FEATURE ARTICLE

Vision for Prehension in the Medial Parietal Cortex

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Abstract

In the last 2 decades, the medial posterior parietal area V6A has been extensively studied in awake macaque monkeys for visual and somatosensory properties and for its involvement in encoding of spatial parameters for reaching, including arm movement direction and amplitude. This area also contains populations of neurons sensitive to grasping movements, such as wrist orientation and grip formation. Recent work has shown that V6A neurons also encode the shape of graspable objects and their affordance. In other words, V6A seems to encode object visual properties specifically for the purpose of action, in a dynamic sequence of visuomotor transformations that evolve in the course of reach-to-grasp action.

We propose a model of cortical circuitry controlling reach-to-grasp actions, in which V6A acts as a comparator that monitors differences between current and desired hand positions and configurations. This error signal could be used to continuously update the motor output, and to correct reach direction, hand orientation, and/or grip aperture as required during the act of prehension.

In contrast to the generally accepted view that the dorsomedial component of the dorsal visual stream encodes reaching, but not grasping, the functional properties of V6A neurons strongly suggest the view that this area is involved in encoding all phases of prehension, including grasping.

Key words: dorsal stream, human and nonhuman primates, object grasping, posterior parietal cortex, reaching movements, visuomotor control

The Medial Posterior Parietal Cortex

The well-known "Two Visual Systems Hypothesis" proposed by Goodale and Milner (1992) condensed into a unique frame a wealth of functional, anatomical, and neuropsychological studies. The model that emerged from these studies is that in the dorsal visual stream, hierarchically directed toward posterior parietal cortex (PPC), visual information is mainly exploited to guide action, as opposed to the ventral visual stream -involving the inferior temporal cortex- where visual information is analyzed for the purpose of recognizing, analyzing, and categorizing visual objects (Milner and Goodale 1995). Although interconnected, the 2 streams appear as separate visual pathways, for action and for perception, respectively (Goodale 2014). This distinction is supported by single-cell studies in awake animals,

by analysis of behavior in healthy subjects and neurological patients, and by neuroimaging studies.

When the 2 stream theory was first advanced (Ungerleider and Mishkin 1982), it was reported that the recipient of visual information in the dorsal stream was the inferior parietal lobule (see Fig. 1A). It subsequently became clear that the cortex lying medially to the intraparietal sulcus, namely the superior parietal lobule (SPL), also receives visual information (Colby et al. 1988; Gattass et al. 1988; Galletti et al. 1991, 1996; Johnson et al. 1993). This other circuit within the dorsal visual stream was termed the dorso-dorsal visual stream (Rizzolatti and Matelli 2003) or dorsomedial visual stream (Galletti et al. 2003), as opposed to the ventro-dorsal (Rizzolatti and Matelli 2003) or dorsolateral (Galletti et al. 2003) stream (Fig. 1B), which involves the inferior parietal lobule.
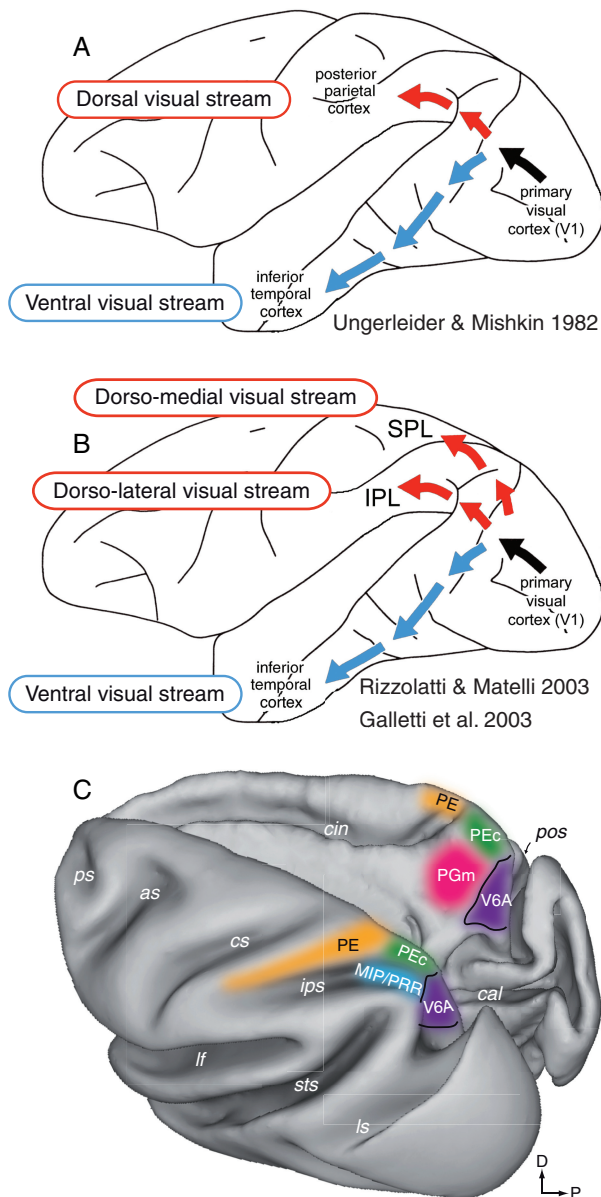
Figure 1. Visual streams in the macaque brain. (*A*, *B*) Lateral views of the macaque brain where (*A*) the dorsal and ventral visual streams are shown according to Ungerleider and Mishkin (1982), and (*B*) the 2 subdivisions within the dorsal visual stream are shown according to Rizzolatti and Matelli (2003) and Galletti et al. (2003). (C) Dorsal view of left hemisphere (left) and medial view of right hemisphere (right) reconstructed in 3D using Caret software (http://brainvis. wustl.edu/wiki/index.php/Caret:Download) showing the location and extent of V6A (purple). The other medial PPC areas are also shown. Green: PEc (Pandya and Seltzer 1982); orange: PE (Pandya and Seltzer 1982); blue: MIP/PRR, medial intraparietal area/parietal reach region (Colby and Duhamel 1991; Snyder et al. 1997); magenta: PGm (Pandya and Seltzer 1982); as, arcuate sulcus; cal, calcarine sulcus; cin, cingulate sulcus; cs, central sulcus; ips, intraparietal sulcus; lf, lateral fissure; ls, lunate sulcus; pos, parieto-occipital sulcus; ps, principal sulcus; sts, superior temporal sulcus; D, dorsal; P, posterior.

The SPL, which occupies the medial part of PPC, is composed of numerous areas (see Fig. 1C), all of which have been implicated in arm reaching movements (Ferraina et al. 1997; Snyder et al. 1997; Battaglia-Mayer et al. 2001; Fattori et al. 2001, 2005; McGuire and Sabes 2011; Hwang et al. 2014; Hadjidimitrakis et al. 2015): areas PE and PEc, located nearby on the exposed surface of SPL, area PGm (or 7 m), on the mesial surface of the hemisphere,

area V6A, located posterior to PEc and hidden in the parieto-occipital sulcus, and the functionally defined parietal reach region (PRR; see Fig. 1C) which includes a number of anatomically defined cortical areas, including MIP (Gail and Andersen 2006), hidden in the medial bank of intraparietal sulcus (Andersen et al. 2014; Hwang et al. 2014).

There is strong evidence that the caudal part of SPL, in particular area V6A, is a crucial node of the dorsal visual stream, at the origin of several pathways for visuo-spatial processing and hand action control (Galletti et al. 2003; Rizzolatti and Matelli 2003; Kravitz et al. 2011). Prehension of an object requires processing of object spatial location and physical attributes, as well as motion prediction and haptic information to sense where the hand is going and what it is touching. The full sequence of object grasping consists of: direction of the arm toward the object; alignment of the hand with the main axis of the object; shaping hand configuration to conform to the object shape; and positioning of the fingers to acquire it. Populations of neurons in area V6A encode all these aspects of prehension. This review will summarize several functional properties of area V6A useful for orchestrating prehensile actions, including visual and somatosensory properties, as well as motor cues dealing with reaching and grasping. On the basis of the evidence summarized herein, we propose an updated view of the medial PPC, in which integration of both reaching and grasping occurs, and we advocate a reinterpretation of the role of the dorsomedial visual stream in the control of prehension.

The Sensory Properties of Area V6A

Visual Properties

Area V6A occupies most of the anterior bank of the parieto-occipital sulcus as well as the caudalmost part of the precuneate cortex (see Fig. 1C). This cortical region belongs to the classic visual association cortex, namely area 19 of Brodmann (for a thorough review on this topic, see Gamberini et al. 2015). However, since the first description of this region, it was evident that not all neurons were visually activated. Cells in the ventral part of the anterior bank of the parieto-occipital sulcus were all very sensitive to visual stimulation, but cells in the dorsal part of it were sometimes insensitive to visual stimulation, or weakly activated by visual stimuli (Galletti et al. 1991). When we began to study this region of the brain in awake animals, we retained the name "V6" (Galletti et al. 1991) given to it by Semir Zeki some years before (Zeki 1986), but later we decided to use the name V6 to indicate only the ventral, fully visual region, and to refer to the dorsal region, which is less sensitive to visual stimulation, as V6A (Galletti et al. 1996).

The majority of visually responsive V6A cells exhibit clear and repetitive responses to visual stimuli rear projected on a tangent screen in front of a monkey that was performing a fixation task. We employed simple visual stimuli, such as light/dark borders, light/dark spots, or bars moved across the visual receptive field with different orientations, directions, and speeds. We also tested more complex stimuli, like light/dark gratings and corners of different orientation, direction, and speed of movement, or complex shadows continuously changing in form, direction, and speed of movement. Approximately 60% of cells in V6A showed visual responsivity, with the majority of them located in the ventral aspect of the area (Gamberini et al. 2011), as shown in Figure 2D, left.

When a neuron responded to the simplest visual stimulations among those we used, it was classified as low-level visual cell,
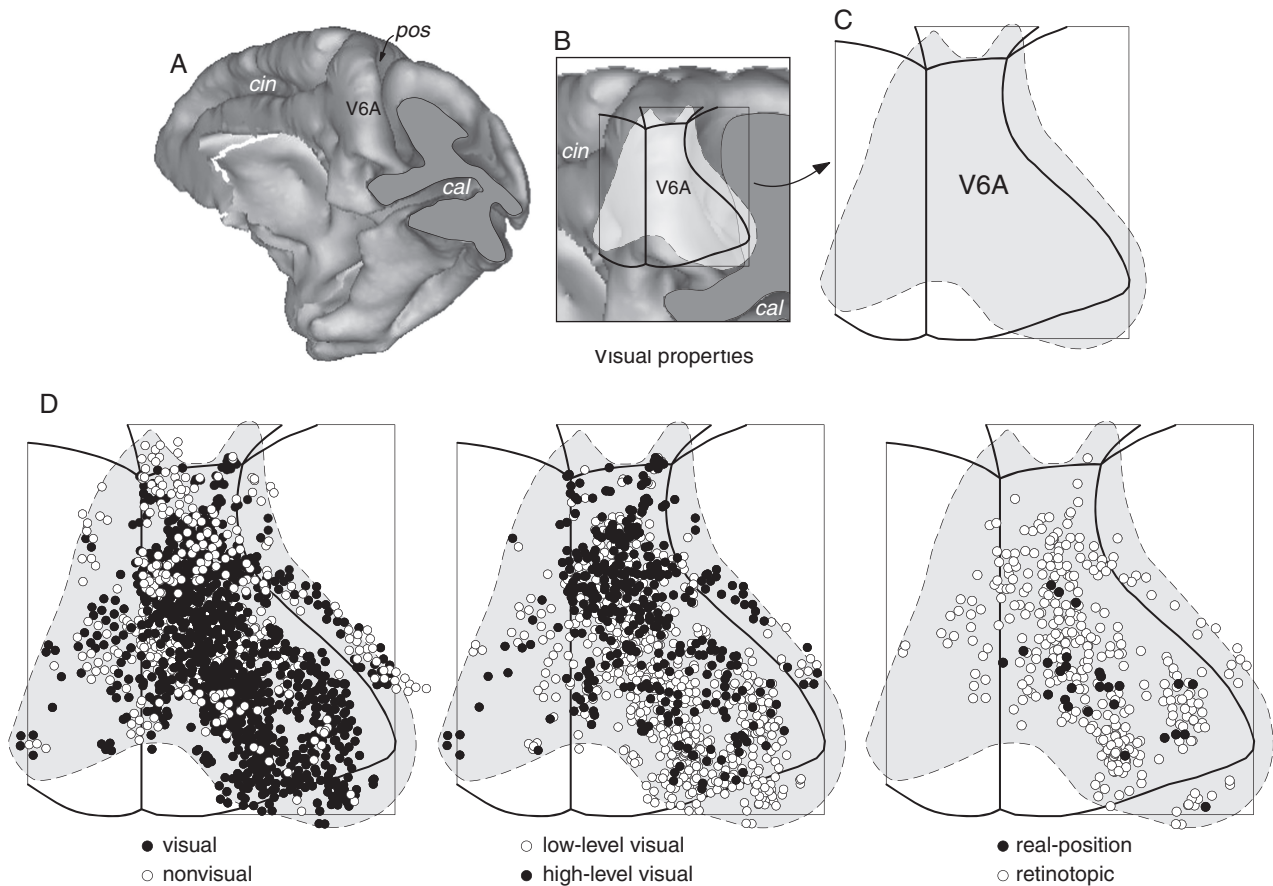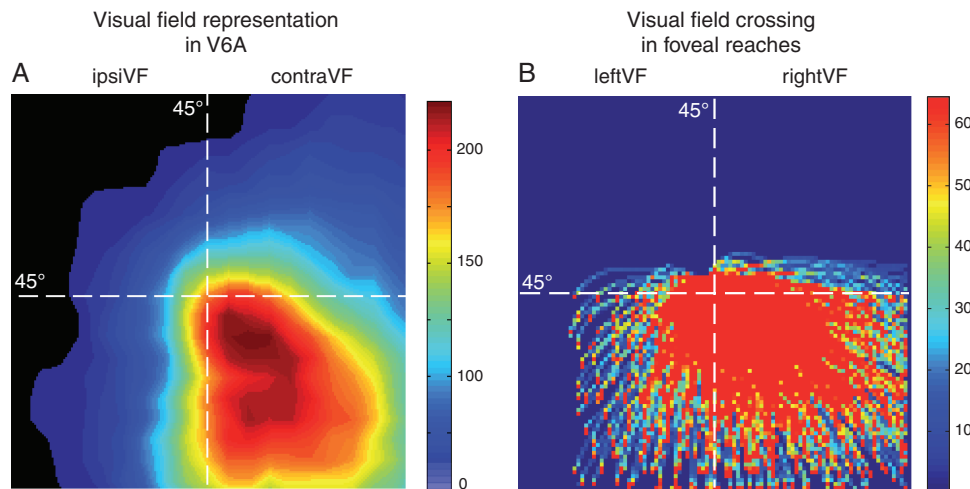
Figure 2. Bidimensional reconstructions of area V6A showing the cortical distribution of visual cells. (A) Posteromedial view of the surface-based 3D reconstructions of the Caret ATLAS brain with the posterior part of the occipital lobe cut away to visualize the entire extent of the anterior bank of parieto-occipital sulcus. The level of the cut is shown in gray. (B) Anterior bank of the parieto-occipital sulcus and, superimposed, a flattened map of the caudal part of the SPL shown in C. Gray: extent of V6A on the 2D map. (C) 2D map of caudal SPL D) SPL map with the locations of cells recorded in area V6A and tested with visual stimulations. Left: distribution of the cells sensitive (visual) and unsensitive (nonvisual) to visual stimuli. Middle: distribution of cells sensitive to simple visual stimuli like light/dark borders, light/dark spots, and bars (low-level visual) and to complex visual stimuli like light/dark gratings and corners of different orientation, direction, and speed of movement, or complex shadows continuously changing in form, direction, and speed of movement (high-level visual). Right: distribution of real position cells. All conventions are as in Figure 1. Modified from Gamberini et al (2011).

whereas neurons that responded only to complex visual stimulation were classified as high-level visual cells. The distribution within V6A of these 2 types of cells is shown in the central panel of Figure 2D. There is a dorso-ventral gradient of this response property, with high-level visual cells predominantly found in the dorsal part of the area and low-level visual cells predominantly in the ventral part (Gamberini et al. 2011).

A peculiar aspect of the visual properties of area V6A is that a minority of visual cells, called real-position cells, show visual receptive fields that remain stable in space, regardless of eye movements (Galletti et al. 1993, 1995). Interestingly, this cell type is confined to the ventral part of area V6A (Gamberini et al. 2011), as shown in the right panel of Figure 2D. Real-position cells have rarely been found in the visual cortex, and reported only in a few parietal areas of the dorsal visual stream [in ventral intraparietal area (VIP), Duhamel et al. 1997; in areas MIP and lateral intraparietal area (LIP) Mullette-Gillman et al. 2005; but see for contrasting results Chen et al. 2013, 2014], and in the ventral premotor cortex (Fogassi et al. 1992; Graziano and Gross 1998). These cells represent about 10% of neurons in V6A (Galletti et al. 1993, 1995), and about 20–25% in VIP (Duhamel et al. 1997), MIP, and LIP (Mullette-Gillman et al. 2005). They are more prevalent in premotor cortex, where they are the majority of cell population (Fogassi et al. 1992; Graziano and Gross 1998).

The receptive fields of V6A visual cells cover a large part of the visual field, but the representation is not a point-to-point retinotopic organization, and nearby neurons within the area often represent completely different parts of the visual field (Galletti et al. 1999). The representation of the lower contralateral quadrant is particularly emphasized, from the fovea to the far periphery (see Fig. 3A). Interestingly, this part of the visual field shows psychophysical advantages for hand action control. In fact, when the visual stimulus is in the lower visual field, the grasping action is more precise (Brown et al. 2005), and pointing is faster and more accurate (Danckert and Goodale 2001). It is worthwhile to notice that the part of the visual field most represented in V6A perfectly matches the region of space that the contralateral hand and arm traverse when reaching for a foveated target. In Figure 3B, we traced trajectories of the dominant-right arm of human subjects while they reached toward foveated targets placed in several positions on a frontoparallel panel. The trajectories were traced by superimposing the arrival points at the center of the panel, as if subjects always looked and reached straight ahead. The coordinate system is referred to the left and right visual fields, allowing for monitoring of the part of the visual field they passed through during the reaching movement. The subjects started the arm movement from 3 different positions in the lower visual field, at the left, center, and right with respect to body midline, and

Visual field representation
in V6A

A   ipsiVF   contraVF

Visual field crossing
in foveal reaches

B   leftVF   rightVF

Figure 3. Visual field representation in V6A, and its possible use in reaching control. (A) Spatial locations occupied by V6A visual receptive fields. Color scale indicates the relative density of receptive fields covering that specific part of the visual field. In the dark red region, more than 200 visual receptive fields are superimposed in the same part of visual field. ipsiVF, ipsilateral part of the visual field; contraVF, contralateral part of the visual field. White dashed lines represent the horizontal and vertical meridians. (B) Arm trajectories of human volunteers performing reaching movements to foveal targets. All trajectories are represented superimposing the reaching point: ipsiVF and contraVF, part of space ipsilateral and contralateral with respect to the reaching arm, respectively. Colors going toward the red indicate the highest number of trajectories occupying that part of the visual field (left and right are referred to the participant's visual field). It is evident a strong coincidence between the visual field representation in V6A and the part of the visual field where the arm passes through during reaching. Methodological details on the data reported in B: participants were seated in front a 90 × 60 cm frontoparallel panel located at 54 cm from the eyes on which they performed 3D reaching movements using their dominant hand. There were 195 positions of targets that participants could reach. The targets were arranged in a rectangle covering the entire area of the panel and were located at a distance of 3 cm from each other. Hand position was measured by a motion capture system following the procedures described in Bosco et al. (2015). The hand movements could start from 3 different positions with respect to the body's midline: −15, 0, and +15 cm, respectively. Participants were tested in 3 repetitions of movements for each target for a total of 585 movements. Each repetition corresponded to 3 different hand starting positions. Participants began the movements after a verbal go signal and were instructed to look at the target during the motor response. Participants executed reaches at a normal speed. For data processing and analysis, see Bosco et al. (2015). To transform spatial coordinates of trajectories in visual coordinates, we computed the new trajectories with respect to the coordinates of the center of panel. In this way, the trajectory endpoints converged on the origin of the new coordinate system representing the fovea, as reaching targets were always foveated.

reached different positions in front of them. This is consistent with movements as usually performed in everyday life. Notably, the trajectories for arm movements to targets located to the right of the hand starting position cover the medial part of the lower left quadrant of the visual field, because the arm crosses that space at the left of gaze. Reach trajectories toward lower targets cover the lower part of the upper hemifield, whereas reaches toward all other targets generate trajectories that mostly pass through the right lower visual field. Of course, only a minor part of the upper visual field is traversed by hand/arm trajectories. All together, the reach trajectories parallel the parts of visual field covered by visual receptive fields in V6A (see Fig. 3A). In other words, visual representation in V6A is focused on the part of visual space where most reach trajectories and grasping actions are performed, and where the visuomotor system controls better skilled actions (Previc and Mullen 1990; Danckert and Goodale 2001; Brown et al. 2005; Graci 2011; Rossit et al. 2013). Interestingly, imaging studies in humans strongly support these data, showing that the human homolog of V6A (Pitzalis et al. 2013) is specialized for processing information in the lower visual field, particularly in the context of object-oriented actions (Rossit et al. 2013).

Somatosensory Properties

Visual input is not the only sensory information available to V6A. This area receives contralateral somatic inputs, especially from the upper limbs (Breveglieri et al. 2002). Approximately 30% of V6A cells are responsive to tactile or proprioceptive stimuli. Most somatosensory cells had somatic receptive fields on the proximal part of the arm, with a smaller fraction on the distal segment, including the hand. Proprioception is more strongly

represented than touch (75% vs. 25%). Among proprioceptive inputs, the best representation is that of shoulder joint (ca. 75%; see the example in Fig. 4D), followed by the elbow (ca. 15%), and finally the joints in the distal part of the arm (ca. 10%). The relative incidence and spatial distribution of somatosensory cells within V6A is shown in Figure 4B. It is evident that somatosensory responses are more represented in the dorsal part of V6A (Gamberini et al. 2011), that is, in the region where visual cells are less abundant. In addition, the map of Figure 4B shows that somatosensory representation is incomplete in V6A, with the head and legs not represented, and no clear somatotopy (Fig. 4C). The body representation in V6A is dissimilar from the well-known homunculus represented in primary somatosensory cortex, as neighboring cells have receptive fields in different parts of the body (Fig. 4B), and the upper limbs are overrepresented in V6A versus the disproportionately large representation of head and hands in primary somatosensory cortex (compare Fig. 4A and C). It is worthwhile to note that the missing parts of the body in V6A are instead well represented in other parietal areas, for example, the head in area VIP (Duhamel et al. 1998) and the leg in area PEc (Breveglieri et al. 2006) and PE (Iwamura 2000). The rich representation of the arm in V6A is indicative of a strong involvement of this area in the somatosensory-based encoding of arm reaching movements. We will further explore this point below, in the treatment of motor-related properties of this area.

The Motor-Related Properties of Area V6A

Reaching

As described above, V6A is a component of Brodmann's area 19, and thus part of classical visual association cortex. Therefore,

V6A somatosensory representation
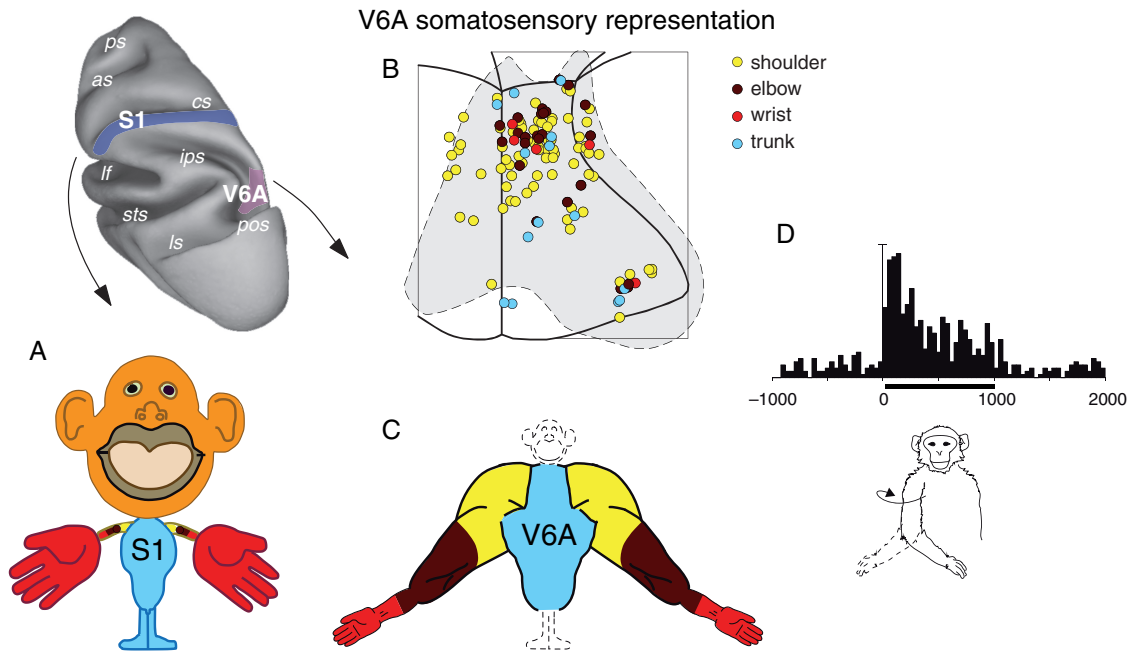
Figure 4. Somatosensory representation in V6A. (A) Top: dorsolateral view of the macaque brain where areas S1 and V6A are shown in blue and pink, respectively. Bottom: homunculus of area S1, reporting S1 body representation from both hemispheres. (B) Flattened 2D map of V6A showing the locations of cells whose somatosensory receptive field is located in the body parts sketched in the homunculus shown in C (for colors, see legend in the figure). (C) Body representation in V6A reporting the body representation from V6A of both hemispheres: the homunculus derived from V6A somatosensory receptive fields shows an over-representation of torso and shoulders and a lack of head and legs. (D) Neural response of a V6A somatosensory cell. Response is shown as peristimulus time histogram, aligned at the stimulus onset (passive rotation of the shoulder). Vertical scale bar: 75 sp/s. This cell was responsive to the passive rotation of the shoulder (in this case, an abduction of the arm, as sketched in the bottom part of the figure). This movement evoked a brisk increase of the neuronal discharge, which slowly returned to baseline toward the end of rotation. The discharge was absent when the shoulder was rotated in the opposite direction, adducting the arm toward the body. Other conventions as in Figures 1 and 2.

when we began the study of this area we expected that all neurons would be sensitive to visual stimulation. On the contrary, not only we were not able to visually activate all of them, but we discovered that some of the neurons were activated by the movements of the arm. The initial demonstration of arm movement-related activity was obtained with the monkey executing a repetitive and stereotyped arm movement outside its field of view, in complete darkness, while keeping the eyes still on a central steady fixation point (Galletti et al. 1997). In this way, confounding activation was precluded, such as that from visual responses, gaze-related activities, or saccade-related activities, all of which are known to activate V6A neurons (Galletti et al. 1995; Kutz et al. 2003). Under these experimental conditions, about 60% of V6A cells showed arm movement-related activity. It is worthwhile to notice that this movement-related activity often preceded the earliest electromyographic activity, thus preceding any possible sensory feedback from the moving limb (Galletti et al. 1997).

In subsequent experiments, we studied arm movement-related activity with more complex movements, in a reaching task to visual targets (Fattori et al. 2001). To measure reach-related discharges, we used a body-out reaching task (see Fig. 5A) performed in darkness. Animals reached a foveated target, starting with the hand from a position near the body, to reach different positions in the peripersonal space in front of them (Fattori et al. 2005). The discharge of a typical V6A reaching neuron is shown at the top of Figure 5A. This neuron was strongly modulated by the direction of arm movement, increasing for rightward reaches (contraversive with respect to the recording side) and going down till silence for leftward reaches (ipsiversive to the

recording side). Tuning of reach-related activity, which was observed in the vast majority of V6A reaching neurons, cannot be ascribed to visual stimulation, as the task was performed in a dark environment (the only visual stimulus was the small foveal reaching target). One possibility is that the observed spatial tuning reflects somatosensory inputs, that is, proprioceptive or tactile signals from the moving limb. By comparing the onset of reaching discharges with the onset of electromyographic activity (Fig. 5B), we found that about 70% of units discharged before the onset of reaching movement, with 20% of those units firing even before the earliest electromyographic activity. For those neurons, at least, the somatosensory input could not be the source of reaching responses. It is likely that these reach-related discharges relied on copies of efferent signals delivered to V6A from motor centers, such as dorsal premotor areas F2 and F7, which are directly and reciprocally connected to V6A (Matelli et al. 1998; Shipp et al. 1998; Gamberini et al. 2009; Passarelli et al. 2011). Of course, corollary discharges from motor centers may not be the only source of arm movement-related activity. Somatosensory inputs from the moving arm, and in particular proprioceptive inputs from the arm joints, are another likely source of reach-related discharges, and could be responsible for those discharges beginning after the onset of the earliest electromyographic activity (Fig. 5B), and in particular after the onset of arm movement.

We specifically tested whether V6A reach-related activity and its spatial tuning were influenced by the presence of visual feedback, by comparing the neuronal activity in reaching to foveated targets performed in dark versus light conditions (Bosco et al. 2010). As recalled above, reaching activity in the dark reflects
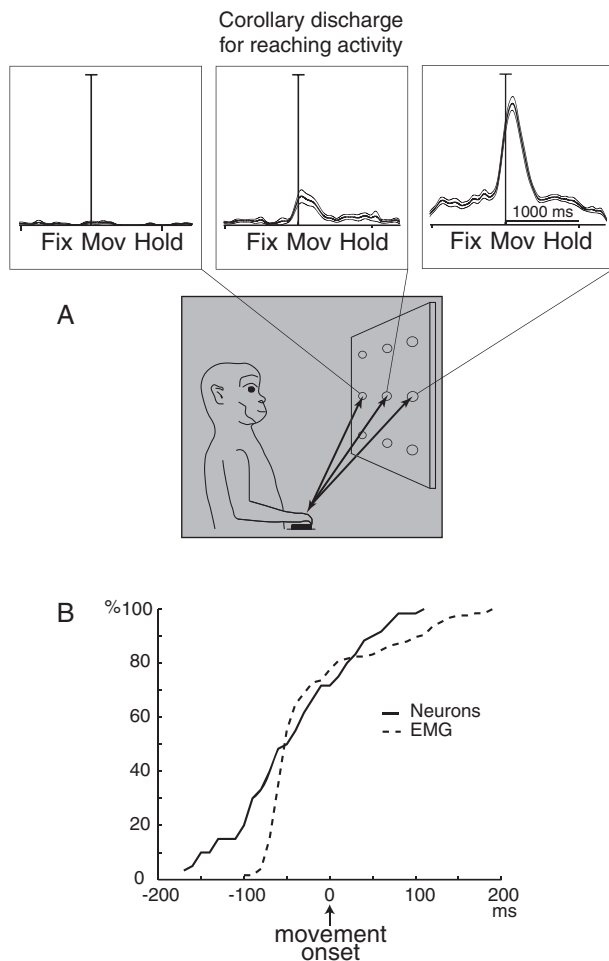
Figure 5. Reaching activity in V6A. (A) Top: neural discharge of a V6A cell tuned for the direction of reaching. Response is shown by spike density functions aligned at the movement onset and placed according to the reaching direction: left, ipsiversive; right, contraversive to the recording side. A clear spatial tuning for reach direction is evident. Bottom: experimental setup. Reaching movements were performed in the dark from a home button (black rectangle) toward one of three targets located on a panel in front of the animal. The task was a foveal reach toward a visual target. (B) Comparison between the latencies of area V6A reach-related activity and of electromyographic (EMG) activity in the reaching task. Plots are cumulative frequency distributions of the latencies of the neural responses to outward reaching movements and of the EMG activity recorded during reaching movements. The horizontal axis shows time in ms, and the vertical axis the percentage of V6A tested cells ($n = 60$) or of muscle EMG activation ($n = 12$). Modified from Fattori et al. (2005).

motor and somatosensory movement-related inputs; in light it also incorporates the visual feedback evoked by the arm movement. Thus, by comparing the neural discharges in these 2 conditions, we could check and weight the modulating effect of visual stimulation. Figure 6 shows some examples of this comparison. We found 3 main categories of cells. Motor cells (Fig. 6, bottom left) displayed equivalent activity for reaching in dark and in light, indicating that they did not receive any visual information during execution of the task. In contrast, the other 2 cell categories shown in the bottom part of Figure 6 did receive visual information during movement execution. Visuomotor "plus" cells (Fig. 6, bottom center) responded more strongly to reaching in light than in dark, suggesting that the visual input and the somatosensory/motor-related input were additive during reaching execution. Visuomotor "minus" neurons (Fig. 6, bottom right)

responded less during reaching in light than in dark, indicating that visual feedback inhibited reaching activity in these cells. The discharge patterns of these 3 types of cells suggest that visual feedback produces complex modulation of firing, characterized by nonadditive interaction between visual and somatosensory-/motor-related signals. The presence of these 3 types of cells suggests that V6A behaves as a "state estimator," that is, it may be involved in comparison of the motor plan with current sensory feedback produced by the moving arm (Bosco et al. 2010). We elaborate upon this hypothesis later, following description of other motor-related properties of V6A.

Grasping

It has been suggested for a long time that the parietal areas of the dorsomedial visual stream, in particular the caudal areas of SPL, encode for reaching, whereas those of the dorsolateral visual stream, especially the anterior intraparietal area (AIP), encode for grasping (Taira et al. 1990; Jeannerod et al. 1995; Gardner et al. 1999, 2007). Involvement of area V6A in the control of arm reaching movement has been repeatedly demonstrated over the past 15 years (e.g., Fattori et al. 2001, 2005). However, experimental demonstration that V6A also shows grasp-related responses and, in particular, that it contains neurons sensitive to wrist orientation and grip formation (Fig. 7), is a recent finding (Fattori et al. 2009, 2010). As with the study of reaching activity, experimental tasks for grasping behavior were performed in darkness, and with the animal maintaining fixation in a constant position. Thus, visual and gaze influences, which are both known to strongly affect the neurons of area V6A (Galletti et al. 1995; Bosco et al. 2010; Breveglieri et al. 2012) were excluded as modulators of grasp-related responses. In the grasping tasks, reach-directional influences were also excluded, as all actions were performed toward objects located in a constant position in the peripersonal space.
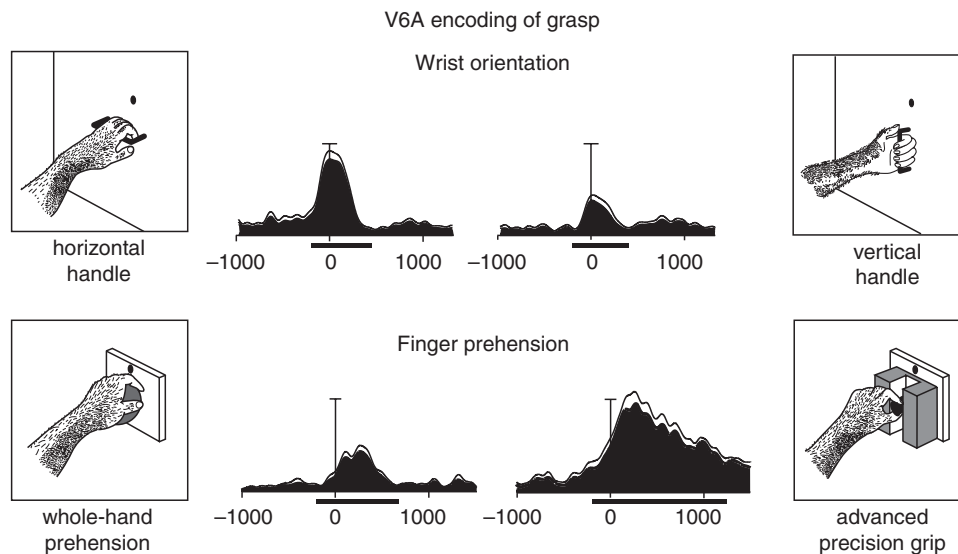
Figure 7 shows examples of cells modulated by wrist orientation (top) and by grip type (bottom). The top part of Figure 7 depicts a cell tuned for orienting the wrist while the animal reached and grasped a handle. Different hand orientations clearly evoked different responses from this cell. The cell's response started well before the onset of movement (alignment line) and peaked immediately afterwards. The discharge was stronger for grasping the horizontally oriented handle. Other neurons showed a clear preference for grasping handles with other orientations. We did not observe a unique preferred orientation in the neuronal population of area V6A (Fattori et al. 2009).

The bottom part of Figure 7 shows a cell tuned for the type of grip used to grasp the object. The left panel illustrates the neural response when the monkey performed a whole-hand "power grasp" of a ball, whereas the right panel shows activity evoked by a precision grip of a small cylinder inserted into a groove. The firing rate increased before the onset of reaching, rose as the hand approached the object, and peaked before the end of the transport phase. The activity of this cell returned to baseline as soon as the object was grasped and held in the monkey's hand. The neuronal response amplitude was modulated by the grip type performed by the monkey, as this neuron clearly distinguished 2 types of grips. In V6A, about half of neurons show grip sensitivity, each with its own grip preference (Fattori et al. 2010).

Overall, we found that the majority of V6A cells were sensitive to both proximal and distal components of reach-to-grasp actions contradicting the theory of separate channels for reaching and grasping (Jeannerod 1986). Neurons encoding the direction of reaching movements represented about 70% of the V6A
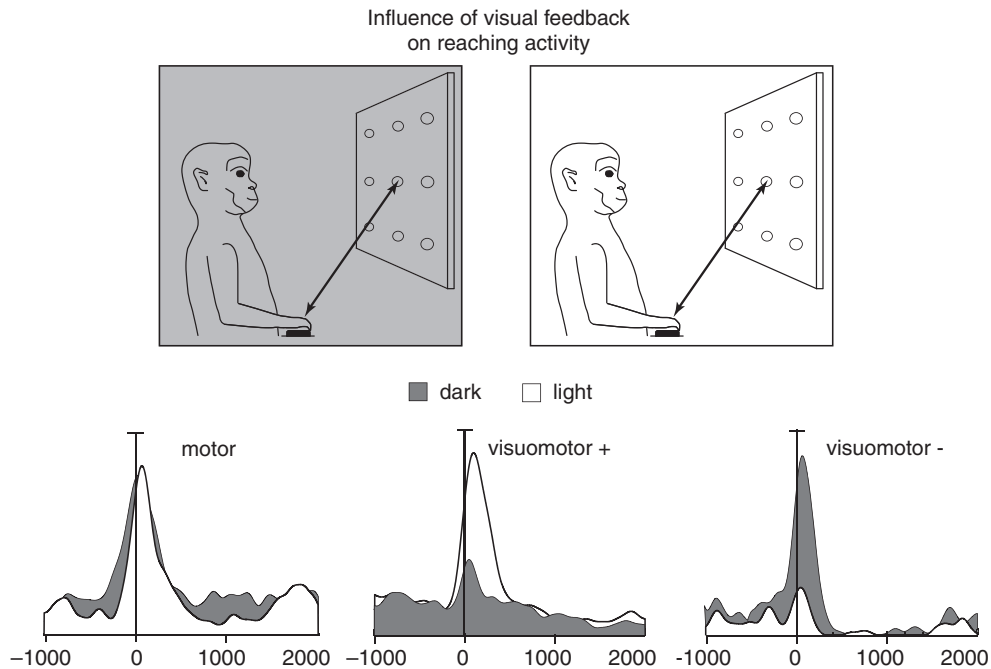
Figure 6. Influence of visual background on reaching activity. Top: sketch of the experimental light conditions where reaching has been tested: complete dark (left) and light (right). Bottom: response of 3 types of neurons to reaching movements performed in light (white) and in dark (gray) towards the central position of the panel (top). Different categories of neurons are shown: motor (left), reaching neurons insensitive to the presence/absence of visual feedback; visuomotor +, cells excited by reaches performed in light (middle); and visuomotor −, cells inhibited by reaches performed in light rather than in dark (right). Activity is aligned on reaching movement onset. Other conventions as in Figure 5. Modified from Bosco et al. (2010).


Figure 7. V6A grasp-related properties. Two examples of cells modulated by wrist orientation (top) and by finger prehension (bottom). Horizontal bars below the spike density functions indicate the duration of the movement epoch considered. On the sides, the sketches of the hand actions performed by the monkey are shown. Other conventions as in Figure 5. Modified from Fattori et al. (2009, 2010).

population, while those sensitive to wrist orientation and to grip formation each accounted for approximately 60% (Gamberini et al. 2011). When the same neuron has been tested for both tuning for reach directions and tuning for wrist orientation, it turned out that 75% of neurons spatially tuned for reach were also sensitive to different wrist orientations used for grasping (Fattori et al. 2009). Moreover, as shown in Figure 8, the spatial distribution of cells sensitive to proximal and distal arm movements is

quite uniform within V6A. Neurons integrating both proximal and distal arm movements are distributed widely within V6A, consistent with the lack of somatotopy shown in Figure 4B.

We have proposed that V6A in monkeys is involved in all phases of reach-to-grasp movements, that is, in the whole act of prehension (Fattori et al. 2010), rather than being limited only to arm reaching movements, as previously supposed for areas of the dorsomedial stream. We believe that convergence
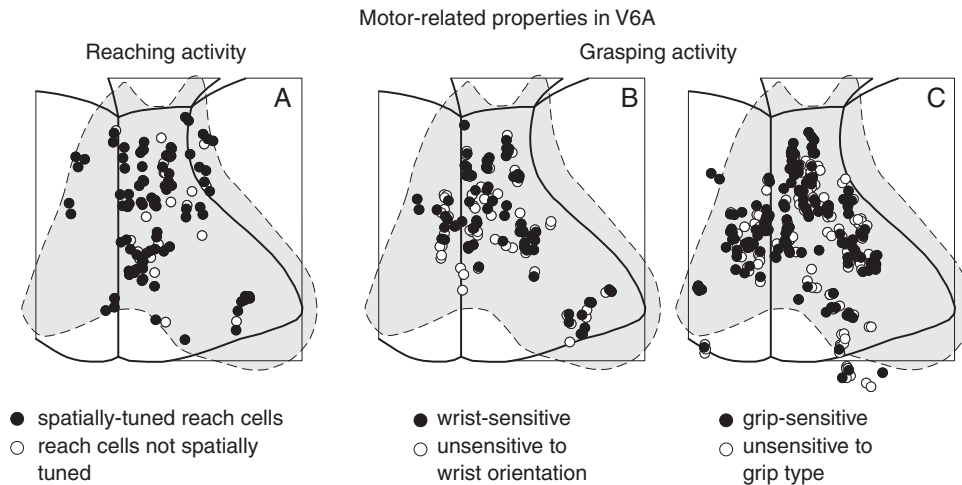
Figure 8. Distribution of prehension-related properties across V6A. Flattened maps showing the distribution of reach cells spatially tuned or not (left), of cells sensitive or not to wrist orientation (middle), and of cells sensitive or not to grip formation (right). Other conventions as in Figure 2. Modified from Gamberini et al. (2011).

of signals from the hand and arm on single cells is the best way to allow a full integration of these signals, in order to plan and execute correct reach-to-grasp arm movements.

These data, together with findings from brain imaging (see next section) and psychophysical studies (Smeets and Brenner 1999; Mon-Williams and McIntosh 2000), challenge the idea of parallel separate channels for reaching and grasping, which was proposed some decades ago (Jeannerod 1981, 1997; Jeannerod et al. 1995) that remains deeply influential (Rizzolatti and Kalaska 2013).

Involvement of Human and Monkey V6A in the Reach-to-Grasp Action

The neurophysiological evidence that V6A is concerned with the control of both proximal and distal movements in reach-to-grasp actions is consistent with neurological studies in humans and lesion studies in monkeys. Human patients with cortical lesions that include the medial PPC typically show misreaching (optic ataxia syndrome; Fig. 9A), but also distal deficits, such as failure to align their hand with the orientation of a slot (Fig. 9B) (Perenin and Vighetto 1988), abnormal finger opening while grasping an object, and failure to scale the grip aperture to the object size (Jeannerod 1986; Jakobson et al. 1991).

In monkeys, selective surgical lesions of area V6A (Battaglini et al. 2002) produce not only misreaching, but also misgrasping, with exaggerated finger extension while the hand approaches the object to be grasped, and erroneous wrist orientation and flexion during object grasping (Fig. 9D). It is therefore likely that optic ataxia patients have cortical lesions that include a human homolog of monkey area V6A (Galletti et al. 2003). In agreement with this view, a reconstruction of cortical lesions in a large number of optic ataxia patients (Karnath and Perenin 2005) showed that the damaged area was centered in the medial parieto-occipital cortex (Fig. 9C) likely involving the human homolog of area V6A (Pitzalis et al. 2013) (compare Fig. 9C and E). The same region was repeatedly shown by imaging experiments to be activated by reaching and pointing movements (Fig. 9F,G; Astafiev et al. 2003; Connolly et al. 2003; Cavina-Pratesi et al. 2010; Vesia et al. 2010; Galati et al. 2011; Striemer et al. 2011; Tosoni et al. 2015). Foci of fMRI activation for reaching in human medial PPC have been identified in proximity to the dorsalmost aspect of parieto-occipital sulcus (Beurze et al. 2007; Tosoni et al. 2008; Filimon et al. 2009; Cavina-Pratesi et al. 2010; Galati et al. 2011; Konen et al. 2013), which is where Pitzalis et al. (2013) reported the human homolog of macaque area V6A (see for a thorough discussion of this aspect, Pitzalis et al. 2015).

Recent neuroimaging studies using decoding techniques from activation patterns and adaptation (Fig. 9H–J) showed that a region of the human brain likely corresponding to V6A plays a role in processing wrist orientation and grip formation (Monaco et al. 2011; Gallivan, McLean, Smith et al. 2011; Gutteling et al. 2015). This agrees with single-cell recording in monkeys (Fattori et al. 2009, 2010), where it has been concluded that V6A is involved in the whole act of prehension, differently from what has been always supposed for the areas of the dorsomedial stream. Together, these results suggest a common role for human and nonhuman primate V6A in the control of reach-to-grasp actions.

Encoding of Vision for Action

The seminal work of Hideo Sakata described a population of hand movement-related neurons involved in grasping behaviors under visual guidance located in area AIP. These grasping neurons are able to match the type of grip with the physical characteristics of the object to be grasped (Taira et al. 1990), and to code small details of visual objects, such as fragments of shapes (Romero et al. 2014). In light of the likely involvement of V6A in encoding prehension, including grasping, we recently tested whether this area is able to encode the visual features of real, 3D graspable objects, and whether single V6A neurons are able to encode both the object and the grip type used for grasping the objects. To do this, we used real objects of different shapes (see Fig. 10) instead of 2D visual stimuli projected on a screen, as we had done previously. The visual responsivity to real objects was tested in tasks where the object was the target of a delayed grasping (Fattori et al. 2012). We found that object presentation activated about 60% of V6A neurons, with about half of them displaying object selectivity.

The majority of object selective cells were also selective for the grip type the monkey performed in the following grasping action (Fattori et al. 2012); cluster analysis showed that object vision (Fig. 10A, top) evoked a visuomotor encoding: the visual responses to objects with a hole (ring and handle; black group)
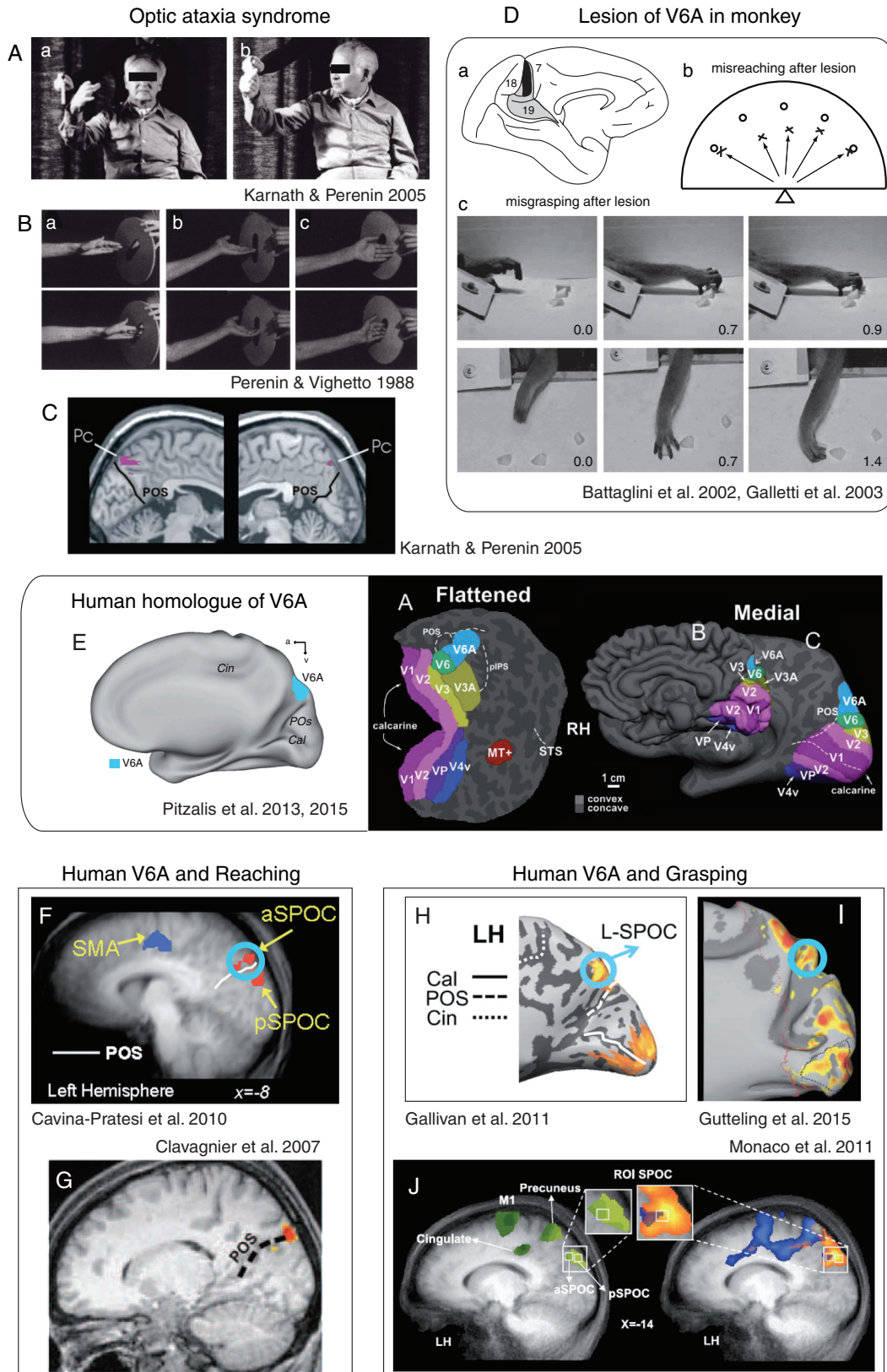
Figure 9. Monkey and human V6A: involvement in reaching and in grasping. (A) Reaching for a target in an exemplary patient with optic ataxia. The left brain-damaged patient showed gross and uncorrected reaching for a target in peripheral vision (when he had to fixate the camera lens in front of him) (a) and normal reaching under foveal vision (when he had to orient eyes and head towards the object while reaching for it) (b) (image taken from Karnath and Perenin 2005). (B) Optic ataxia patients, besides misreaching, also exhibit deficits in adjusting hand orientation to match object orientation (image taken from Perenin and Vighetto 1988). (C) Medial surface views of the center of lesion overlap (pink region) from dozens of optic ataxia patients. The parieto-occipital sulcus (POS) is marked by a black contour (image taken from Karnath and

were in a cluster separated from that of objects lacking a hole (stick-in-groove, ball, plate; gray group). In motor terms, although we are describing visual responses, objects which require insertion of the fingers in a hole for grasping evoked responses that were segregated from those requiring wrapping of fingers around the object.

During execution of reach-to-grasp actions, clustering of neural responses displayed stricter adherence to the motor pattern (Fig. 10A, bottom). The ring stimulus, which needs to be grasped with a hook grip, and both the plate and stick-in-groove, which require precision grips (black group in Fig. 10A, bottom), were clustered together very closely. Note that for these grasps, the use of the index finger is indispensable. The other 2 objects, the handle and the ball, whose grasps (finger prehension and whole-hand prehension, respectively) do not require fine control of the index finger, were widely separated from the other cluster.

It seems that V6A neurons perform a dynamic encoding in which vision is used for the subsequent action. Responses to the presentation of objects to be grasped depended on the specific visual features required for grasping the targets (the hole or the wide surface where fingers will be wrapped around). During prehension, a visuomotor transformation occurred such that the neuronal activity depended more strictly on motor-related elements, for example, type of grip used to grasp the object.

The role of vision for action in V6A was further investigated by comparing responses elicited by the presentation of 2 graspable objects with similar visual appearance, but which required different grips. We used a handle and a plate that, seen from the animal's point of view, looked very similar (Breveglieri et al. 2015). The objects were the same size, with thin, elongated shapes, and were composed of the same materials. Both objects were positioned in the same spatial location in front of the animal, but each required a different grip to be employed: either finger insertion or primitive precision grip. This pairing allowed us to assess whether responses evoked by object presentation reflected the coding of visual features or that of object affordance. Since the 2 objects looked very similar from the monkey's point of view, we expected similar responses if the cell encoded the visual attributes, and different responses if the cell encoded object affordances.

We found that 32% of visual cells were strongly modulated by object affordance (Breveglieri et al. 2015). An example of an affordance neuron is shown in Figure 10B. The cell displayed a clear visual response for the handle, regardless of thickness, whereas the plate did not evoke any response at all, despite the visual similarity. We suggest that the activity of this neuron reflects the different affordances of the objects. Permutations of visual features (thickness) with the same affordance did not affect the activity of this cell (see rows in Fig. 10B), whereas different

affordances with similar visual features produced substantial changes in the response (see columns in Fig. 10B). These data further support the view that V6A neurons are involved in processing grasp-relevant object features, that is, they employ visual information for action. Object selectivity of V6A neurons may serve in the rapid transformation of visual representations into object specific motor programs, a property very useful in visually guided grasping.

Possible Role of V6A in the Motor Control of Prehension

As described above, visual and somatosensory properties of V6A cells are well suited for localizing prehension targets in the peripersonal space, and for monitoring the occurrence and correctness of arm movements and hand/object interactions. In addition, the motor-related activity of V6A cells is suitable for control of the entire act of prehension, and seeing real objects evokes neural signals in V6A that encode affordance and features critical for graspability. This complete neuronal machinery places V6A in a suitable position to act as comparator between the expected state of an arm movement and the visual/somatosensory feedback evoked by the movement itself. In other words, area V6A could compare anticipated and actual sensory feedback evoked by the moving arm. In particular, the visuomotor cells described in V6A (Bosco et al. 2010) could compute an error signal that indicates the mismatch between the actual and expected sensory feedback, allowing for correction of arm movements and hand preshaping, as needed. This role may be shared with other parietal areas, such as areas AIP and MIP, the former particularly for grasping and the latter for reaching.

The left part of Figure 11 summarizes a possible circuit involving V6A in the control of reach-to-grasp movements. Visual and somatosensory information related to the target and to the arm/hand may be sent by V6A to the dorsal premotor cortex, signaling the motor error between hand location and object location, the mismatch between hand shaping and object shape, and between grip orientation and object orientation. Dorsal premotor cortex, in turn, could adjust the motor plan required to reach and grasp the object, and send it in parallel to the primary motor cortex (Dum and Strick 1991) and directly to the spinal cord (Dum and Strick 1991; He et al. 1993) to guide correct grasping of the object. An efference copy of the resulting motor plan could be sent back, as corollary discharge, to PPC, and specifically to V6A. Area V6A might thus act as a state estimator (Kawato 1999; Desmurget and Grafton 2000; Shadmehr and Krakauer 2008; Grafton 2010; Shadmehr et al. 2010), comparing the desired position of moving limb and the desired configuration of preshaping hand (estimated through forward models of the movement to execute) with the

Perenin 2005). (D) Lesion of V6A in monkeys shows impairments of reach-to-grasp (image taken from Galletti et al. 2003). (a) Reconstruction of location and extent (black area) of the brain damage (see Battaglini et al. 2002). Dorsal area 19 is shown in gray; its location and extent, as well as locations of areas 18 and 7, are according to Brodmann (1909). (b) Misreaching after V6A lesion. Food (raisins) was distributed on a semicircular plate placed horizontally in front of the animal. The plate is seen here from above, and the position of the monkey is indicated by the triangle. Open circles indicate food locations. Crosses indicate the locations where the hand landed in the first attempt to reach the food. Misreaching is evident. (c) Frames from a video camera illustrating the excessive widening of grip aperture, and the anomalous rotation of the wrist that led the fingers to close laterally rather than downward. Time below frames is in seconds. (E) Brain location of the putative homolog of area V6A in humans. Left, medial view of the inflated surface of the human brain showing the typical arrangement of area V6A (in cyan) along the POS. Main labeled sulci: Cal, calcarine; POS; Cin, cingulate sulcus (image taken from Pitzalis et al. 2015). On the right, human V6, and V6A together with other visual areas mapped with wide-field retinotopic stimuli. Maps of visual areas (in colors) shown in medial views of flattened (A), folded (B), and inflated (C) representations of a right hemisphere of a human subject. Light gray indicates gyri (convex curvature); dark gray indicates sulci (concave curvature). The location and topography of the cortical areas are based on functional and anatomical magnetic resonance scans of each subject (image taken from Pitzalis et al. 2013). (F) Activation of area SPOC (putative homolog of V6A) during the transport of the arm to the spatial position of the target (image taken from Cavina-Pratesi et al. 2010). (G) Activation of putative V6A when reaching a target in a peripheral position (image taken from Clavagnier et al. 2007). (H) Higher decoding from multivoxel-pattern analysis of fMRI data for reach-to-grasp rather than for reach-to-touch (image taken from Gallivan, McLean, Valyear et al. 2011) and (I) for preparation of object grasping (image taken from Gutteling et al. 2015) in the medial parietal area with the cyan circle, that indicates the location of the homolog of monkey area V6A. (J) Effect of hand orientation in grasping derived from fMRI activations in SPOC, the homolog of monkey V6A (image taken from Monaco et al. 2011).
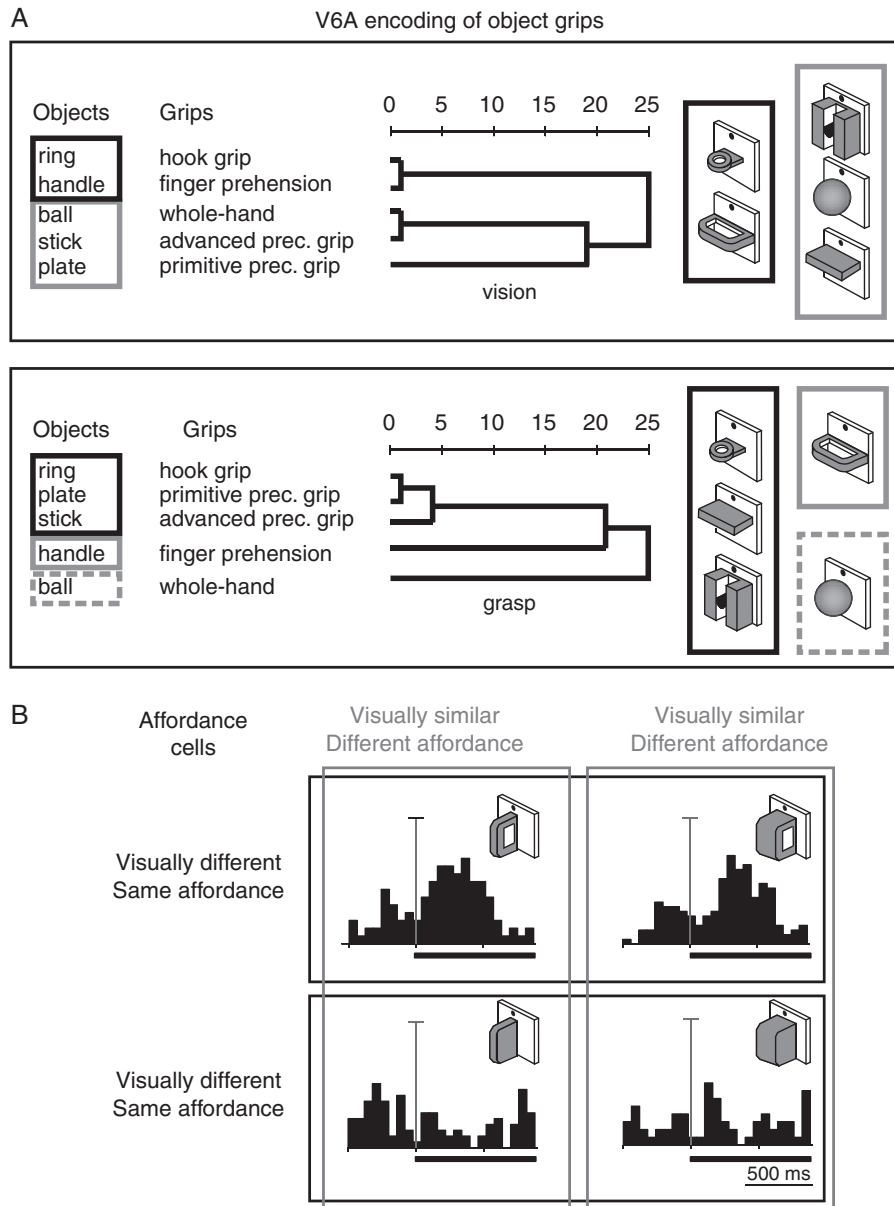
Figure 10. Grasp and affordance encoding in V6A. (A) Dendrograms illustrating the results of the hierarchical cluster analysis of the responses in the reach-to-grasp task of V6A cells to object observation (top) and grasping (bottom). Horizontal axis in the dendrogram indicates the distance coefficients at each step of the hierarchical clustering solution. Actual distances have been rescaled to the 0–25 range. Visuomotor encoding of the objects in object presentation (top) changes to a motor encoding in the reach-to-grasp execution (bottom). Modified from Fattori et al. (2012). (B) Encoding of affordance in V6A. Example neuron tested for same/different affordance and same/different visual features. Activity is shown as peristimulus time histograms, aligned (long vertical line) on the onset of the object illumination (thick black line: time of object illumination). Vertical scale bars on histograms: 45 spikes/s. Top: responses to handles; bottom: responses to plates. Left: responses to thin versions of the objects; right: responses to thick versions of the same objects. Very different visual features do not evoke different neural responses, but different affordances do. Modified from Breveglieri et al. (2015).

actual configuration (possibly monitored through vision and somatosensation). Future single-cell experiments could directly test this hypothesis, for example by manipulating moving arm position (to elicit different trajectories) or configuration of the preshaping hand (i.e., by grasping the same object in the same position, but with different grips) and evaluating whether single V6A cells change their pattern of discharge accordingly.

As motor performance continuously changes the limb/hand state, sensory inputs are continuously changing too. V6A neurons are suitable for online signaling of possible discrepancies, and their output could be used to adjust the motor plan in order to maintain consistency between the ongoing movement

and the desired one (Bosco et al. 2010). This hypothesis is supported by behavioral data showing that without the functionality of area V6A, monkeys (Battaglini et al. 2002) and humans (Ciavarro et al. 2013) perform inaccurate reaching movements.

The circuit shown in the left part of Figure 11 is compatible with the anatomical connections of area V6A, as summarized on the right side of Figure 11. Visual information can be conveyed to area V6A from the classic extrastriate areas of the occipital lobe (Gamberini et al. 2009; Passarelli et al. 2011), including V6 (Galletti et al. 2001), and from the visual areas of the superior temporal sulcus and PPC (Gamberini et al. 2009; Passarelli et al. 2011). These include area AIP (Borra et al. 2008; Gamberini et al. 2009),

Neural circuitry involving V6A
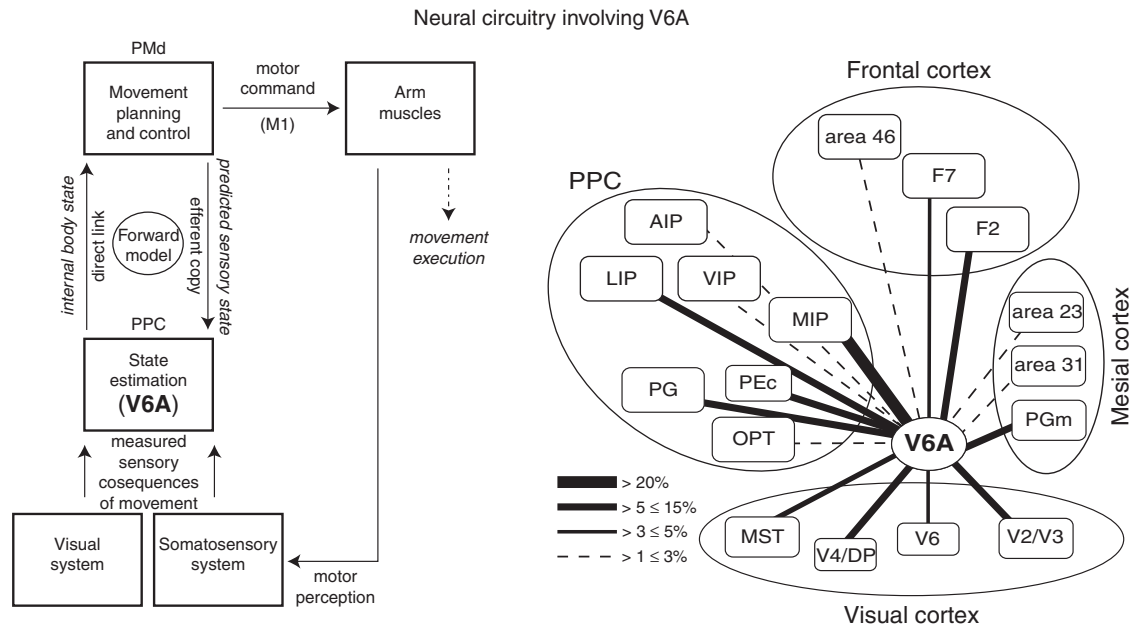
Figure 11. Neural circuitry involving area V6A in the neural control of movement. Left, flow chart of a possible circuit involving V6A in the control of reach-to-grasp movements. Sensory information may be sent by V6A to dorsal premotor cortex, to which it is directly connected. V6A may be involved in the comparison of the anticipated motor plan with the current sensory feedback produced by moving hand and by visual background. Right, summary of connections of area V6A modified from Gamberini et al. (2009) and Passarelli et al. (2011). The boxes representing different areas are organized approximately in a caudal to rostral sequence, from the bottom part of the figure to the top. The proportion of neurons forming each connection is indicated by the thickness of the bars linking different areas. The neuroanatomical data shown in the right part of the figure give experimental foundation to the circuitry hypothesized on the left.

which has a pivotal role in organizing visual information for grasping (Murata et al. 2000; Baumann et al. 2009). The strongest connection of V6A is with area MIP (often indicated as PRR, see Fig. 1C), which is involved, along with V6A, in encoding reach-directional signals (Snyder et al. 1997; Pesaran et al. 2008; Gail et al. 2009; Hwang et al. 2014). Lesions of MIP result in errors for reaches to visual stimuli (Hwang et al. 2012; Christopoulos et al. 2015).

Area V6A is also directly connected with area PEc (Gamberini et al. 2009; Bakola et al. 2010), from which V6A likely receives somatosensory information related to arm actions and posture (Breveglieri et al. 2006). The integration of visual signals with somatosensory/somatomotor signals elicited by the arm movement would allow efficient localization of targets and recognition of actions, and the generation of the appropriate command signals (Sabes 2011).

Area V6A is also connected with areas of the mesial cortex, whose functions remain to be explored in detail, and with frontal cortex, especially area F2 of dorsal premotor cortex, which shares with V6A the encoding of both visual and somatosensory information (Fogassi et al. 1999; Raos et al. 2003) and of proximal and distal aspects of prehension (Raos et al. 2004; Stark et al. 2007). Note that area V6A is bidirectionally connected with area F2 (Matelli et al. 1998; Shipp et al. 1998; Gamberini et al. 2009; Passarelli et al. 2011), which is consistent with the view that V6A sends sensory information to dorsal premotor cortex, and that the dorsal premotor cortex sends motor information back to V6A, as modeled in Figure 11 (left).

Conclusions

The combined sensory- and motor-related properties of V6A, along with its pattern of cortical connections, collectively suggest that V6A is involved in controlling reach-to-grasp actions. Single-cell recordings in awake animals indicate that sensory and motor properties useful to control reach and grasp in the act of prehension converge on V6A cells. These data, supported by recent brain

imaging data from humans, suggest a reinterpretation of the role of the dorsomedial visual stream, not limited to the control of reaching, as previously thought, but involved in the control of the entire act of prehension (Grol et al. 2007; Verhagen et al. 2012, 2013). This does not mean that the dorsomedial visual stream is the only route encoding prehension. Rather, we believe that it is a parallel route which supplements and complements the dorsolateral visual stream, which is well known to be involved in encoding grasping (Jeannerod et al. 1995). One possibility is that the dorsomedial stream is particularly called into action when temporal constraints are imposed, that is, when there is not enough time to organize prehension on the basis of the more detailed visual information derived from the ventral stream (see also Rizzolatti and Matelli 2003; Galletti et al. 2003). We believe that, in most cases, however, the dorsomedial and the dorsolateral stream interact together to skillfully orchestrate prehension.

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