feedback projections tend to avoid the middle layers of the cortex and target layers 1 and 5 (fig. 2). The feedback projection from V4 to V2, for example, forms most of its synapses on the distal dendrites of pyramidal cells in layer 1. The interplay between these ascending and descending cortical pathways is the subject of a great deal of speculation and some physiological data. The physiological data are extremely hard to obtain because isolating one or the other stream is virtually impossible, only one part of the cortical circuit can be silenced. Nevertheless, it seems clear that the interaction between these two streams is nonlinear. For example, when V1 is inactivated by cooling, then all visual responses are lost in V2, but the neurons in area MT remain active [12]. This means that the feedback projections from MT to V2 are not able to drive the V2 neurons. Nevertheless, when MT is cooled, the visual responses of neurons in V2 are substantially reduced [13]. The feedforward and feedback connections between areas thereby provide convenient means of modulating and altering the properties and functions of the visual system as a whole. Thus, it is readily conceivable that one mechanism of plasticity in these early visual areas involves rapid modifications of the interactions of the feedforward and feedback pathways, for example the rapid changes associated with a phenomenon called 'perceptual learning'.

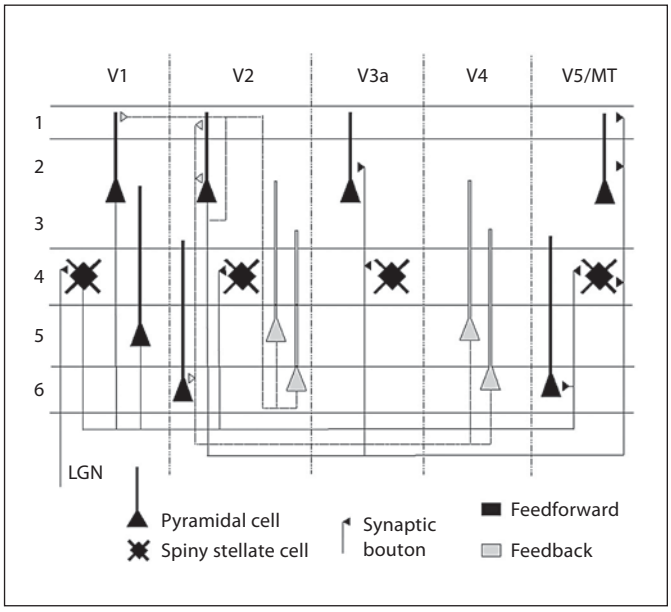

Fig. 2. Schematic representation of the connectivity between visual cortices in the macaque. The axonal projections were traced with light microscopy and the synaptic connections established by electron microscopy. Cortical laminae are numbered and the visual areas are indicated by V1, V2 etc. Feedforward connections: black, feedback connections: gray.

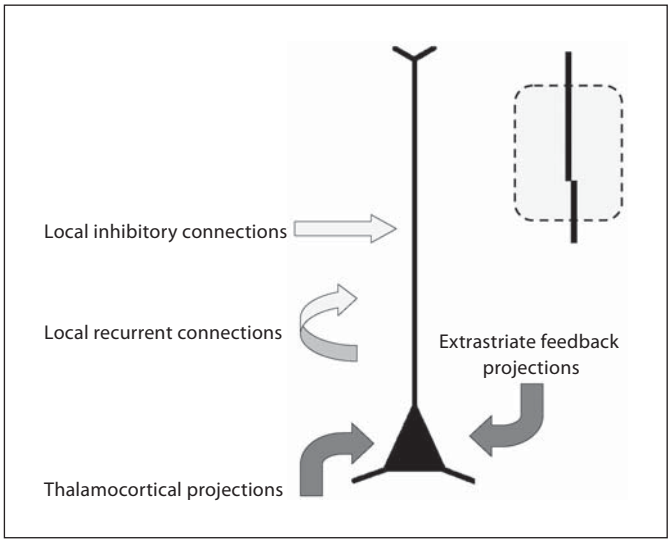

Fig. 3. A schematic primary visual cortex neuron with an elongated, oriented receptive field (dashed, light gray). Visual neurons with orientation-selective receptive fields can detect the presence or absence of an offset in a Vernier target (black lines over the receptive field). The receptive field properties can be modified either by plasticity of the synapses from external afferents (arrows) and/or internal connections.

The Model of Perceptual Learning

Among the many forms of plasticity shaping the properties of the primate cortex, those associated with practice in perceptual tasks provide researchers with a unique opportunity to probe the neural mechanisms of cortical plasticity. The improvement of performance due to practice is called perceptual learning (PL). To date, the mechanisms underlying PL are unknown. In most cases, it is not even clear which cortical areas are involved, let alone what type of synaptic or cellular processes are at play.

In the visual domain, PL is particularly strong in relative spatial position tasks, collectively known under the name of 'hyperacuities'. Although not the only type of task subject to PL [14, 15], hyperacuities improve significantly and rapidly with training. One form of hyperacuity, called Vernier acuity, has been used extensively to study the characteristics of PL and its neural basis. In a Vernier acuity task, a subject is asked to judge whether a line segment is offset to the left or to the right of an abutting reference segment (fig. 3). Vernier thresholds, which can be as low as a few seconds of arc in untrained subjects, can improve further by as much as a factor of 5 after a few hundred practice trials [16]. The training duration on the scale of hours necessary to observe significant PL is relatively long, and therefore consistent with many potential underlying mechanisms, such as synaptic potentiation or depression, or the establishment or deletion of synaptic contacts.

The high accuracy of Vernier judgments was shown to be consistent with the spatial properties of initial, oriented filters, which are known to exist in the primary visual cortex [17]. The nature and location of the neural events underlying improvement in performance are, however, unknown.

Thalamocortical Projections and PL

Assuming that the locus of PL is the primary visual cortex (V1; fig. 1, 2), PL could be implemented in at least three different elements of the neural circuitry. First, PL could reflect synaptic changes in the feedforward projections from the lateral geniculate nucleus (LGN) of the thalamus. Feedforward thalamocortical projections are known to play an important role in the generation of orientation selectivity in cortical neurons. Practice-induced changes in the synaptic weight of these connections could induce a sharpening of the neuron's selectivity for orientation, thereby yielding more acute performance in numerous hyperacuity tasks, including Vernier acuity. The fact that little or no interocular transfer is observed during learning in Vernier acuity is consistent with this hypothesis [16, 18]. Indeed, in primates most primary visual cortex neurons are binocular, although their LGN afferents are not. The lack of interocular transfer could be explained by modulation of the thalamocortical synapses, which are monocular (i.e. LGN afferents are from monocular neurons). Similarly, PL was shown to be specific to orientation: thresholds for Vernier targets at an orientation different from that trained do not benefit from the training [16]. This observation is also consistent with the hypothesis that PL is due to changes in the spatial characteristics of early, oriented, cortical filters. Another result consistent with the involvement of thalamocortical synapses is that PL is location-specific [16, 19]. Training one region of the visual field does not yield learning at other retinal locations. This suggests involvement of mechanisms with localized receptive fields. Thalamocortical projections are known to be highly location-specific, providing the basis for the small, localized, classical receptive fields of V1 neurons.

Local Cortical Circuits

The lack of interocular transfer, the orientation and location specificities of PL are all qualitatively consistent

with the hypothesis that PL results from modulation of the thalamocortical synapses. However, other mechanisms could be responsible as well. The orientation selectivity of primary visual cortex neurons is not only determined by feedforward projections, but is refined by local cortical circuitry. Local inhibitory feedback or recurrent excitatory connections have both been proposed as central mechanisms for the tuning of orientation selectivity [20]. In that view, local recurrent connections serve to amplify the signals coming from the thalamus, thereby enhancing a neuron's response to its preferred orientation. In addition, inhibitory signals from neighbor neurons tuned to other orientations can reduce a neuron's responses to nonpreferred orientations. Plasticity in these local synapses is thus a second potential mechanism that could induce sharpening of the cell's tuning, and support PL. This would be consistent with the orientation specificity of PL, as well as with its location specificity.

Distinguishing between the respective contributions of thalamocortical synapses and local cortical circuitry proves difficult, as exemplified by the controversy about their role in determining orientation selectivity [20]. The lack of interocular transfer favors involvement of the thalamocortical synapses, although it does not rule out alternatives [21].

Extrastriate Cortical Influences on PL

The data reviewed so far are qualitatively consistent with the notion that primary visual cortex neurons could be the site of PL. However, a number of observations are not consistent with this notion: quantitative measures of PL's orientation specificity, the role of perceptual feedback and attention during practice, PL's specificity to the complexity of the trained stimulus, and recent recordings of primary visual cortex neurons suggest involvement of extrastriate mechanisms in PL.

Several reports document the importance of feedback during practice [22, 23]. These studies demonstrate that PL is possible in the absence of behavioral feedback, but that it is considerably slower and less pronounced than when feedback is provided. These data indicate that signals pertaining to the correctness of behavioral responses influence the rate of learning. Because these signals are thought to originate in the extrastriate cortex, this result suggests the involvement of higher visual areas of the extrastriate cortex in PL. Similarly, an important role of attention in PL has been reported [24, 25]. Attentional signals are also known to be generated outside of V1. These results thus further support the notion that the extrastriate cortex has an important role to play in PL, although the precise mechanisms implementing that role are currently unknown.

Involvement of the extrastriate cortex in PL is also suggested by the fact that PL is not only orientation- and location-specific, but restricted to stimuli of the same complexity as that trained. Indeed, Poggio et al. [26] showed that PL does not transfer from a task trained with line segments to a similar task with dot stimuli. This is inconsistent with the implication of early oriented filters that should give similar responses to both types of stimuli. Similarly, Crist et al. [27] showed that PL is highly task-specific. Training in one task does not lead to improvement in other tasks thought to use the same underlying neural mechanisms. These high stimulus and task specificities are more reminiscent of extrastriate than primary visual cortex neurons.

Physiological Studies of PL

Numerous physiological studies attempted to find the mechanisms of cortical plasticity. Among those, a number of findings pertinent to PL have been described [for a review see ref. 28]. Because different tasks yield somewhat different results [15, 28], we focus on those using hyperacuity tasks, with particular emphasis on Vernier acuity. Although somewhat equivocal, the findings described above led most researchers to focus on the primary visual cortex. After training in a bisection task (in which monkeys indicated whether the central of three parallel line segments was closer to one or the other of the flanking lines), Crist et al. [27] failed to find any changes in V1 receptive field size, location, or orientation tuning. They did find, however, that contextual effects (measured through the effect of additional line segments placed outside the cells' classical receptive field) did increase with PL. Similarly, Ghose et al. [29] could not detect any change in orientation bandwidth, peak response, tuning amplitude, variance, preferred spatial frequency, spatial frequency bandwidth, or receptive field size in V1 and V2 cells of monkeys who had trained on an orientation discrimination task (a hyperacuity task thought to involve similar mechanisms as Vernier acuity). They did, however, report a slight decrease in the number of cells tuned to the trained orientation. To date, it is however not clear how a population decrease would yield better perceptual performance.

Few studies have reported classical receptive field changes following extensive training in a PL task [30]. Using an orientation task as well, the authors reported a decrease in the number of cells responding to the trained orientation, consistent with the findings of Ghose et al.

[29]. In addition, they reported changes in the neurons' orientation tuning, such that neurons tuned to the trained orientation showed a steeper slope in their orientation tuning function. Such a slope increase would be consistent with a higher ability to perform orientation discriminations. It is, however, not clear whether the changes reported by Schoups et al. [30] are sufficient to account for the observed reduction in behavioral thresholds.

Several years of research on the neural basis of PL have left many questions unanswered. Although there are strong indications that primary visual cortex neurons should exhibit PL, most studies aiming to reveal practice-induced changes in the classical receptive field of V1 neurons have failed. Because PL shows high intersubject variability, and because small changes in receptive field properties might be sufficient to account for the behavioral changes, it is possible that PL-related effects have gone unnoticed. Thus, it is necessary to perform additional, precise measures of the spatiotemporal properties of V1/V2 neurons during learning. If such changes indeed occur at later stages than V1/V2, the precise locus has to be determined. Moreover, quantitative analysis of the spatial and temporal characteristics of practice-induced changes will help us determine whether PL is induced by plasticity of the afferent synapses, the local cortical circuitry, or feedback from later stages of processing.

Cortical Circuits for Perception Action

The circuits of the occipital cortex are the best studied and form the basis of a wide range of concepts of cortical processing. The quantitative studies of synaptic connections referred to above have not been repeated for any other region of the neocortex. This lack of knowledge of the circuits is a major barrier to our understanding of the structural basis of plasticity in any of the other major divisions of the primate neocortex. This ignorance becomes particularly evident as we move from the occipital cortex to the temporal and parietal cortex. In these more rostral regions, the association of information from a variety of sources and modalities becomes more dominant. One of the most important perceptuomotor skills in primates is their dexterity of arm and hand movements, skills that are undoubtedly of considerable evolutionary significance. It is clear that the planning of purposeful hand movements from sensory information is a complex task that requires the coordinated action of many sensory and motor areas of the brain. This is immediately apparent from the fact that we normally use our hands in coordination with other actions like eye and arm movements and that all of these actions are based on a wealth of sensory, and in particular visual, information [31–34].

Hand movements are extremely versatile and span a range that extends from powerful grips to extremely delicate and precise manipulations of tools. In the premotor and parietal cortex, higher-level motor areas have been found that are involved in the formulation and generation of hand movement instructions. This is in contrast to neurons in the primary motor cortex that represent more precisely the hand movement details like trajectories and muscle forces. In the parietal cortex, the group of Sakata described neurons in the anterior intraparietal area (AIP, fig. 1) that encode the visual appearance of the object to be grasped [35, 36], or the grasping movement itself [37, 38]. These investigations emphasized the major role of this area for the transformation of visual information into high-level grasping plans. In the premotor cortex, the group of Rizzolatti found grasping neurons in the rostroventral aspect of the premotor area that are specifically active for a particular type of grasping or for hand orientation [39–41]. This area was termed 'frontal area 5' (F5, fig. 1) after careful histological examination [41, 42]. Taken together, the premotor and parietal grasping regions F5 and AIP play a prominent role for providing higher-order planning signals and the thereby necessary sensorimotor transformations [43–46].

Tract tracing studies show that the parietal and premotor areas are reciprocally connected [47–49], and most likely both are involved in coordinate transformation, decision making, and motor learning. In AIP, many cells are selective for the visual appearance of the object in addition to the appropriate movement to grasp the object [35, 36], while a reversible inactivation of AIP revealed a clear deficit in hand preshaping [50]. These studies demonstrated the functional relevance of AIP for object grasping and its role for the transformation of visual information into motor plans. In F5, many grasping neurons were found to be highly specific for a particular type of grasping movement (e.g., precision or power grip) or a particular hand orientation [40, 41]. Likewise, reversible inactivation of F5 also demonstrated its functional relevance for hand grasping [51]. These studies clearly indicate that both AIP and F5 are crucial for the generation of grasping movements. However, at this point, it is unknown how these areas interact and how the required computations are achieved.

To shed light on this fundamental problem, adaptation experiments that probe the plasticity of these brain areas might be of particular interest. In the parietal cor-

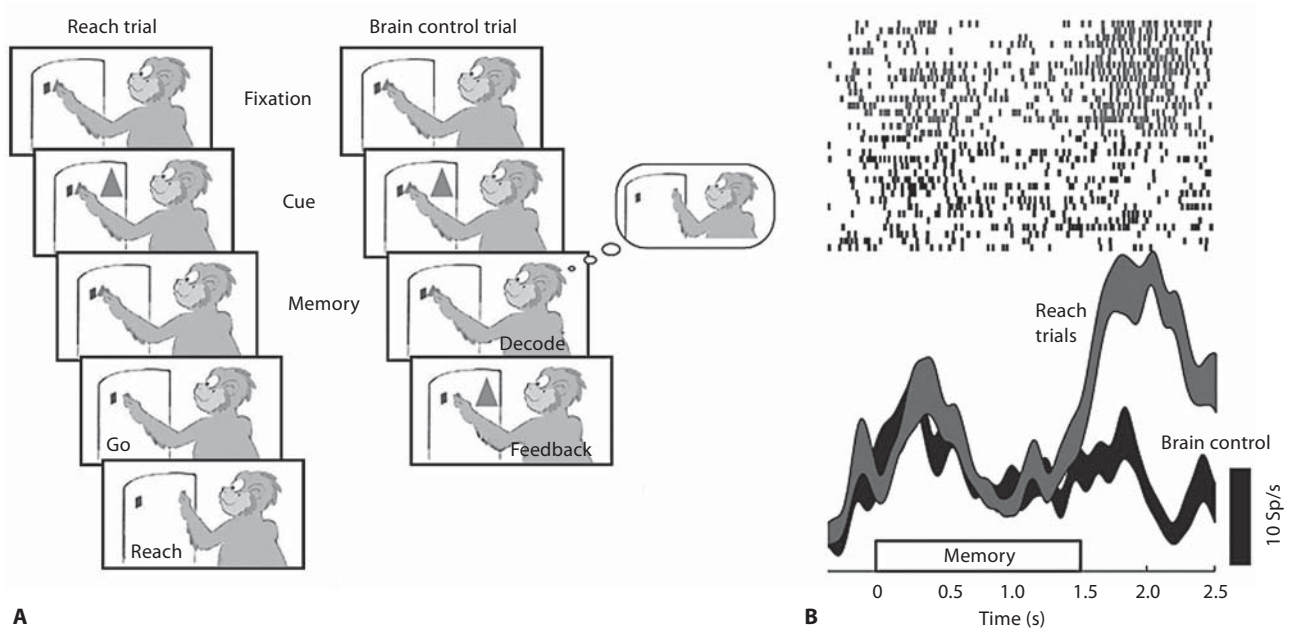

Fig. 4. Neural activity in the parietal reach region (PRR) during reach trials and brain control trials. **A** Behavioral task. Monkeys are trained in a reach task, where they first fixate and touch a central fixation spot on a touch screen (fixation). Then a visual cue indicates the location of a peripheral reach target (cue). During the following memory period, the animal continues to touch and fixate the fixation spot until a go signal appears, upon which the animal reaches to the remembered location in order to receive a juice reward. In the brain control task, the monkey plans a reach movement as in the reach task, however, neural activity during the memory period is decoded on-line by a computer (decode) and the decoded prediction of the reach is fed back to the animal (feedback). Importantly, the animal receives a reward if the decoded reach is correct, while an actual arm movement is not required (and the animal indeed does not move its arm). **B** Neural activity of an example cell of PRR. Spike rasters are shown on top of a peristimulus time histogram for reach trials and brain control trials. Activity increases at the beginning of the memory period (time zero), to which all trials are aligned. Activity stays elevated until the movement is executed (reach trials) or until the animal receives a reward (brain control trials) after the memory period for correctly decoded reach plans [modified from ref. 56].

tex, both learning and adaptation are important features in the context of sensorimotor transformations [52, 53]. Neural plasticity seems at work in the continuous fine-tuning of neural representations to keep various sensory and motor signals in register. An experiment specifically designed to disrupt this alignment is prism adaptation. Human subjects wearing vision-displacing prisms initially miss visual targets, but when provided with appropriate feedback about their errors, they recover and reach correctly within a time scale of a few minutes [54]. This suggests that a recalibration between sensory and motor coordinate frames takes place more or less continuously. A positron emission tomography study further demonstrated that prism adaptation selectively activates the parietal cortex contralateral to the reaching arm [55], which directly links this area to the adaptation effects, in agreement with its role in sensorimotor transformation.

There are some key experiments in which plasticity could be tested by perturbing the motor output signal. In the case of grasping movements, for example, activity in the areas AIP and F5 could be recorded from many permanently implanted electrodes while animals perform an instructed grasping task (e.g., precision or power grip with different hand orientations). Using statistical classification, the activity could be analyzed on-line to predict the animal's grasping intention during the task. The decoded hand grasping plan could be utilized to control a robotic hand in a real or virtual environment [56–58] (fig. 4). The robotic hand would execute the required grasping behavior instead of the animal, but the visual feedback to the animal would be realistic. By perturbing

such realistic feedback, one can investigate to what extent hand movement representations in AIP and F5 will change when the robotic command signals are systematically perturbed from the decoded signals. Such experiments can directly test the capacity of AIP and F5 for short- and long-term adaptation and might uncover functional differences between these areas.

Conclusion

This short review indicates how important the nonhuman primate studies of cortical plasticity are for understanding the full complexity and adaptability of human behavior. Cortical plasticity expresses itself through many different mechanisms. Both short- and long-term changes in the multiple representations involved in perception, cognition, and action are effected at multiple levels of synapses and circuits. These studies on structure and function reviewed above indicate how even in the nonhuman primate many questions that are central to our understanding of cortical structure and function remain unanswered. While there are well-developed computational models of plasticity (e.g., associative learning, reward learning), we have only started to understand the means by which these mathematical abstractions are actually implemented in the brain. The goal of our present work is to provide answers to some of these questions about the neural implementation of plasticity. Our integrated program of multidisciplinary research will link not only different levels of analysis such as structure, neurochemistry, high-resolution physiology in behaving monkeys, but will draw on human studies of psychophysics and brain imaging to develop as comprehensive a picture as possible of the extent to which cortical circuits modify themselves to adapt to new conditions by generating new behaviors, whether they be effected through natural or artificial means.

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