41 Forward Models and State Estimation in Posterior Parietal Cortex

GRANT H. MULLIKEN AND RICHARD A. ANDERSEN

ABSTRACT During on-line control of movement, the posterior parietal cortex (PPC) serves as a functional bridge between sensory and motor areas in the brain. One of the sensorimotor functions of this area appears to be prediction of the state of the arm during movement. Because sensory information is substantially delayed, it has been proposed that the brain makes use of an internal forward model that integrates both sensory and motor feedback signals to estimate current and upcoming positions and motions of the limb during reaching. These predicted states are more useful for rapid on-line control than are delayed sensory signals. The first part of this chapter focuses on investigations of on-line control mechanisms in PPC. The results of these studies indicate that one of the functions of PPC is to serve as a forward model. The second section highlights research that aims to read-out forward state estimates from PPC neurons and harness them for direct control of neural prostheses.

A growing body of clinical and psychophysical evidence supports the theory that the brain makes use of an internal model during control of movement; a sensorimotor representation of the interaction of one's self with the physical world (Jordan, 1995; Kawato, Furukawa, & Suzuki, 1987). Two primary types of internal models for sensorimotor control have been proposed: the forward model and the inverse model. A forward model (i.e., forward output model) predicts the sensory consequences of a movement (Jordan & Rumelhart, 1992; Miall & Wolpert, 1996; Wolpert, Ghahramani, & Jordan, 1995). That is, it mimics the behavior of a motor system by predicting the expected, upcoming state of an end effector (e.g., sensory feedback of one's own limb) using knowledge of the characteristic dynamics of the system as well as stored copies of recently issued motor commands. Conversely, an inverse model encodes the motor commands necessary to produce a desired outcome (Atkeson, 1989). That is, an inverse model estimates the set of proce-

dures (e.g., motor commands) that will cause a particular state of the motor system to occur. While inverse models likely play an important role in sensorimotor control, they will not be discussed further in this chapter; instead, we will place emphasis on the forward model and, in particular, the role of the posterior parietal cortex (PPC) in forward state estimation for motor planning and control.

Movement intention and anticipation in PPC

PPC is a critical node for bridging sensory and motor representations in the brain. PPC associates multiple sensory modalities (e.g., visual—the dominant sensory input to PPC, somatosensory, and auditory) and transforms these inputs into a representation that is useful for guiding actions to objects in the external world (Andersen & Buneo, 2002). Evidence from lesions studies indicates that damage to PPC results in an inability to link the sensory requirements of a task with the appropriate motor behavior necessary to complete it. For example, parietal lesion patients can have difficultly planning skilled movements, a condition known as apraxia (Geshwind & Damasio, 1985). Impairments from apraxia can range from an inability to properly perform an instructed or desired arm movement to how to coordinate a specific sequence of movements to accomplish an end goal.

Numerous neurophysiological studies in monkeys have shed light on the neural correlates of reach planning in PPC. Monkeys have served as a successful model for studying sensorimotor representations in humans since the two species engage in a variety of similar sensorimotor behaviors. Moreover, functional magnetic resonance imaging (fMRI) studies have provided evidence that PPC's functional role is similar in both monkeys and humans (Connolly, Andersen, & Goodale, 2003; DeSouza et al., 2000; Pellijeff, Bonilha, Morgan, McKenzie, & Jackson, 2006; Rushworth, Paus, & Sipila, 2001). When trained monkeys plan a reach to an illuminated target, the firing rates of neurons in the medial bank of the intraparietal sulcus (MIP) generally reflect a combination of both sensory and motor parameters

GRANT H. MULLIKEN Computational and Neural Systems, California Institute of Technology, Pasadena, California
RICHARD A. ANDERSEN Computation and Neural Systems, Division of Biology, California Institute of Technology, Pasadena, California

(Andersen & Buneo, 2002; Mountcastle, Lynch, Georgopoulos, Sakata, & Acuna, 1975; Robinson, Goldberg, & Stanton, 1978). Importantly, during a memory period in which the monkey must maintain a reach plan to the remembered location of an extinguished target, elevated neural activity persists in PPC before the reach is executed, suggesting that these neurons likely encode the *intention* to reach rather than the visual stimulus location (Snyder, Batista, & Andersen, 1997). Furthermore, neural responses in MIP are generally correlated more strongly with the motor goal, and not the visual cue, during antireach paradigms in which the target cue direction is dissociated from the reach direction (Eskandar & Assad, 1999; Gail & Andersen, 2006; Kalaska & Crammond, 1995).

PPC is a reasonable location for a forward model of the arm to reside (which would predict the sensory consequences of an upcoming arm movement command) given its substantial reciprocal connections with downstream motor areas (Johnson, Ferraina, Bianchi, & Caminiti, 1996; Jones & Powell, 1970). Along these lines, many researchers have suggested that the "early" discharge of neurons in area 5 prior to initiation of an arm movement might reflect the integration of an efference copy signal fed back to PPC from frontal motor areas (Kalaska, Caminiti, & Georgopoulos, 1983; Seal, Gross, & Bioulac, 1982). Interestingly, Seal and colleagues also showed that area 5 responses that occurred prior to movement onset were generally not sensory in origin and further demonstrated that these early responses persisted even after deafferentation. However, some caution should be advised in attempting to infer the causal flow of information in parietofrontal circuits during reach preparation using single-area correlation analyses. For instance, it is possible that planning and forward model prediction (which relies on efference copy) may be carried out by distinct neural processes within PPC. Future simultaneous multiarea recordings, combined with microstimulation approaches, may help to shed light on the directional flow of information in these recurrent interarea circuits during movement preparation.

A FORWARD MODEL FOR EYE POSITION PPC is also a possible candidate for a forward model of eye position, since a variety of eye behavior–related signals, such as saccade and fixation responses, have been described in this region (Mountcastle et al., 1975). Area 7a saccade responses begin largely after a saccade occurs, while lateral intraparietal (LIP) saccade responses can occur before, during, or after saccades (Andersen, Essick, & Siegel, 1987). Interestingly, Duhamel, Colby, and Goldberg (1992) showed that the receptive fields (RFs) of neurons in LIP can update their receptive fields before an eye movement occurs. Forty-four percent (16 out of 36) of their LIP sample anticipated the sensory outcome of an impending saccade (i.e., a stimulus

appearing in the future location of the RF), and adjusted their responses approximately 80 ms before the saccade was launched. It is conceivable that this predictive updating relies upon a forward model of eye position within PPC, which estimates the upcoming eye position from oculomotor commands, though direct evidence of the anticipatory eye position signal itself in PPC has not been reported. An eye position signal in PPC could potentially be derived from passive sensory feedback from the eye muscles (Wang, Zhang, Cohen, & Goldberg, 2007) and/or the integration of saccade command signals. It would be interesting to see whether a component of the eye position signal in PPC might also encode anticipatory information (ahead of passive sensory feedback) about the current state of the eye position during fixations between saccades. Evidence of updating RFs has also been reported in other brain areas; therefore it is quite possible that multiple regions are involved in encoding a forward model of the state of the eye. For instance, Sommer and Wurtz (2006) discovered a feedback circuit in which the superior colliculus conveys a copy of the oculomotor command (i.e., corollary discharge) to the frontal eye field (FEF), which they showed to be necessary for accurate updating of RFs in the FEF. Last, response field updating neurons in PRR, which predominantly encode an intended reach direction in eye-centered coordinates, update their response fields when an intervening saccade occurs and thereby maintaining an eye-centered motor plan even when gaze is shifted (Batista, Buneo, Snyder, & Anderson, 1999; Buneo, Jarvis, Batista, & Andersen, 2002). It would be interesting to test whether the reach response fields of these PRR neurons also exhibit anticipatory updating just before the eye moves, similar to the cells found in LIP by Duhamel and colleagues (1992).

REAFFERENCE CANCELLATION IN PPC A forward model's ability to predict the sensory consequences of an action is useful to an organism because a given sensory outcome can be produced by a variety of potential causes (Claxton, 1975; Cullen, 2004; Poulet & Hedwig, 2003; Roy & Cullen, 2004; Sperry, 1950; Weiskrantz, Elliott, & Darlington, 1971). In particular, the output of a forward model can be used as an internal reference signal to cancel the sensory effects of self-motion. For example, motion on our retina can occur because of movement in the physical world (afference) or because of motion induced by an eye movement itself (reafference). Therefore to correctly perceive the motion of an external stimulus, the brain must distinguish afferent motion from reafferent motion. A subtractive comparison between a forward model's estimate of the expected sensory outcome of an eye movement and the actual sensory signals could remove this retinal shift from our perception. For example, such an internal reference signal is used for perceptual stability during smooth-pursuit eye movements

(Bradley, Maxwell, Andersen, Banks, & Shenoy, 1996; Haarmeier, Bunjes, Lindner, Berret, & Thier, 2001). Interestingly, clinical evidence presented by Haarmeier, Thier, Repnow, and Peterson (1997) suggested that parieto-occipital regions may be involved in performing the comparison between self-induced and external sensory motion during smooth-pursuit eye movements.

Reafference generation and comparison mechanisms are also likely employed for the perception of arm movements, for example, to distinguish self-generated arm movement from movement in the environment (e.g., the movement of others) and/or the movement of one's arm by an external force. Positron emission tomography (PET) imaging studies have provided evidence supporting PPC's role in reconciling intentions with sensory consequences. For instance, Fink and colleagues (1999) displayed nonveridical visual feedback of a subject's left hand by displaying a mirror image of a subject's right hand while they performed a bimanual coordination task. Such incongruent visual feedback resulted in an increase in bilateral PPC activation (area 40 and area 7) as well as bilateral dorsal prefrontal cortex activation. Later, Farrer and colleagues (2003) performed an experiment in which they systematically manipulated the degree of control with which subjects were able to perform a joystick task by perturbing visual feedback of their hand movements, rotating the direction of the virtual hand movement by a variable amount (i.e., 25°, 50°, and a condition with no correspondence). They found a graded activation in the inferior parietal lobule, such that regional cerebral brain flow increased with decreasing levels of control felt by the subject.

Lesion studies have shown that damage to PPC can lead to deficits in the attribution of agency. For example, Sirigu, Daprati, Pradat-Diehl, Franck, and Jeannerod (1999) showed that apraxia patients with left parietal lesions have a greater tendency to confuse their own movements with the movements of an experimenter. When patients' visual feedback was substituted with the hand movements of an experimenter (who attempted to perform the same movement), patients were more likely to confuse their right hand with the "alien" hand (19% correct ownership judgment), relative to normal control subjects (79% correct). Since the patient's intention and the outcome of the experimenter's movement were largely congruent, patients needed to detect subtle spatiotemporal discrepancies between the time-varying state of the expected state of their hand and the virtual hand on the computer screen. The authors suggested that these deficits were caused by damage to an internal model, which maintains a time-varying representation of a movement in space. In a related study, MacDonald and colleagues tested whether transient disruption of PPC using transcranial magnetic stimulation (TMS) could affect subjects' ability to determine the agency of an observed movement (MacDonald & Paus, 2003). Specifically, they introduced a lag time into the display of the visual feedback of the subject's hand on the computer screen and asked subjects to detect trials in which they perceived a delay between the onset of their own hand movement and the onset of the virtual movement on the screen. Interestingly, the researchers found that during self-generated movement, TMS impaired subjects' ability to detect asynchrony between the onset of actual and virtual hand movements. In contrast, when subjects' hands were passively moved without prior notice to the subject, their judgments were not significantly impaired from pre-TMS control conditions. These results suggest that PPC maintains a time-dependent representation of action that relies upon anticipatory mechanisms (and not only sensory feedback), such as a forward model, to update the state of the arm. This internal state representation is important for making decisions about both the temporal state and the attribution of agency of a movement.

Forward state estimation for on-line control

During execution of a goal-directed arm movement to continuously guide the arm to a target, the brain must maintain an estimate of the time-varying state of the arm (e.g., position and velocity of the arm, coded in a variety of potential coordinate frames) and compare that state measurement with the desired state of the movement. Unfortunately, the human brain, in particular PPC, does not have direct access to the true state of the arm owing to delayed and noise-corrupted measurements of the state from the visual and proprioceptive domains; for example, visual signals typically reach sensorimotor association areas of cortex after a delay of approximately 90 ms (Raiguel, Xiao, Marcar, & Orban, 1999), or 30 ms in the case of proprioception (Petersen, Christensen, Morita, Sinkjaer, & Nielsen, 1998). Subsequent processing delays are incurred during control, owing to sensorimotor integration, motor command generation, and execution, resulting in an average loop delay of more than 100 ms for proprioceptive control (Flanders & Cordo, 1989) and over 200 ms for visuomotor control (Georgopoulos, Kalaska, & Massey, 1981; Miall, Weir, Wolpert, & Stein, 1993). These long delay times severely limit a feedback control system's ability to make rapid adjustments to an ongoing movement and thus increase the likelihood that a reach trajectory might become erroneous and/or unstable.

THE OBSERVER FRAMEWORK Fortunately, the brain can also monitor recently issued motor commands (i.e., efference copy), which can be transmitted centrally (e.g., from frontal motor areas) with little delay time (e.g., one synapse + transmission time < 10 ms) and used by a forward model to form an estimate of the current or upcoming state of the arm well in advance of late-arriving sensory information.

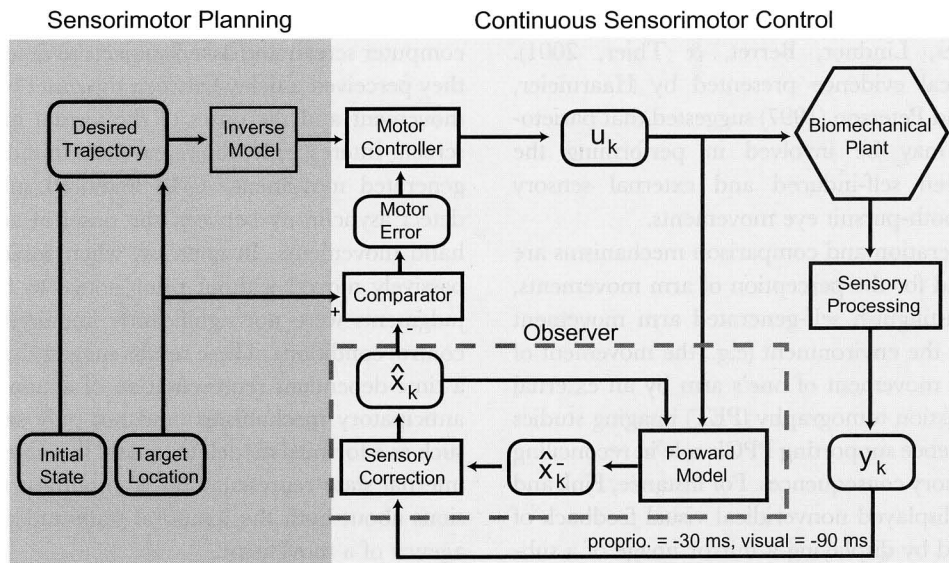Sensorimotor Planning | Continuous Sensorimotor Control

FIGURE 41.1 Flow diagram illustrating sensorimotor integration for reach planning and on-line control. Items in rounded boxes denote pertinent sensorimotor variables; computational processes are contained in rectangular boxes. Prior to a reach, an intended trajectory is formulated as a function of both the initial state of the arm and the desired endpoint, the target location. An inverse model is used to determine a set of motor plans that will result in the desired trajectory. Motor plans are then issued (e.g., by primary motor cortex, M1) and subsequently executed by muscles acting upon the physical environment (i.e., biomechanical plant hexagon).

Following movement onset, the state of the arm is continuously monitored and corrected, if necessary, to ensure successful completion of the reach. Critical to rapid on-line correction of movement is the forward model, which generates an anticipatory, a priori estimate of the next state of the arm, $\hat{x}_k$, as a function of the previous state and efference copy. Intermittent sensory feedback is used to refine the a priori estimate of the forward dynamics model (observer). The a posteriori current state estimate, $\hat{x}_k$, can then be evaluated to make corrections to subsequent motor commands. (After Desmurget & Grafton, 2000.)

Since the output of the forward model reflects a best guess of the next state of the arm, errors due to various sources of noise will inevitably accumulate over time for this estimate. Therefore it is likely that sensory observations, which arrive at later times, are also continually integrated by the brain to update and refine the estimate of the forward model (Miall & Wolpert, 1996) (figure 41.1). A system that estimates the state of a movement by combining the output of a forward model with sensory feedback about the state is generally referred to as an observer (Goodwin & Sin, 1984). For linear systems in which the noise is additive and Gaussian, the optimal (i.e., in the mean squared error sense) observer is known as a Kalman filter (Kalman, 1960). Wolpert and colleagues first applied the Kalman filter to model how subjects estimate the sensorimotor state of the hand during goal-directed reaches. They showed that a Kalman filter could accurately account for subjects' estimates of the perceived end location of their hand while making arm movements in the dark (Wolpert et al., 1995). Therefore the Kalman filter can serve as a useful theoretical model for studying sensorimotor state estimation in the brain.

Two linear stochastic equations govern the basic operation of the Kalman filter:

$$x_k = A_k x_{k-1} + B u_{k-1} + w_{k-1} \quad \text{(forward model)} \quad (1)$$

$$y_k = H_k x_k + v_k \quad \text{(state observation model)} \quad (2)$$

where x_k is the time-varying state of the arm at time step k and is modeled as a linear function of the previous state, x_{k-1}, and the control term, u_{k-1}. The control term is considered to be a known motor command, which is likely specified by frontal motor areas (e.g., primary motor or premotor cortex) and then fed back to sensorimotor circuits performing state estimation. For instance, the motor command at each time step might be determined by using an optimization procedure that minimizes a cost function associated with carrying out a particular trajectory (Todorov, 2006). Here, y_k is a sensory measurement (visual and proprioceptive) made at time step k. (Note that sensory feedback is in fact a delayed representation of the state of the arm.)

To estimate the state of the arm at each time step k, the output of the forward model, $\hat{x}_k^-$ (i.e., the a priori estimate), is linearly combined with the difference between the output of the observation model (i.e., the predicted sensory measurement) and the actual sensory measurement. This discrepancy, the "sensory innovation," is then optimally scaled by the Kalman gain, K_k, to produce an a posteriori estimate of the state of the arm:

$$\hat{x}_k = \hat{x}_k^- + K_k \left(y_k - H\hat{x}_k^- \right) \quad (3)$$

In brief, discrete state estimation consists of a two-step recursive procedure such that the forward model generates an a priori estimate of the state, which is next refined by potentially innovative information gleaned from the sensory input to form the final, a posteriori estimate. PPC, specifically the parietal reach region (PRR) and area 5, seems to be a reasonable site for an observer for on-line control to reside, since it has access to two key inputs to the observer model: a large number of internal feedback connections from frontal areas (i.e., efference copy) and substantial sensory input from both visual and somatosensory domains (Johnson et al., 1996; Jones & Powell, 1970).

Continuous sensorimotor control and state estimation in PPC

Clinical and psychophysical studies in humans have established that PPC is involved not only in specifying movement plans, but also in the execution and control of ongoing movement. For example, it is well known that lesions in parietal cortex often lead to optic ataxia, that is, impairment in locating and reaching to stimuli in three-dimensional space (Balint, 1909; Perenin & Vighetto, 1988; Rondot, Recondo, & Ribadeaudumas, 1977). For instance, optic ataxia patients have difficulty making rapid and "automatic" corrective movements when guiding the hand to targets that have been jumped (Pisella et al., 2000). Similarly, Grea and colleagues (2002) reported a patient with bilateral parietal lesions who was unable to amend her movement to pick up a cylinder after it had been jumped to a new location at movement onset. Interestingly, instead of making corrective movements during an initial trajectory, the subject needed to perform two distinct movements: one that represented the initial plan and a second movement to reach to the new location of the cylinder. Using TMS applied to the posterior parietal cortex, Desmurget and colleagues (1999) were able to transiently disrupt the ability of most of their subjects to correct reaching trajectories made to targets that were displaced around the time of movement onset. Later, Della-Maggiore, Malfait, Ostry, and Pans (2004) showed that TMS applied to PPC interfered with the ability of subjects to adapt to novel force-field environments. An intriguing, potentially unifying explanation for all of these deficits, which was originally suggested by Wolpert, Goodbody, and Husain (1998), is that PPC may serve as an observer, which forms an internal estimate of the state of the arm during movement. A failure to accurately maintain this estimate on-line could result in an inability to monitor and therefore correct an ongoing movement. For example, Wolpert, Goodbody, and Husain reported a parietal lesion patient who was unable to maintain an internal estimate of the state of her hand. She could not maintain a constant precision grip force in absence of vision; with no vision of her stationary arm, she perceived it to drift slowly in space over 10–20 seconds until eventually reporting it to disappear. When she was asked to make slow-pointing movements to peripheral targets while maintaining central fixation, large errors accumulated in her trajectories (although self-paced movements were not impaired).

MENTAL SIMULATION OF MOVEMENT   Evidence that PPC is involved in sensorimotor state estimation also comes from the study of the mental simulation of movement, which presumably activates circuits that overlap with those engaged during motor control but inhibits execution of a movement itself (Decety, 1996; Gerardin et al., 2000; Stephan et al., 1995). When normal healthy subjects imagine making a goal-directed movement, mental simulation time typically matches the time needed to execute that same movement (Decety & Michel, 1989; Donders, 1969). This suggests that the brain is able to maintain a realistic estimate of the state of the hand over time while imagining a movement, despite sensory feedback being unavailable. Shadmehr and Krakauer (2008) interpreted this finding in the context of observer theory, suggesting that this capability indicates that the brain/observer is able to rely entirely upon the output of a forward model (in the absence of sensory feedback) to estimate the state of the arm during mental simulation (e.g., Kalman gain in equation 3 is set to zero). Interestingly, patients with unilateral motor cortex lesions (Sirigu et al., 1995) who show prolonged movement times compared to normal control subjects are still able to accurately imagine the duration of their movements (i.e., the simulation time and execution time remain well matched for these patients). Therefore, aberrant motor commands (u in equation 1) that are produced by the motor cortex could theoretically still be used by an intact observer to predict the correct temporal sequence of hand states (and therefore the trajectory duration), even for an impaired movement. Similarly, patients with lesions of the cerebellum (Kagerer, Bracha, Wunderlich, Stelmach, & Bloedel, 1998) and of the basal ganglia (Dominey, Decety, Broussolle, Chazot, & Jeannerod, 1995) also do not show a difference between simulation and execution times.

While M1, the cerebellum, and the basal ganglia do not appear to be critically involved in state estimation during simulated movements, PPC, by contrast, does appear to be essential for maintaining an internal representation of the state of the hand, which is necessary for producing a consistent relationship between simulation and execution time. Sirigu and colleagues (1996) later reported an impairment in the ability to simulate a movement in patients with right PPC lesions: the time needed to mentally simulate a movement was significantly different (generally less) than the time needed to execute the same movement. (Note that, similar to motor cortex lesion patients, actual execution time was

prolonged in comparison to control subjects.) This inconsistency suggests that the brain was unable to reliably estimate the state of the hand after damage to PPC. This impairment could be explained by multiple possible failures of the observer model: (1) an error in the forward model (i.e., faulty A or B matrices in equation 1), (2) an error when incorporating sensory feedback into the a priori estimate of the forward model (i.e., faulty H or K matrices in equation 3) or (3) a combination of these. On the basis of known strong sensory input to PPC, it is probable that PPC is involved in integrating sensory feedback into the state estimate. However, because visual and proprioceptive inputs were effectively removed during the above mental simulation tasks (e.g., eyes were closed, muscle activity was absent), it is less likely that erroneous state estimation was due exclusively to faulty integration of sensory feedback. Also, most parietal lesion patients significantly underestimated the time it would take to complete a movement when simulating it. Such a systematic decrease in imagined movement duration may have arisen due to an erroneous a priori estimate made by a forward model, whose transition matrices A and B govern the rate at which the arm propagates through space. Therefore these mental simulation results suggest that PPC is also involved in propagating the state of the arm forward in time using a forward model (equation 1). If we assume that PPC incorporates sensory information into the forward model state estimate as well, then PPC would be best described as an observer, as Wolpert and colleagues suggested.

Neural correlates of sensorimotor state estimation in PPC

Psychophysical and clinical reports have pointed to both the parietal lobe and the cerebellum as candidate neural substrates for a forward model (Blakemore & Sirigu, 2003; Miall et al., 1993; Wolpert, Goodbody, & Husain, 1998; Wolpert, Miall, & Kawato, 1998). For example, Desmurget and colleagues suggested that PPC encodes a forward model of the arm's dynamics, from which it may also compute an estimate of the motor error (i.e., the difference between the target vector and the movement vector), which could then be transformed into a corrective motor command by the cerebellum (Desmurget & Grafton, 2000). While numerous studies have shown that PPC and the cerebellum are likely to be involved in forward model control, finding direct neural correlates of forward model state estimation in the brain has proven difficult.

ON-LINE DIRECTIONAL CONTROL SIGNALS IN PPC   Previous encoding studies have shown that area 5 neurons are correlated with a variety of movement- and task-related parameters (most notably velocity and target position)

during reaching movements made with a manipulandum (Ashe & Georgopoulos, 1994; Averbeck, Chafee, Crowe, & Georgopoulous, 2005). These studies concluded that area 5 largely encodes a sensory (i.e., proprioceptive) representation that slightly lags the state of the movement (i.e., lag time = −30 ms). More recently, we further investigated the neural representation of on-line directional control signals in both area 5 and MIP while monkeys performed center-out and obstacle avoidance joystick trajectories under central eye fixation (Mulliken, Musallam, & Andersen, 2008a) (figures 41.2A and 41.2B). We analyzed the correlations of single neurons recorded in both area 5 and PRR with the static goal angle (fixed angle from the starting cursor position to the target) and the dynamic movement angle of the cursor (angle of heading) during a joystick task.

To characterize a neuron's dynamic tuning for movement angle, we constructed a space-time tuning function (STTF). Each horizontal slice in the STTF plots a neuron's instantaneous firing rate as a function of the angle measured at a particular lag time (Paninski, Fellows, Hatsopoulos, & Donoghue, 2004). For each lag time in the STTF, we also calculated the mutual information between firing rate and movement angle. The resultant temporal encoding function (TEF) indicated how strongly a neuron's instantaneous firing rate encoded the movement angle at different lag times (i.e., from past (lag time < 0) to future (lag time > 0) angles). The lag time corresponding to the peak of the TEF was considered to be the optimal lag time (OLT). Figure 41.2C shows a representative movement angle STTF for a single neuron. This neuron encoded the most information about the movement angle at an OLT of 0 ms and therefore best encoded the current state of the movement angle (figure 41.2D).

For our PPC population, during the center-out task, 56% of task-related neurons encoded significant information about the movement angle, and 75% of these significantly encoded the goal angle (note that PPC neurons appeared to be more engaged during the obstacle task: 79% encoded movement angle, and 93% encoded goal angle). Interestingly, we found an anatomical correlate for the representation of goal angle and movement angle in PPC: Mutual information for goal angle increased gradually with recording depth in the sulcus, while movement angle information (peak information measured at OLT) decreased with depth. A stronger encoding of target-related signals deeper in the intraparietal sulcus (IPS) and, conversely, a favored representation of hand movement–related activity in surface regions of the IPS are consistent with findings from previous PPC studies of reach planning, in which eye-centered target signals were commonly found in deeper structures such as PRR and more hand-related activity was reported for surface area 5 neurons (Buneo et al., 2002).
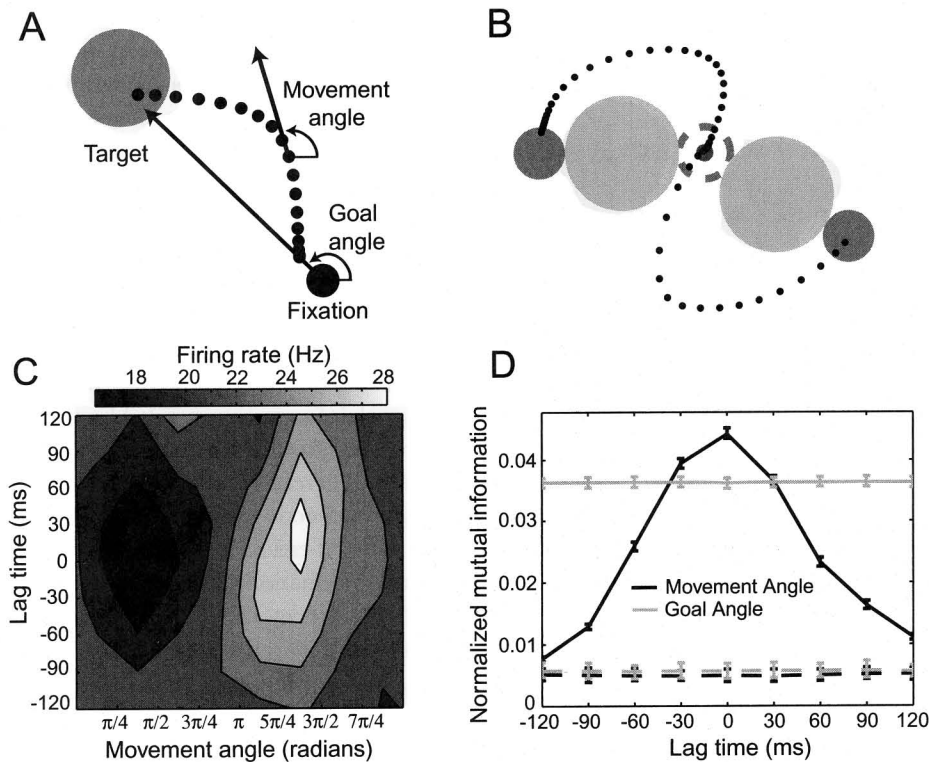
FIGURE 41.2 Experimental design and representative neuron. (A) Example center-out trajectory showing the goal angle and movement angle, and their respective origins of reference. Large and medium-sized circles represent the target and fixation point, respectively. Dots denote cursor position sampled at 15-ms intervals along the trajectory. (B) Example trajectories for obstacle task. The dashed circle depicts the starting location of the target and is not visible once the target has been jumped to the periphery. The large gray circles represent the visual obstacle. (C) Movement angle space-time tuning function (STTF). The contour plot shows the average firing rate of a cell that occurred for different movement angles measured over a range of lag times ($-120\ \text{ms} \leq \tau \leq 120\ \text{ms}$) relative to the firing rate. (D) Movement angle temporal encoding function (TEF) and corresponding goal angle TEF, where mutual information between firing rate and movement angle is plotted as a function of lag time. The firing rate contained the most information about the movement angle at an optimal lag time of 0 ms. The dashed lines denote surrogate TEFs, for both movement (black-dashed) and goal (gray-dashed) angles, that were derived from surrogate spike trains and actual angles. (Reprinted with permission from Mulliken, Musallam, & Andersen, 2008a.)

Neurons that are significantly tuned for goal angle persistently encode the static direction to the target, independent of the changing state of the cursor. These cells were consistent with previous reports of target-sensitive tuning in area 5 (Ashe & Georgopoulos, 1994). Therefore, the intended goal of the trajectory is maintained in PPC during on-line control of movement. PPC neurons that are tuned for movement angle encode dynamic information about the time-varying state of the cursor. Figure 41.3A shows TEFs for the movement angle population. The histogram in figure 41.3B summarizes the distribution of OLTs for the movement angle population, which was centered at 0 ± 90 ms and 30 ± 90 ms, for the center-out and obstacle tasks, respectively (median ± interquartile range (IQR)). These plots show that movement angle neurons contained a temporal distribution of information about the state of the ongoing movement; some neurons best represented states in the near future (positive-lag time), some best represented states in the recent past (negative-lag time), and many peaked around the current state (zero-lag time).

It is helpful to interpret the OLT results in the context of the observer framework. Passive sensory feedback (e.g., y in equation 2) would require at least 30–90 ms (proprioceptive-visual) to reach PPC; consistent with some of the negative OLTs (≤ -30 ms) observed here (Decety et al., 1994; Flanders & Cordo, 1989; Miall & Wolpert, 1996; Petersen et al., 1998; Raiguel et al., 1999). Conversely, if PPC neurons were responsible for generating outgoing motor commands (u in equation 1), subsequent stages of processing and execution of the movement would require at least 90–100 ms to produce the corresponding cursor motion (Miall & Wolpert, 1996). For instance, similar analyses for velocity have been performed in the primary motor cortex and report average OLTs of approximately 90–100 ms (Ashe & Georgopoulos, 1994; Paninski et al., 2004). Therefore, it is unlikely that PPC is primarily driving motor
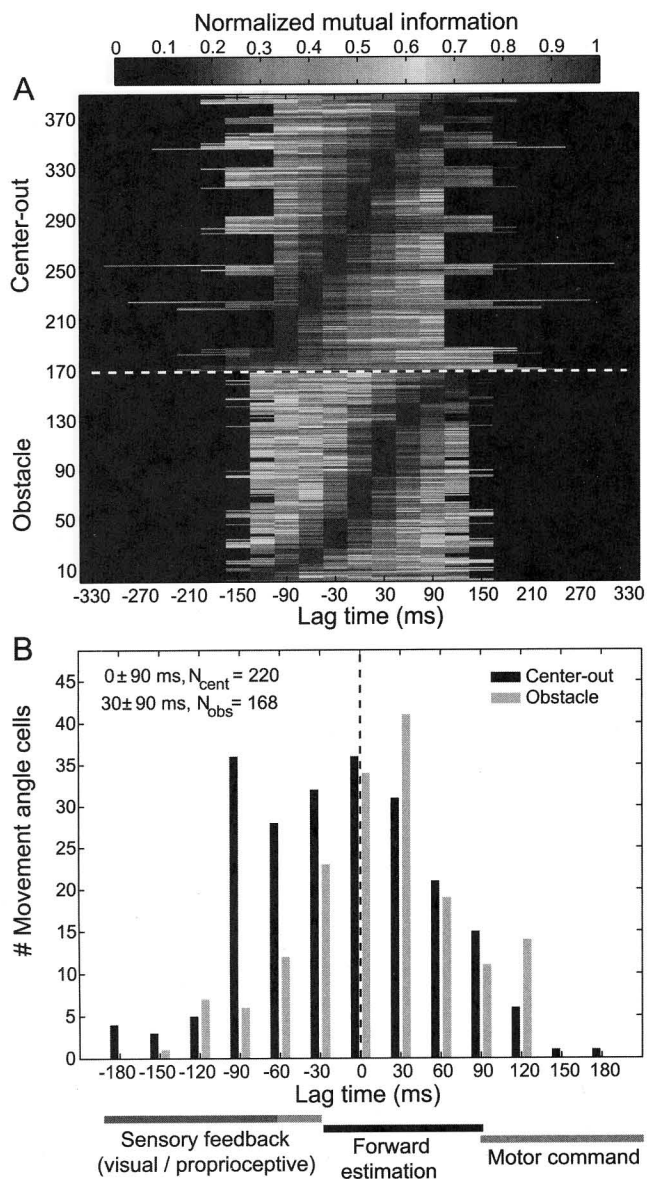
A

Normalized mutual information

0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1

Center-out / Obstacle (y-axis labels): 370, 330, 290, 250, 210, 170, 130, 90, 50, 10

Lag time (ms): -330 -270 -210 -150 -90 -30 30 90 150 210 270 330

B

0 ± 90 ms, N_{cent} = 220
30 ± 90 ms, N_{obs} = 168

■ Center-out ▨ Obstacle

Movement angle cells: 0, 5, 10, 15, 20, 25, 30, 35, 40, 45

Lag time (ms): -180 -150 -120 -90 -60 -30 0 30 60 90 120 150 180

Sensory feedback (visual / proprioceptive) — Forward estimation — Motor command

FIGURE 41.3 Population temporal encoding results. (*A*) Population TEFs plotted for all movement angle neurons showing cell-normalized mutual information as a function of lag time. (*B*) Histogram summarizing the OLTs for movement angle neurons for both center-out and obstacle tasks (summary statistic in upper-left corner: median ± interquartile range). Many of these neuron's OLTs were consistent with a forward estimate of the state of the movement angle, which did not directly reflect delayed sensory feedback to PPC, nor were they compatible with outgoing motor commands from PPC. (Reprinted with permission from Mulliken, Musallam, & Andersen, 2008a.) (See color plate 53.)

cortex with feedforward commands, since it would be expected that PPC should lead the movement state by more than motor cortex does, on average (i.e., OLT > 90 ms). Neither passive sensory feedback nor efferent motor explanations best account for the responses of neurons whose OLTs fall between −30 and 60 ms. Instead, these cells appear to encode a forward-state estimate,

which allows PPC to monitor the current and upcoming states of the movement angle prior to the arrival of delayed sensory feedback. It does not appear that this current-state estimate is merely a blend of incoming sensory and outgoing motor representations (i.e., a simple summation of two modal distributions centered at negative and positive lag times should result in a bimodal or potentially "flat" distribution), since our OLT distributions appear to show a pronounced unimodal peak around 0 ms. Furthermore, the peak information (mutual information at the OLT) encoded by neurons that were most clearly forward-estimating (0 ≤ OLT ≤ 60 ms) was significantly larger than the peak information encoded by the remaining population of movement angle neurons (OLT ≤ −30 ms, or OLT ≥ 90 ms). Therefore not only does PPC have a central tendency to encode the current state of the movement angle, but forward-estimating neurons also contained significantly more information about the movement state than did neurons with other OLTs, suggesting that these state estimates are generated by some active computational process (i.e., a forward model).

While it is likely that PPC relies upon a forward model to estimate the current state of the cursor (i.e., a priori estimate), it is also possible that sensory information is integrated by PPC to update this estimate. As mentioned above, it has been suggested that the a priori state estimate is generated by the cerebellum and then sent to PPC (Shadmehr & Krakauer, 2008). In this situation, these authors suggested that PPC is responsible only for processing afferent signals (i.e., matrix *H* in equation 2), specifying the Kalman gain to optimally incorporate sensory information into a refined, a posteriori state estimate. Given known afferent projections to PPC (both visual and proprioceptive) as well as evidence from our data demonstrating that some movement angle neurons appear to encode a passive sensory representation of the state (i.e., OLT <= −30 ms), it seems likely that PPC does integrate delayed sensory information. However, on the basis of our data and evidence from the mental simulation literature (discussed above), we suggest that PPC is also involved directly in performing forward model computations, perhaps within a reciprocal, functional loop that includes the cerebellum (Blakemore & Sirigu, 2003). That is, the forward state estimates found in PPC most likely reflect the output of an observer, which is involved in both performing the computations of the forward model and integrating sensory feedback into the state estimate.

DYNAMIC TUNING AND SEPARABILITY OF MOVEMENT ANGLE STTF Further support for state estimation in PPC was obtained from analyzing the spatiotemporal encoding properties of movement angle STTFs. We measured changes in the preferred direction of a neuron, θ_{pd}, over a range of

lag times. θ_{pd} is the movement angle at which a neuron fired maximally for a particular lag time. We reasoned that if θ_{pd} did not vary significantly as a function of lag time compared to changes that occurred in the movement angle itself, then that neuron encoded a mostly straight trajectory. Across the population of movement angle neurons, most neurons' STTFs exhibited small changes in θ_{pd} as a function of lag time, which were significantly less than changes observed in the actual movement angle in the trajectories themselves (figure 41.4AB).

We performed an additional separability analysis to further characterize the relationship between angle and lag time encoded by a neuron's STTF. A perfectly separable STTF indicates that the lag time and angle were encoded independently of one another. We determined that the population of movement angle neurons was largely separable in the angle-time plane by using singular value decomposition (SVD) (Mazer, Vinje, McDermott, Schiller, & Gallant, 2002; Pena & Konishi, 2001). We calculated the fractional energy contained in the singular values for each cell's movement angle STTF; 92.0 ± 14.7% and 78.9 ± 25.8% of energy (median + IQR) was contained in the first singular value, for

the center-out and obstacle tasks, respectively (figure 41.4C). The distribution of fractional energies contained in the first singular value is shown in figure 41.4D.

These results suggest that dynamic sensorimotor control mechanisms in PPC encode mostly straight and instantaneous trajectories, with a less substantial component of the neurons' firing rates arising because of nonlinear encoding mechanisms that may reflect the slight curvature we observed in the STTFs. This interpretation is consistent with PPC neurons encoding a state estimate of the movement direction, such that the majority of information is encoded at a cell's OLT, with decreasing information encoded away from the OLT. (Note that a perfectly instantaneous state estimate, that is, a delta function, should not be expected due to autocorrelation present in continuous motor variables such as movement angle.)

Reading out the dynamic state of a cursor from PPC

It would be interesting to test whether a dynamic state estimate in PPC, presumably reflecting the operation of an observer, could be used to causally control an external device
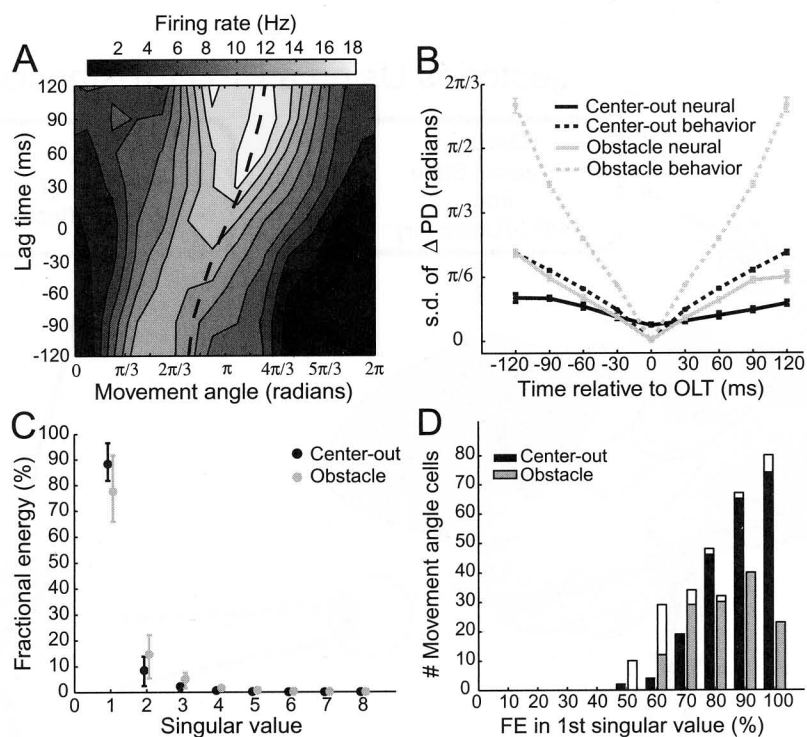

FIGURE 41.4 Curvature and separability of STTFs. (A) Example STTF containing slight curvature. The θ_{pd} of this cell (dashed line) changed smoothly but slightly as a function of lag time. (B) Standard deviation of the population's distribution of θ_{pd} changes ($\sigma_{d\theta}$), plotted as a function of time relative to the OLT. For both center-out and obstacle tasks, the population $\sigma_{d\theta}$ (neural, solid lines) was significantly less than the $\sigma_{d\theta}$ for the actual movement angle (behavior, dashed lines) over the same time range. (C) Population summary of fractional energy (FE) accounted for by each singular vector in the singular vector decomposition (SVD) analysis. The majority of energy in movement angles STTFs was captured by the first singular vectors for the center-out and obstacle tasks, respectively. (D) Population histogram showing distribution of FE of the first singular value for all movement angle cells. (Reprinted with permission from Mulliken, Musallam, & Andersen, 2008a.)

besides our own limbs. During recent years, several groups have leveraged the findings from decades of primate neurophysiology toward the development of an important medical application: a neural prosthesis to assist paralyzed individuals. A neural prosthesis would directly read out the desired movement intentions of a patient from regions of the brain that are not affected by injury or disease.

Several groups have successfully extracted continuous movement information (i.e., trajectories) from motor cortices, such as M1 and dorsal premotor cortex (PMd) (Carmena et al., 2003; Kennedy, Bakay, Moore, Adams, & Goldwaithe, 2000; Musallam et al., 2004; Patil, Carmena, Nicolelis, & Turner, 2004; Santhanam, Ryu, Yu, Afshar, & Shenoy, 2006; Serruya, Hatsopoulos, Paninski, Fellows, & Donoghue, 2002; Shenoy et al., 2003; Taylor, Tillery, & Schwartz, 2002; Wessberg et al., 2000; Wolpaw & McFarland, 2004). In contrast to signals extracted from M1, which are more likely to encode movement execution signals that are represented in a musculoskeletal reference frame, high-level visuomotor signals can be found in earlier stages of the dorsal visual pathway, such as in PPC or PMd. For example, the goal of a reach in visual coordinates has been decoded successfully from both PPC and PMd neurons

(Musallam, Corneil, Greger, Scherberger, & Andersen, 2004; Santhanam et al., 2006). Sensorimotor areas of cortex, particularly those that are strongly innervated by visual feedback projections (e.g., PPC) represent candidate regions that are potentially useful for driving a neural prosthesis since a primary source of input, visual information, is typically uncompromised after paralysis (figure 41.5).

OFFLINE DECODING OF TRAJECTORIES We recently built upon the work of Musallam and colleagues and demonstrated that a PPC prosthesis can also be used to perform continuous control of a computer cursor (Mulliken, Musallam, & Anderson, 2008b). First, we showed that we could reliably reconstruct monkeys' trajectories off-line using a small ensemble of PPC cells. For example, decoding from just five single neurons using a Kalman filter, we demonstrated that we could account for more than 70% of the variance in the cursor position. Interestingly, by extracting information about the goal of a trajectory (i.e., target information that is also known to be encoded in PPC) and incorporating it into the Kalman filter framework, we were able to significantly improve the accuracy of the decoded estimate (on average by 17% over a standard Kalman filter).

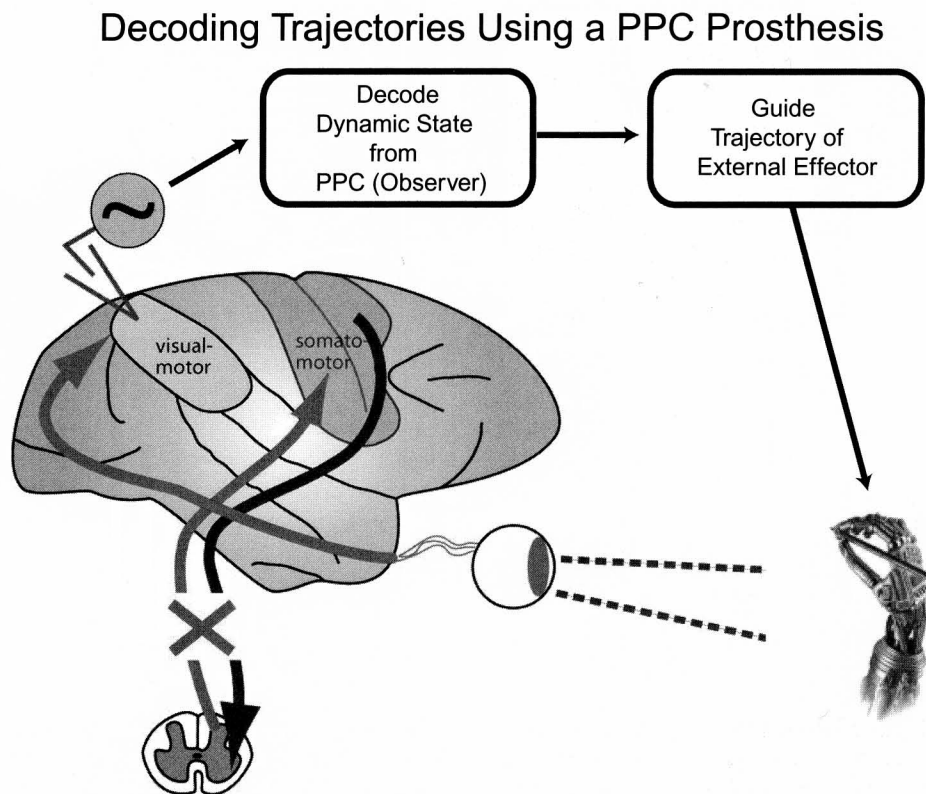## Decoding Trajectories Using a PPC Prosthesis

FIGURE 41.5 A neural prosthesis using PPC for trajectory control. A spinal cord injury can render communication (afferent and efferent) between somatosensory and motor areas of cortex and the limbs useless. However, the integrity of the "vision for action" pathway may still be largely intact, which includes PPC. Decoding algorithms are designed to optimally estimate the state of the effector from the measurement of neural activity from PPC ensembles.

In these decoding experiments, we presumably were decoding from the output of an observer, thereby harnessing a forward estimate of the expected (e.g., current) sensorimotor state of the cursor. To verify this, we also decoded the state (in this situation, the position and velocity) of the cursor shifted in time relative to the instantaneous firing rate measurement, with lag times ranging from −300 ms to 300 ms, in 30-ms steps (where negative lag times correspond to past movement states and positive lag times correspond to future movement states). The optimal lag time (OLT) for decoding velocity using the G-Kalman filter was 10 ms in the future, consistent with previous claims that PPC best represents the current state of the velocity (Mulliken, Musallam, & Andersen, 2008a). The position of the cursor was best decoded slightly further into the future, at an OLT of approximately 40 ms. These temporal decoding results suggest that the current or upcoming state of the cursor could be best extracted from the PPC population by using the Kalman filter. These results are by and large similar to the encoding analyses reported above, and they suggest that PPC is involved in maintaining an estimate of the current and upcoming state of the cursor, consistent with the output of a forward model.

Closed Loop Brain Control Decoding   In addition to off-line decoding, we demonstrated that we could decode trajectories during closed loop brain control sessions, in which the real-time position of the cursor was determined solely by a monkey's thoughts. Initially, the monkey performed brain trajectories at approximately a 30% success rate (for eight targets), but he quickly improved his performance to an 80% success rate after just four to five sessions. This increase in behavioral performance was accompanied by a corresponding enhancement in neural tuning properties, showing that learning effects occurred in the PPC ensemble. For instance, off-line analyses showed that the neurons' average tuning depth increased by more than 70%, the average coverage of two-dimensional space of the population increased by 35%, and the off-line decoding performance (i.e., R^2) of the PPC ensemble increased by more than twofold. These data show that PPC ensembles can be harnessed independently for real-time continuous control of a cursor. In addition, the ability of PPC to causally control a cursor indicates that the state representation in PPC does not rely entirely on visual/proprioceptive information but instead may reflect current and future state estimates generated by a forward model. Last, we expect, on the basis of our findings here and PPC's known functional role in combining visual and motor representations, that PPC will be particularly well suited to serve as a target for a prosthesis that relies upon visually guided feedback for continuous control and error-driven learning.

The ability to extract both trajectory and goal information from neural activity makes this brain area an attractive target for a neural prosthesis. For example, a continuous decoder that estimates the dynamic state of the cursor could be improved by using target information to constrain the decoded trajectory on the basis of its inferred endpoint (Srinivasan & Brown, 2007). The observation that these neurons appear to encode mostly straight lines in visual space may prove to be more straightforward to decode. For instance, PPC neurons may be more flexible for controlling a variety of end effectors, including but not limited to the human arm. Finally, when training a prosthetic in a clinical setting, the operator must rely on a patient's ability to imagine moving an effector in space. Motor imagery studies suggest that PPC is a critical node for maintaining an accurate estimate of the state of the hand during mental simulation of movement. Therefore, we expect that PPC will be a useful site for extracting time-varying trajectory information that accurately matches the desired, real-time sensory outcome of an intended movement trajectory. These findings mark an important step forward in the development of a neural prosthesis using signals from PPC.

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