Humans reach to and acquire objects by transforming visual targets into action commands. How the brain integrates goals specified in a visual framework to signals into a suitable framework for an action plan requires clarification whether visual input, per se, interacts with gaze position to formulate action plans. To further evaluate brain control of visual–motor integration, we assessed brain activation, using functional magnetic resonance imaging. Humans performed goal-directed movements toward visible or remembered targets while fixating gaze left or right from center. We dissociated movement planning from performance using a delayed-response task and manipulated target visibility by its availability throughout the delay or blanking it 500 ms after onset. We found strong effects of gaze orientation on brain activation during planning and interactive effects of target visibility and gaze orientation on movement-related activation during performance in parietal and premotor cortices (PM), cerebellum, and basal ganglia, with more activation for rightward gaze at a visible target and no gaze modulation for movements directed toward remembered targets. These results demonstrate effects of gaze position on PM and movement-related processes and provide new information how visual signals interact with gaze position in transforming visual inputs into motor goals.

Keywords: delayed-response task, event-related functional MRI, gaze position, goal-directed movement, human, vision

Introduction

Humans routinely interact with their environment by reaching for objects, often using vision and proprioception to compute object and hand position. Experience and empirical evidence provide ample evidence that humans use visual input for efficient actions since inaccurate reaching occurs when vision is not optimal (Woodworth 1899; Bédard and Proteau 2001; Lemay and Proteau 2001; Heath et al. 2004; Heath and Binsted 2007). A series of sensory–motor transformations mediates accurate reaching by remapping visual cues of the object and hand location into a common reference frame, likely using a gaze or a hand framework to yield a hand action plan (Beurze et al. 2006; McGuire and Sabes 2009). Despite a large body of relevant findings providing important insights into brain structures and mechanisms involved in visual–motor transformations (Andersen and Cui 2009), key elements of how the brain computes these transformations require additional investigation.

After initial processing in striate cortex, visual signals used to guide impending actions become modified along a parietal–frontal neural stream to yield action commands (Milner and Goodale 2008). Neurons in parietal and frontal regions that process visual cues become modified by gaze orientation (Andersen and Mountcastle 1983; Mushiake et al. 1997; Boussaoud et al. 1998; Bremmer et al. 1998; Batista et al. 1999; Jouffrais and Boussaoud 1999; Bunco et al. 2002; Gisele and Kalaska 2002; Pesaran et al. 2006). Relatedly, gaze orientation has an analogous influence on functional magnetic resonance imaging (fMRI) activation related to voluntary movement (Baker et al. 1999; DeSouza et al. 2000; Medendorp et al. 2003; Bédard et al. 2008; Bédard and Sanes 2009). Typically, fMRI signals increase in parietal and frontal cortical and subcortical regions when gaze and the end effector become aligned in the same sector of space (Baker et al. 1999; Bédard et al. 2008; Bédard and Sanes 2009; DeSouza et al. 2000). In aggregate, the gaze effects on neuronal spiking and neuroimaging signals commonly entail gain-like modulation of a neuronal computation (Andersen and Mountcastle 1983; Boussaoud et al. 1998; Bremmer et al. 1998; Baker et al. 1999; DeSouza et al. 2000; Pouget and Snyder 2000; Bédard et al. 2008; Bédard and Sanes 2009), thereby suggesting that mechanisms related to eye position should be incorporated into understanding how visual inputs become transformed in limb action commands.

Despite these findings, the understanding of how the brain transforms visual cues into movements remains incomplete since many prior human neuroimaging studies did not directly assess how visual signals interact with gaze orientation. Prior studies assessing the role of gaze orientation on movement-related brain activation either used continuously visible cues (Bédard et al. 2008; Bédard and Sanes 2009) or cues that disappeared before movement onset forcing participants to remember their location before moving (DeSouza et al. 2000). Thus, although these studies assessed how gaze orientation influenced brain activation they did not directly assess whether visual signals, by themselves provided key inputs to the movement-related modulation by gaze orientation. We note that reaching to remembered compared with visible targets impairs not only behavioral performance but also influences brain processing in occipital, temporal, and parietal cortices (Himmelbach et al. 2009; see also Battaglia-Mayer et al. 2000, 2001, 2003; Ogawa et al. 2007). Gaze effects on movement-related brain activation also occur across frontal and parietal cortex and subcortical structures when visual cues remained visible (Bédard et al. 2008; Bédard and Sanes 2009) but were observed only in the intraparietal sulcus (IPS) when participants remembered the visual cue location (DeSouza et al. 2000). Also unresolved is whether gaze influences on brain activation and their potential interaction with visual cues have the same organization during planning and actual performance or whether the gaze-related effects emerge when movement occurs.

Patrick Bédard, Min Wu and Jerome N. Sanes

Department of Neuroscience, Alpert Medical School of Brown University, Providence, RI 02912, USA

Address correspondence to Jerome N. Sanes, Department of Neuroscience, Brown University, Box GL-N, Providence, RI 02912, USA. Email: Jerome_Sanes@Brown.edu.
Here, we conducted an fMRI experiment in which participants performed goal-directed hand movements to visible or remembered targets with different gaze orientations. We also designed the experiment to disentangle planning from performing the movements. From prior results, we predicted greater fMRI signal when hand and gaze orientations had spatial alignment (i.e., gaze effects; Bédard and Sanes 2009) and that availability of visual cues would result in more areas in parietal and frontal cortex exhibiting gaze-related effects.

**Materials and Methods**

**Participants**

We recruited 18 participants from the Brown University community (22 ± 6 years, mean ± standard error of the mean [SEM]; 11 females), all right handed as assessed by a modified handedness scale (Oldfield 1971); they received modest monetary compensation. No participant had a history of neurological or motor or sensory disorder. All participants provided written informed consent according to established and approved Institutional Review Board guidelines for human participation in experimental procedures at Brown University. We adhered to the principles of the Declaration of Helsinki.

**Tasks, Apparatus, and Procedures**

Participants performed a goal-directed wrist movement using an MRI-compatible joystick (Mag Design and Engineering; http://www.magconcept.com/MRI) with their right hand. They lay supine in the MRI system with the right arm in a semiprone position and fully extended beside their right side while wearing a set of headphones for ear protection and communication. We used no restraint to maintain arm position, but due to the small 60-cm diameter of the MRI bore, the arm fit snugly but comfortably between the inner margin of the MR bore and the participant's body. All visual stimuli appeared on a projection screen positioned at the rear of the MRI system, and these were viewed by participants via an angled mirror mounted on the head coil. Joystick movements displaced a cursor (a black round dot; diameter 0.75 cm; 1:1 ratio between displacements of joystick and cursor) on the visual display over a white background. The position cursor remained visible for the entire experiment. Participants always initiated their movements from a “home” position located either to the left or right (47.75 cm which corresponded to 87°) from the visual display’s center; that consisted in an annulus (diameter 1.25 cm) with a "+" sign in its center (Fig. 1A). The annulus served to position the cursor and the "+" sign served as a gaze fixation point (FP). Targets appeared as black dots (diameter 1 cm) either 5 cm (4.5°) above or below the “home” position. We instructed participants before entry into the MRI system, to align the joystick cursor with the target using a single movement, thereby avoiding online movement corrections, and then to reposition the cursor at the home position right after each movement. We also urged them to gaze continuously on the FP for the whole experiment. This gaze requirement, nearly always followed, reduced possible confounds related to different gaze behavior when reaching to visual compared with remembered targets (Admiraal et al. 2003; Flanagan et al. 2008).

We monitored gaze position in real-time via a long-range camera (SensoMotoric Instruments; 60 Hz, 0.5° precision) and recorded gaze position for offline analysis. Participants practiced the procedures outside the MRI system before data collection for ~10 trials. We used the Windows version of PsychToolbox v.2.54 (http://www.psychtoolbox.org; Brainard 1997; Pelli 1997) for Matlab 6.5 (Mathworks) to generate visual stimuli and record the joystick position at 500 Hz.

To achieve our experimental goal, we designed an fMRI event-related experiment with 16 conditions, each condition having 10 trials, in a factorial design as follows: Gaze orientation (Left, Right), Target visibility (Visible, Remembered), Events (“Target appearance,” “Go Cue”), and Movement (“Move,” “Fixate”). We divided the fMRI data acquisition procedures into eight 20-trial blocks, with a short break (<1 min) between each set of 20 trials (Fig. 1B). Each trial block contained 2 sets of 10 trials during which the visual cues (“home” position and targets) appeared to the left or the right of the visual display’s center. All trials began with the appearance of the “home” position and the FP, followed 1 s later by the appearance of a target (Target appearance) either up or down of the “home” position (Fig. 1C). The target remained visible for the remainder of the trial or disappeared after 500 ms. A variable delay, 5.44, 6.12, 6.8, or 7.48 s jittered across blocks of 4 trials, began 500 ms after appearance of the target. After this variable delay, a Go Cue appeared; this consisted of a thickening of the home position cue and the FP, thereby signaling participants to perform a hand movement to acquire the target; the Go Cue remained visible for 5.44, 6.12, 6.8, or 7.48 s jittered across blocks of 4 trials. Half of the trials required movement, Move trials in which the “home” position and the FP appeared green, while for the other half of the trials, the “home” position and the FP appeared red to instruct participants not to perform hand movements (Fixate). The Move and Fixate trials occurred randomly 5 times for each gaze position within a set of 10 trials. Note that for each Move and Fixate trial, participants experienced the same event sequence except for the color of the “home” position cue and FP and requirement to move for the Move trials. For an entire block of 20 trials, the target remained visible or disappeared; across the total of 8 trial blocks, the target remained visible for 4 blocks and disappeared after 500 ms for 4 blocks.

**MR Imaging**

We used a 3T TIM Trio MRI system (Siemens Medical Solutions) to acquire anatomical and fMR images. Participants lay supine inside the magnet bore with the head resting inside a receive-only 8-channel volume head coil used for radio frequency reception; the body coil
transmitted radio frequency signals. Cushioning and mild restraint reduced head movements. After shielding the magnetic field, we acquired a high-resolution 3D anatomical image of 160 1-mm parasagittal slices (magnetization prepared rapid acquisition gradient echo sequence, using a time repetition [TR] = 1900 ms, time echo [TE] = 2.98 ms, 1 mm isotropic voxels, and a 256-mm field of view). We then generated $T_2$-weighted gradient echo planar images (EPIs) using the blood oxygenation level-dependent mechanism (Kwong et al. 1992) using a TR = 2.72 s, TE = 28 ms, field of view = 192 mm, image matrix = $64 	imes 64$, flip angle 90°, 3 mm slice thickness for 3 mm isotropic voxels, and 46 slices per volume to acquire activation signals from the entire brain. The MRI system acquired the functional MR images in an ascending interleaved manner and did not collect any data for the first 2 EPI volumes of each fMRI 20 trial run to eliminate saturation effects. We acquired 120 EPI volumes per block of trials to yield a total of 960 volumes and a duration of 43.52 min.

**Behavioral Data Analysis**

For the Move trials ($n = 80$), we first filtered the data with a low-pass Butterworth filter using a 7-Hz cutoff. We then calculated the cursor trajectory by calculating the square root of the sum of squared $x$ and $y$ coordinates and finally computed tangential velocity via differentiation. We determined movement onset as the first sample that the cursor’s velocity reached 1% of peak velocity and remained positive for the remaining trajectory; we defined the end of movement as the first sample that the cursor velocity fell below 1% of peak velocity. We measured the time elapsed between movement onset and movement end and movement error as the radial distance between movement end and the target. We used MATLAB (R2008b; The MathWorks), the $R$ project (R Development Core Team 2009), and G*Power (Faul et al. 2007) for our data and statistical analyses of the kinematic data.

**MRI Signal Processing and Statistical Analysis**

We used the Analysis of Functional Neuroimages (AFNI; Medical College of Wisconsin; National Institute of Health, http://afni.nimh.nih.gov/afni; Cox 1996; Cox and Hyde 1997) and the FSL software packages (FMRIB software Library, http://www.fmrib.ox.ac.uk/fsl/; Smith et al. 2004) to process, analyze, and visualize MR images and results derived from them. For each block of 20 trials and for each voxel within the brain treated independently, we first scaled the EPI time series by its mean, multiplied the result by 100 to yield values of percentage signal change, and then concatenated these time series. We used a 6-parameter rigid-body cubic polynomial interpolation (3dvolreg tool in AFNI) to motion correct the time series referring to the third image acquired and then corrected for slice timing offset. Across the group, participants exhibited subvoxel rotation and translation as group, with no significant main effect of Gaze, $F_{17,1} = 0.96$, $P = 0.34$, and no significant interaction, $F_{17,1} = 0.90$, $P = 0.36$. The main effect of Target visibility indicated lower error when participants moved to visible than to remembered targets ($F_{17} = 3.21$, $P = 0.005$; mean ± SEM of 0.69 ± 0.088 vs. 0.88 ± 0.09 cm respectively). We then analyzed variable error and found a significant main effect of Target visibility, $F_{17} = 7.54$, $P = 0.05$, with no significant main effect of Gaze, $F_{17} = 0.17$, $P = 0.68$, and no significant interaction, $F_{17} = 3.66$, $P = 0.07$. The main effect of Target visibility indicated lower variability when participants moved to visible than to remembered targets ($F_{17} = 2.75$, $P = 0.05$; mean ± SEM of 0.39 ± 0.03 vs. 0.47 ± 0.04 cm, respectively). While these effects might appear small, we noted that participants had visual cues about target location in half of the trials and the remembered targets had the same location. Concerning MT, the ANOVA revealed a significant main effect of Gaze $F_{17} = 11.88$, $P = 0.005$, a significant main effect of Target visibility $F_{17} = 10.22$, $P = 0.01$, but no significant interaction $F_{17} = 0.99$, $P = 0.33$. The main effect of Gaze indicated lower MT when participants gazed left than right ($F_{17} = 3.43$, $P = 0.01$; mean ± SEM of 0.58 ± 0.05 vs. 0.63 ± 0.05 s, respectively) and the main effect of Target visibility indicated higher MT when participants moved to visible than remembered targets ($F_{17} = 3.14$, $P = 0.01$; mean ± SEM of 0.63 ± 0.05 vs. 0.57 ± 0.04 s, respectively).

Participants generally conformed to the requirement of fixing gaze at a location ±7° from center; exemplar eye position...
records obtained from 2 study volunteers demonstrated their compliance with the task instructions (Fig. 2C). The figure illustrates the time-varying records for vertical eye position. Note that vertical gaze remained directed to the FP across the temporal evolution of the task, including the period when participants moved the joystick to acquire the vertically displaced target. Across participants, we found breaks of fixation on fewer than 1% of trials; thus, we did not exclude any data from analysis due to breaking of fixation. Figure 2D illustrates cursor trajectories for the same 2 participants (only the first 2 trial blocks are illustrated) that demonstrate similarity between movements performed when gazing leftward and rightward and the slight advantage in terms of reaching accuracy and variability when the target remained visible.

**Task-Related Brain Activation**

We first report upon task-related brain activation corresponding to the onset of the Target and the Go Cue; thus, the activation difference for Move compared with Fixate trials pooled across gaze and target visibility (Fig. 3A,B, respectively). Each event yielded activation in areas traditionally involved in movement planning and performance such as the primary motor cortex, the somatic sensory cortex, the premotor (PM) and supplementary motor cortices, regions of the posterior parietal cortex, cerebellum, and basal ganglia, as well as other areas in the frontal and temporal lobes. Despite the similarity of activation between these 2 events, the Go Cue yielded more than twice the volume of activation than that observed to Target appearance (10,777 compared with 4,819 voxels). Furthermore, we confirmed that the Go Cue elicited more activation than the Target in the sensory–motor cortex, cerebellum, and across visual, temporal, and parietal cortices (paired t-test, t(17) ≥ 3.943, P < 0.001; Fig. 3C); the Target appearance elicited more activation than the Go Cue only in the prefrontal cortex, a region generally thought to have a role in action planning and working memory.

**Gaze Orientation and Target Visibility Effects**

We next assessed how Gaze orientation and Target visibility modulated fMRI signals of regions that exhibited task-related brain activation (Fig. 3 A,B). We used a 2-way ANOVA with Gaze (Left, Right) and Target visibility (Visible, Remembered) as factors.
repeated measures and participants as the random factor for each event separately (Target appearance and Go Cue).

For Target appearance (Fig. 4A1-2 and Table 1), this analysis revealed 6 areas that exhibited a main effect of Gaze orientation; we localized these areas in the left hemisphere in the angular gyrus (Brodmann Area [BA]39), IPS (BA7), postcingulate gyrus (BA23), putamen, and fusiform gyrus (BA37), and in the right precuneus (BA7). Figure 4A2 plots the fMRI signal obtained from these clusters at Target appearance (note that, on the right side of these plots, we also depict fMRI signal obtained at the Go Cue; group mean ± SEM). For 3/6 of these clusters, we surprisingly found that leftward gaze yielded more activation than rightward gaze (note that postcingulate gyrus expressed deactivation; thus, it might be more appropriate to describe its profile as exhibiting less deactivation for rightward than for leftward gaze). This analysis also revealed an interaction between Gaze orientation and Target visibility in the left superior frontal gyrus corresponding to the PM region (BA6), 2 clusters in the left IPS (BA7), and one in the left fusiform gyrus (BA37, Fig. 4B1-2 and Table 1). To interpret this interaction further, we computed the slope between each Gaze position for each Target visibility condition and tested the null hypothesis of no difference between the slopes which we rejected for all clusters ($t(17) = 2.76, 2.81, 2.78, 3.29, \text{all } P \leq 0.05$). Further, for the clusters located in PM and IPS, we found more activation for rightward than leftward gaze when the target remained visible, but this effect did not reach statistical significance ($t(17) = 1.51, 1.42, 0.42, \text{all } P > 0.15$). However, when participants remembered the target location, gaze orientation–related activation in these clusters was greater for leftward than rightward gaze ($t(17) = 2.80, 2.60, 3.41, \text{all } P < 0.05$). Finally, when the target remained visible, we found significantly more activation in the fusiform gyrus for leftward than rightward gaze ($t(17) = 3.39, P \leq 0.05$) and a marginal significant gaze effect when the target had to be remembered with $R > L (t(17) = 1.93, P < 0.07$; a power analysis (Faul et al. 2007) revealed that a total of 21 participants, thus, 3 more than what we currently studied, would be required to potentially achieve a $P=0.05$ with power of 0.5).

For brain activation evoked by the Go Cue, the 2-way ANOVA revealed a main effect of Gaze orientation in 19 clusters (Fig. 5A and Table 2); this outcome has consistency with prior observations (e.g., Baker et al. 1999; Bedard et al. 2008). These clusters included those located in middle occipital gyrus (MOG, BA19) and the supramarginal gyrus (BA40), both bilaterally; the superior frontal gyrus (SFG, BA6) (BA6), corresponding to PM, the angular gyrus (BA39), the cerebellum (CR VI and CR VIIIB), inferior frontal gyrus (IFG; BA44), and insula in the right hemisphere; and in the sensory–motor cortex (BA1–4), precentral gyrus (BA4), superior temporal gyrus (BA41), the parahippocampal gyrus, and the cingulate cortex in the left hemisphere. Figure 5B depicts the measured fMRI signal for many of these clusters obtained during rightward and leftward gaze related to Go Cue onset (group mean ± SEM; this figure also depicts the fMRI signal obtained from the same clusters at Target appearance). At the onset of the Go Cue, rightward gaze yielded more activation than leftward gaze in 17/19 clusters, with 2 clusters in the parahippocampal gyrus exhibiting an opposite pattern.
one illustrated); note that these 2 clusters showed deactivation. Furthermore, Gaze orientation did not exert a differential influence on the fMRI signal at Target appearance. This result seems to imply that Gaze orientation modulated brain activation in these clusters only during movement performance and not during movement preparation.

The ANOVA also revealed interactions between Gaze orientation and Target visibility in 14 clusters (Fig. 6A and Table 2). These interactions occurred in several neocortical areas including the IFG (BA44) bilaterally, SFG (BA6) bilaterally, regions corresponding to PM, IPS (BA7) bilaterally, left superior parietal lobule (BA7), and right anterior cingulate cortex (BA24). Interactions between gaze position and target visibility also occurred in subcortical structures including the left (CR VI) and right cerebellum (CR V–VI), left putamen, right thalamus, and right globus pallidus. Figure 6B illustrates the fMRI signal for leftward and rightward gaze when the target
remained visible throughout the trial and when it blanked. All clusters exhibiting an interaction between gaze position and target visibility had an activation pattern with increased fMRI signal for rightward gaze at a visible target and the reverse pattern, that is, more activation for leftward gaze at the presumed location of a remembered target. To confirm these observations, we calculated the slopes of the fMRI signal between each gaze position for the 2 target visibility conditions. This test revealed that each of these clusters (visible and remembered) and then tested the null hypothesis of no slope difference between these 2 visual conditions. This test revealed that each of these clusters exhibited a significant difference between the slopes of visible compared with remembered targets ($t$-test, $P$ values $<$ 0.05). Further, when the target remained visible, rightward gaze yielded significantly more activation than leftward gaze for each of these clusters ($t$-test, $P$ values $<$ 0.05; except for left cerebellum (CR-VI), $P$ = 0.066). By contrast, when participants remembered the target location, the apparent leftward gaze advantage could only be termed a trend (all $P$ values $>$ 0.09); note that for the cluster with the lowest $P$ value (i.e., 0.09), a power analysis (Faul et al. 2007) revealed that a total of 24 participants would be required to perhaps achieve a $P = 0.05$ with power of 0.5; for the second lowest $P$ value (i.e., $P = 0.11$) a total 20 participants would be required to achieve a $P = 0.05$ with power of 0.5. Finally, the ANOVA did not reveal any region
with a main effect of Target visibility, indicating that target visual cues by itself had no evident effect on brain activation.

**Discussion**

We intended to reveal additional information about brain mechanisms related to transforming visual inputs into voluntary action commands. Visual features of a target used to program and perform arm movements could become coded into any number of reference frames including those centered on gaze, the shoulder, the hand, or an object (McGuire and Sabes 2009). This may relate to potential changes of reference frames for reaching as a function of visual conditions (McIntyre et al. 1997; Carrozzo et al. 1999). The understanding of the brain processes mediating integration of visual inputs and gaze orientation for arm movements have remained somewhat incomplete since earlier studies have not typically assessed these signals while they interact (but see Ferraina et al. 2001). Therefore, we aimed to determine whether visual input, per se, controlled the modulation of gaze orientation on hand movement-related brain activation (Baker et al. 1999; Bédard et al. 2008; Bédard and Sanes 2009), finding that vision of the action target exerted its modulation predominantly during goal-directed movements, with little effects during action planning.

**Interaction of Visual Inputs with Gaze Orientation**

Our most significant finding concerns the evolving modulation of brain activation by gaze orientation and target visibility as preparation (Target appearance) shifted into action (Go Cue). During preparation, left PM and IPS exhibited interactions between gaze orientation and target visibility on hand movement-related activation (Fig. 4B). By contrast, many more regions exhibited these interactions during movement performance, including cortical and subcortical areas. Perhaps even more significantly, the activation pattern related to actual movement changed qualitatively from that observed during movement preparation. That is, when participants had a visible target available to guide actions performed by the right hand, we found that rightward gaze yielded more activation than when gazing leftward. However, when participants used recall to guide targeted actions (i.e., without benefit of a visible target), this gaze effect disappeared, sometimes even showing a trend for more activation for leftward than rightward gaze. This may cause the change of reference frame from an eye-centered to a shoulder-centered when arm movements occur under full compared with degraded visual conditions (McIntyre et al. 1997; Carrozzo et al. 1999). An additional concern in interpreting the current results relates to a modest shift in forearm rotation when participants aligned the joystick at the "home" position while fixing gaze leftward or rightward from center. While this shift was small, it may have caused gain-like shifts in activation for the 2 gaze conditions.

Prior work has demonstrated functional coupling between eye and hand movements, such as gaze becoming locked upon the end point object targeted by reaching (Johansson et al. 2001) and that the spatial alignment of gaze and hand positions optimizes reaching accuracy (Land 2009). Consistent with these behavioral observations in humans, one also finds selective enhancement of hand movement-related activation when gaze and hand positions are aligned in the workspace (Baker et al. 1999; DeSouza et al. 2000; Bédard et al. 2008; Bédard and Sanes 2009). This observation may have synergy with a related result demonstrating that more difficult visual–motor transformations yielded less activation (Gorbet et al. 2004). These and the current results may suggest that complexity of a visual–motor transformation augments activation in brain networks engaged in integrating gaze and target locations with hand movements. However, spatial compatibility that drives gaze–hand interactions depend, at least in some structures, on visibility of the movement goal, that is, the target, and seemingly occurs most strongly during action. Thus, the dynamic aspects of gaze modulation across the phases of a delayed-response task seem novel and potentially significant to how various brain regions contribute to eye–hand coordination.

The interplay among visual inputs, gaze position, and hand movement on brain activation provides additional support for reliance on vision processing while humans interact with their environment. Despite the ability to navigate successfully and to perform arm movements without vision, ostensibly using other sensory modalities or internal models, there is overwhelming support for visual enhancement of motor functions (e.g., Bédard and Proteau 2001; Johansson et al. 2001; Lemay and Proteau 2001; Heath et al. 2004; Heath and Binsted 2007). The dynamic aspects of gaze influences on hand movement–related activation may represent a mechanism whereby visual cues become "properly" transformed into movements. Additionally, the absence of gaze effects on preparation- and movement-related activation for remembered targets could be a substrate for the degraded performance in nonoptimal visual conditions. Further, these results agree with the view that various reference frames for reaching depend on, at least, visual conditions (McIntyre et al. 1997; Carrozzo et al. 1999; McGuire and Sabes 2009). While our prior and other related work did not focus on whether and how gaze modulation of activation affected performance, we note that parietal lesions can yield optic ataxia, a reaching impairment particularly evident when using visual guidance (Milner et al. 1999; Himmelbach and Karnath 2005; Battaglia-Mayer et al. 2006). The deficits of optic ataxia may relate to loss of spatial tuning of parietal neurons, that is, their capacity to combine sensory signals, such as visual inputs and gaze position, to perform arm movements (Battaglia-Mayer et al. 2006). Thus, the observations of interactions among gaze orientation, target visibility, and hand movement–related activation could suggest a mechanism whereby visual inputs become optimally transformed into hand movements, with performance degradation when these interactions breakdown.

We found interactions between gaze position and visual input in parietal cortex and PM cortex bilaterally, regions having substantial anatomical interconnections and with key roles in visual–motor integration (Marconi et al. 2001; Battaglia-Mayer et al. 2003). These areas process visual and proprioceptive inputs, gaze orientation, and hand position, and their neural and activation properties seemingly combine them to yield egocentric and allocentric spatial representations (Galati et al. 2001; Buono et al. 2002; Cisek and Kalaska 2002; Battaglia-Mayer et al. 2003; Pesaran et al. 2006; Bédard and Sanes 2009; Gail et al. 2009). Neuronal mechanisms in these areas may use gain-like mechanisms to combine signals (e.g., Andersen and Mountcastle 1983). Although, the current and prior results (Baker et al. 1999; Bédard et al. 2008) do not necessarily suggest existence of gaze gain fields in humans, they may indicate system-level mechanisms for integrating gaze orientation into a motor plan.

Basal ganglia and cerebellar areas also exhibited interactive effects. These regions have direct or relatively direct
anatomical interconnections with parietal and PM regions (Alexander et al. 1986; Hoshi et al. 2005; Lemon 2008). Collectively, these results could argue that interplay among relevant cortical and subcortical regions yields evolution of reach-related signals in a stream of transformations, before a final change into signals accessible to the motor plant. Note, however, that Yanai et al. (2008) suggested that the final sensory-to-motor transformation may occur subcortically; our data do not provide evidence for or against this proposition; it would seem to require further study since many prior findings suggest that motor primitives and elemental features of kinematics and dynamics already are represented in neocortical regions implicated in voluntary actions (e.g., Hamel-Paquet et al. 2006).

Interactions between gaze position and target visibility evolved from near absence at Target appearance to occurring in many neocortical and subcortical structures when the Go Cue appeared. This temporal evolution suggests the existence of neural mechanisms that dynamically compute integrative and output signals needed for reaching across a delay period and not necessarily occurring only when a Go Cue appears. Prior work has demonstrated that activity in many brain areas increases as movement-onset approaches and more signals, such as those related to hand, eye, body, and target position and efference copy, became mutually integrated (Hoshi and Tanji 2004; Beurze et al. 2009). Thus, an ever-increasing set of interactions between gaze, visual input, and motor output would likely appear in more naturalistic conditions when planning and performance are not as dissociated as occurs in laboratory experiments.

Gaze and Visual Inputs Effects

In addition to interactions among gaze orientation, visual input, and hand actions, we also observed that gaze orientation could influence activation independently of the availability of a visual target, thereby confirming prior findings (e.g., Andersen and Mountcastle 1983; Bédard and Sanes 2009; Introduction). However, we found that leftward gaze yielded more hand movement–related activation than rightward gaze during the initial portion of the delay period; this effect reversed when the Go Cue appeared, thus, confirming prior observations (e.g., Bédard et al. 2008) that rightward gaze yields more activation than leftward gaze for movements performed with the right hand. As discussed above, we found evidence that different brain regions could express different activation patterns related to how gaze modulated, activated, and associated with hand movements. These differential effects likely suggest that the functional role of various brain regions may shift as planning morphs into performance, and they highlight the importance of separating movement planning from performance as is often done in neurophysiological studies (Battaglia-Mayer et al. 2007). Unfortunately, our design and limitations in interpreting the relatively slow time course of fMRI signals currently permits assessment of this evolution only at 2 moments, the target and Go Cue onsets. Nevertheless, the gaze effects and interactions between gaze and target visibility quite probably have a more continuous character (Battaglia-Mayer et al. 2007); future investigations might provide additional insight into this matter, perhaps using time-resolved fMRI (e.g., Dux et al. 2006) or electrically based neuroimaging methods.

Finally, we note that the experimental conditions entailed an additional sensory–motor transformation since the visual cues and movements were not oriented in similar planes. Thus, the findings should be interpreted in the context of this design feature. While movements performed in the current work were rather simple, they likely produced greater overall activation than conditions that did not require a fundamental sensory–motor transformation (Gorbet et al. 2004). Despite using conditions that required addressing a mismatch between movement and the visual cues, we note that most participants likely have experienced such a mismatch, typically during the commonplace activity of manipulating a mouse while working with an upright video monitor. Thus, we would argue that the conditions of the current experimental procedures have significance to one’s everyday experience.

Funding

National Eye Institute; National Institutes of Health (grant EY01545) and the Dr Ralph and Marian Falk Medical Trust (to J.N.S.).

Notes

Portions of this work fulfilled the requirements for a Senior Honors Thesis in Neuroscience for M.W. P.B. and J.N.S. participated in all phases of the project; M.W. participated in the experimental design, data collection and analysis, and manuscript preparation. Conflict of Interest None declared.

References


