Gaze and Hand Position Effects on Finger-Movement-Related Human Brain Activation

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Bédard P, Sanes JN. Gaze and hand position effects on finger-movement-related human brain activation. J Neurophysiol 101: 834–842, 2009. First published November 12, 2008; doi:10.1152/jn.90683.2008. Humans commonly use their hands to move and to interact with their environment by processing visual and proprioceptive information to determine the location of a goal-object and the initial hand position. It remains elusive, however, how the human brain fully uses this sensory information to generate accurate movements. In monkeys, it appears that frontal and parietal areas use and combine gaze and hand signals to generate movements, whereas in humans, prior work has separately assessed how the brain uses these two signals. Here we investigated whether and how the human brain integrates gaze orientation and hand position during simple visually triggered finger tapping. We hypothesized that parietal, frontal, and subcortical regions involved in movement production would also exhibit modulation of movement-related activation as a function of gaze and hand positions. We used functional MRI to measure brain activation while healthy young adults performed a visually cued finger movement and fixed gaze at each of three locations and held the arm in two different configurations. We found several areas that exhibited activation related to a mixture of these hand and gaze positions; these included the sensory-motor cortex, supramarginal gyrus, superior parietal lobule, superior frontal gyrus, anterior cingulate, and left cerebellum. We also found regions within the left insula, left cuneus, left midcingulate gyrus, left putamen, and right tempo-occipital junction with activation driven only by gaze orientation. Finally, clusters with hand position effects were found in the cerebellum bilaterally. Our results indicate that these areas integrate at least two signals to perform visual-motor actions and that these could be used to subserve sensory-motor transformations.

INTRODUCTION

Everyday we interact with our environment by moving our hands to grasp objects, type, and implement other goal-directed upper-limb movements. To generate accurate and efficient visually guided hand movements, one determines the position of a visible target and the initial hand position using vision and proprioception and an internal model. The importance of computing gaze and hand positions for successful arm movements is well established because misreaching can occur when one or both of these sources of information is absent or altered (Bédard and Proteau 2001, 2005; Bock 1986; Desmurget et al. 1998; Enright 1995; Henriques et al. 1998; McIntyre et al. 1997; Prablanc et al. 1979; Rossetti et al. 1994; Rothwell et al. 1982; Sanes et al. 1984). Many neurophysiological studies in monkeys and neuroimaging studies with humans have revealed that gaze orientation and hand position represent prominent parameters computed by the brain when generating hand movements.

Gaze orientation modulates neuronal spike counts in parietal cortical areas (Andersen and Mountcastle 1983; Andersen et al. 1985; Batista et al. 1999; Battaglia-Mayer et al. 2000, 2003; Buneo et al. 2002; Cisek and Kalaska 2002; Pesaran et al. 2006) and the ventral and dorsal parts of the premotor cortex (PMv and PMd) (Boussaoud et al. 1998; Cisek and Kalaska 2002; Jouffrais and Boussaoud 1999; Mushiake et al. 1997). Neurons in the visual cortex also exhibit gaze-related modulation of spiking on processing visual information (Rosenbluth and Allman 2002; Trotter and Celebrini 1999). In humans, neuroimaging studies have shown that gaze orientation modulates visual processing in visual areas (Andersson et al. 2007; Bédard et al. 2008; DeSouza et al. 2002) and hand-movement-related activation in parietal (Baker et al. 1999; Bédard et al. 2008; DeSouza et al. 2000; Medendorp et al. 2003) and frontal motor-related areas (Baker et al. 1999; Bédard et al. 2008). Importantly, these gaze effects on visual processing and arm movements yield a structured spatial organization. Neuroimaging studies have revealed that more functional MRI signal is generated in a gradient-like fashion as gaze deviates from the left toward the right of the body midline for movements made with the right hand (Baker et al. 1999; Bédard et al. 2008; DeSouza et al. 2000) and the converse holds true for left hand movements (DeSouza et al. 2000).

Prior results have also demonstrated that the brain codes for geometric configuration of the arm insofar as neural spiking in monkey Brodmann area 5 seems to represent updates of the location of the initial hand position (Graziano 2001; Graziano et al. 2000; Lacquinti et al. 1995) and that arm configuration in the workspace modifies the activity in parietal cortex, PM, and M1 on reaching and isometric force exertion (Caminiti et al. 1990, 1991; Kakei et al. 2001; Pesaran et al. 2006; Scott and Kalaska 1997; Scott et al. 1997; Sergio and Kalaska 2003).

In humans, a frontal-parietal network appears to code arm configuration because parietal cortical damage impairs the internal representation of the body’s state (Wolpert et al. 1998), and neuroimaging studies have revealed frontal-parietal activation on updating body’s configuration to plan arm movements or to localize visual stimuli (Lloyd et al. 2003; Makin et al. 2007; Pellijef et al. 2006; Rushworth et al. 1997).

Studies done with monkeys have also revealed that some areas in a parietal-frontal network, such as PM and within the
intraparietal sulcus, code movements with respect to both gaze and hand positions (Battaglia-Mayer et al. 2000, 2001, 2003; Buneo et al. 2002; Pesaran et al. 2006). In humans, however, prior studies required that participants point or saccade to a set of targets while their eyes or hand, respectively, remained stationary (e.g., Astafiev et al. 2003; Bédard et al. 2008; Beurze et al. 2007; Connolly et al. 2003; Gorbet et al. 2004; Medendorp et al. 2003; Simon et al. 2002), or the data were analyzed only across gaze or hand positions (DeSouza et al. 2000). Finally, others assessed how the brain integrates target location and choice of effector (eyes, right or left hand) (Beurze et al. 2007; Connolly et al. 2003; Medendorp et al. 2005). These studies with humans have not systematically varied both gaze and hand positions as done in monkeys studies. Therefore knowledge is missing on whether gaze and hand signals are combined in these parietal-frontal areas as in the monkey brain or whether each area uses a single code.

As evident from the preceding text, prior investigations of eye-hand interactions have typically occurred in the context of goal-directed reaching movements intended to mimic plausible real-life actions. By design and necessity, these interactions have a level of complexity that cannot necessarily address whether eye-hand interactions occur during eye fixation and movements without a spatial goal. Our prior work (Baker et al. 1999; Bédard et al. 2008) demonstrated that these interactions do occur, even for simple, repetitive finger movements with gaze fixed at different locations, thereby suggesting that brain systems controlling skeletal and ocular movements have a fundamental substrate for interactions. However, our prior observations (Baker et al. 1999; Bédard et al. 2008) did not address whether representations for low-level skeletal-ocular interactions exhibit specificity for one or another coordinate reference frame, such as eye- or hand-centered. Parallel to work done with neural recording in non-human primates, we would predict the existence of both eye- and hand-centered representations in humans for these postural and nongoal-directed movements.

To address these issues, we designed an event-related fMRI experiment to determine how the human brain combines gaze orientation and hand position on generating arm muscles commands. Building on previous work (e.g., Baker et al. 1999; Bédard et al. 2008; Buneo et al. 2002; DeSouza et al. 2000), we hypothesized that the spatial organization of gaze effects will be altered by changing hand position in the workspace. This manipulation also tests an underlying conclusion of prior work in our lab on gaze effects of finger-movement-related activation (Baker et al. 1999; Bédard et al. 2008): that pertaining to maximal effects of gaze on movement-related activation when gaze and hand were aligned in the same spatial sector. We further reasoned that these hand-gaze interaction effects should appear in the brain areas along a frontal-parietal network and possibly subcortical structures such as the cerebellum and putamen.

METHODS

Participants, tasks, and apparatus

We recruited 15 healthy adults from the Brown University community (aged 19–34 yr; 8 females, 7 males, all right-handed as assessed by a modified handedness scale) (Oldfield 1971). They had no history of neurological, sensory, or motor disorder. All participants provided written informed consent according to established Institutional Review Board guidelines for human participation in experimental procedures at Brown University and Memorial Hospital of Rhode Island (the site of the MR imaging). We adhered to the principles of the Declaration of Helsinki. Participants received modest monetary compensation for their participation.

The experiment was divided in six runs of scanning (6.18 min/run; Fig. 1A). During each run, participants received instructions to fix gaze at one of three visible targets (black annulus): left, center, or right, and to tap three times with the right thumb (Fig. 1B). The experiment comprised a series of 5–10 trials per target, with a variable time interval of 1 sec. Participants were instructed to press the space bar to begin each trial, to fixate at one of the targets for 1 sec, and to tap 3 times with the right thumb as quickly as possible. The targets were presented in a pseudo-randomized order, 5–10 times per run. A short intertrial interval of 1 sec was used to allow participants to make a saccade to the new target location. There was no feedback on response accuracy.

FIG. 1. Experimental design and eye position record. A: task schematic. During each of 6 runs, participants gazed at 1 of 3 targets (black outlined ring, lower section, left box) for 10 consecutive tapping trials. During each trial, the color of the ring center changed from white to black to cue participants to tap 3 times with the right thumb; trial-onset-asynchronies were 3.86, 4.825, 5.79, 6.755, or 7.72 s. B: experimental set-up. Participants positioned their right hand on their right side for one-half of the experiment and across their body midline aligned with the left shoulder for the other half of the experiment. They wore a pair of magnetic resonance imaging (MRI)-compatible goggles that displayed visual stimuli and recorded eye positions. C: eye positions across the experiment of 2 participants for the 1st 600 ms after the cue to tap appeared.
right of their body midline; only one annulus was visible at any given time. Each target was used once per run, and the order of target presentation occurred randomly for each run. Thus gaze was maintained at a target location for one-third of each run (~2 min). At the end of that interval, the target disappeared and a new target appeared. For each gaze position, participants tapped thrice (at 3 Hz) with their right thumb when the center of the annulus turned from white to black (Fig. 1A, tap). These movement cues occurred 10 times per gaze position. We also included 10 null trials in which no cue to tap appeared; these occurred randomly within the 10 movement trials. We added null trials to allow better disentanglement of the tapping-related functional MRI signals by stretching out the time in between events. We considered these data points as a baseline control. The order of presentation of both types of trials was randomized. Both types of trials occurred with varying trial-onset asynchronies (3.86, 4.825, 5.79, 6.755, or 7.72 s), and these occurred randomly (and on the average) once every five trials to facilitate the subsequent event-related functional MRI data analysis procedures. The design did not include a traditional preparatory period, that is, one have a warning stimulus. While, participants might have elected to prepare upcoming movements during the interval between trials, they could not accurately predict the onset of any one trial.

Participants performed the task while positioning their right arm in one of two configurations (Fig. 1B). In one configuration, the right arm was fully extended and half-pronated beside a participant’s right side. In the other configuration, the arm crossed the body midline in midflexion so that the right hand became aligned with the left shoulder. Half of the participants performed the first half of the experiment with the hand on the right side of the body and the second half of the experiment with the right hand on the left side of the body. The other half of participants did the experiment in the reverse order. The experimenter moved each participant’s arm in between the third and fourth run while participants remained motionless. Figure 1B (lower schematic) illustrates how participants lay in the scanner.

After receiving task instructions, participants practiced the procedures for a few minutes before entering the MRI system and becoming positioned in the standard supine body position. Participants wore a set of headphones, for ear protection and communication with the experimenter, and they held an optically coupled, MRI-compatible push-button (Bull Engineering, Rehoboth, MA) in their right hand that sensed the right thumb movements. They wore a pair of MRI-compatible LCD-based goggles for delivery of visual stimuli and eye movement monitoring with an embedded infrared camera (Resonance Technology: 800 × 600 pixels resolution; accuracy of ±1°, sampling rate 30 Hz; Viewpoint software, Arrington Research, Scottsdale, AZ). We used PsychToolbox for Matlab 5.2 [http://www.psychtoolbox.org/] (Brainard 1997; Pelli 1997; Mathworks, Natick, MA) running on a Macintosh G3 Powerbook to present visual stimuli and to store the occurrences of thumb movements and a Windows-operated Dell computer to run software to measure eye position (Viewpoint, Arrington Research). To ensure accurate timing between the recordings of gaze positions and events in the experiment, the Macintosh G3 Powerbook triggered the acquisition of gaze position with a TTL pulse. We did not record vertical eye position.

**MRI procedures**

We used a 1.5 T Symphony MRI Magnetom MR system equipped with Quantum gradients (Siemens Medical Solutions, Erlangen, Germany) to acquire anatomical and functional MR images. Participants lay supine inside the magnet bore with the head resting inside a circularly polarized receive-only head coil used for radio frequency reception; the body coil transmitted radio frequency signals. Head movements were reduced by cushioning and mild restraint. After shimming the standing magnetic field, we acquired a high-resolution three-dimensional anatomical image consisting of 160 1-mm parasagittal slices [magnetization prepared rapid acquisition gradient echo sequence, MPRAGE; repetition time (TR) = 1,900 ms, echo time (TE) = 4.15 ms, inversion time = 20 ms, 1-mm isotropic voxels, 256 mm field of view]. We then acquired T2*-weighted gradient echo images using the blood-oxygenation-level-dependent (BOLD) mechanism (Kwong et al. 1992; Ogawa et al. 1992). For each of the six runs, the sequence acquisition contained 96 volumes. We acquired functional MR images across the entire brain using isotropic voxels of 3 mm and 48 axial slices (TE = 38 ms, TR = 3.86 s, field of view = 192 mm, image matrix = 64 × 64). The MRI system acquired the images in an interleaved manner. The MRI system did not collect any data for the first volume of each run because of T1 saturation effect leaving 95 volumes of data per run.

**MRI SIGNAL PROCESSING.** We used AFNI (Analysis of Functional NeuroImages; Medical College of Wisconsin; National Institute of Health: http://afni.nimh.nih.gov/afni) (Cox 1996; Cox and Hyde 1997) and FSL software packages (FMRIB software Library, http://www.fmrib.ox.ac.uk/fsl/) to process, analyze, and visualize MRI images. For each run, separately we removed the linear trend in the time series and then scaled the time series by its mean to yield percentage signal change; we then concatenated the time series acquired from all runs. Then the BOLD data set for each participant was motion corrected to the third image acquired using a six-parameter rigid-body cubic polynomial interpolation (3dvolreg tool in AFNI). We then co-registered and normalized the anatomical and functional data sets to the MNI152 template using FSL and finally spatially smoothed the functional data set with a 6-mm full-width-half-maximum Gaussian kernel.

**MRI STATISTICAL ANALYSIS.** The occurrence of each tapping cue in each of the six conditions (2 hand positions × 3 gaze positions) was convolved with a gamma variate function (waver tool in AFNI) (Cohen 1997) to yield an impulse response function. We then used these six reference functions and the six motion correction parameters as inputs to a multiple regression analysis (3dDeconvolve tool in AFNI) to estimate the weight of each condition on a voxel-wise base. Reported results come from group-wise, random-effect analyses.

To assess condition-dependent activation, we first identified voxels having significant finger-movement-related activation by testing the null hypothesis that finger movement did not elicit activation using a t-test for each target separately and retaining voxels that passed a threshold of P ≤ 0.001 for at least one of the six conditions. We then corrected the resulting voxel-level analysis for multiple comparisons by setting a cluster threshold of P ≤ 0.05 corresponding to 12 adjacent voxels. The cluster-level analysis used the Monte Carlo sampling procedure implemented in AFNI (AlphaSim tool) and yielded 19 clusters deemed to have finger movement-related activation (Fig. 2; Table 1; RESULTS). We then submitted the functional MRI data (expressed in percentage signal relative to a global mean) to a two-way ANOVA contrasting the two hand positions (left and right) by two gaze positions (left and right) with repeated measures on each factor at P ≤ 0.05. For these analysis, we excluded from further consideration the functional MRI signals obtained when participants fixed gaze centrally because the main experimental hypothesis bore directly on alignment of hand and eye position, thus only the left and right positions for eye and hand. While we did exclude data related to central gaze for this analysis, we note that when the hand was positioned to the right, finger-movement-related activation when gaze was directed centrally or rightward ubiquitously exceeded that for leftward gaze; however, for some participants and for some regions, we found nonlinear effects as gaze shifted from left to center to right. To evaluate the time course of physiological responses, we used a deconvolution procedure (3dDeconvolve tool in AFNI) and estimated the hemodynamic response for each TR following the finger-tap response from 0 to 12 s and re-sampled it to half-TR for illustration. To localize activation to brain areas, we used the brain atlas of

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GAZE AND HAND BRAIN REPRESENTATIONS

RESULTS

Behavior

We first determined whether participants maintained their gaze on the target as they tapped their thumb by inspecting the eye position samples corresponding to the first 600 ms after the target turned black. During this interval, we identified gaze position samples $>3^\circ$ beyond the median gaze position required for a particular target and considered these samples as eye movements only if four or more consecutive samples fell outside that range. Using this criterion, $<$2% of the trials across the group contained eye movements. Figure 1C illustrates gaze positions in the horizontal dimension for two representative participants. Note that gaze remained anchored on the target during finger movements for both hand positions (separated by the vertical dashed line). With this preponderance of evidence that participants fundamentally and continuously maintained fixation on the required target, we decided not to reject any trials from the functional MRI analysis.

Next we tested whether manual reaction time (RT, defined as the elapsed time between the onset of the tapping cue and the occurrence of the 1st tap) differed as a function of hand and/or gaze positions. We eliminated two behavioral data sets due to hardware malfunctions. We tested the null-hypothesis of no difference of RT across all conditions, using a two-way ANOVA (2 hand positions $\times$ 2 gaze positions) with repeated measures. This analysis revealed a significant interaction, $F(1,12) = 23.18$, $P \leq 0.001$. Exploration of the interaction ($t$-test) revealed that RT was not significantly different between gaze position with the hand on the right (404 $\pm$ 13 and 410 $\pm$ 13, means $\pm$ SE, for left and right gaze, $P = 0.09$), but with the hand on the left RT were significantly slower when gazing right (407 $\pm$ 13 and 429 $\pm$ 14, $P \leq 0.001$).

### TABLE 1. Cluster report for the finger-related activation

<table>
<thead>
<tr>
<th>Brain Regions (BA)</th>
<th>Volume</th>
<th>Mean Intensity</th>
<th>Maximum Intensity</th>
<th>Coordinates (xyz)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cortical areas</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L Sensorimotor cortex (1-4)</td>
<td>21168</td>
<td>0.24</td>
<td>0.7</td>
<td>42 21 57</td>
</tr>
<tr>
<td>L ACC/SMA (6, 24, 32)</td>
<td>1917</td>
<td>0.1</td>
<td>0.16</td>
<td>5 -5 48</td>
</tr>
<tr>
<td>L Cuneus (31)</td>
<td>972</td>
<td>0.08</td>
<td>0.11</td>
<td>16 71 10</td>
</tr>
<tr>
<td>L Superior frontal gyrus (8)</td>
<td>648</td>
<td>-0.05</td>
<td>-0.08</td>
<td>1 -32 45</td>
</tr>
<tr>
<td>R Supramarginal gyrus (40)</td>
<td>513</td>
<td>0.1</td>
<td>0.17</td>
<td>-56 25 49</td>
</tr>
<tr>
<td>R Pre-central gyrus (4)</td>
<td>459</td>
<td>-0.12</td>
<td>-0.17</td>
<td>-42 20 63</td>
</tr>
<tr>
<td>L Mid-cingulate gyrus (24)</td>
<td>432</td>
<td>0.07</td>
<td>0.1</td>
<td>12 22 41</td>
</tr>
<tr>
<td>L Pre-cuneus (5, 7)</td>
<td>405</td>
<td>-0.05</td>
<td>-0.07</td>
<td>7 46 65</td>
</tr>
<tr>
<td>R Tempo-occipital junction (39, 22)</td>
<td>324</td>
<td>0.06</td>
<td>0.09</td>
<td>-49 51 8</td>
</tr>
<tr>
<td><strong>Sub-cortical areas</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R Cerebellum (CR-V)</td>
<td>9018</td>
<td>0.15</td>
<td>0.24</td>
<td>-16 57 -20</td>
</tr>
<tr>
<td>R Cerebellum (CR-VII)</td>
<td>2241</td>
<td>0.11</td>
<td>0.17</td>
<td>-15 64 -50</td>
</tr>
<tr>
<td>L Cerebellum (CR-VIIIb)</td>
<td>540</td>
<td>0.08</td>
<td>0.1</td>
<td>28 51 -56</td>
</tr>
<tr>
<td>L Cerebellum (CR-VI)</td>
<td>432</td>
<td>0.08</td>
<td>0.11</td>
<td>17 64 -17</td>
</tr>
<tr>
<td>L Putamen</td>
<td>2997</td>
<td>0.08</td>
<td>0.13</td>
<td>26 2 -5</td>
</tr>
<tr>
<td>L Putamen</td>
<td>351</td>
<td>0.08</td>
<td>0.1</td>
<td>19 1 14</td>
</tr>
<tr>
<td>L Caudate nucleus/thalamus</td>
<td>2835</td>
<td>0.09</td>
<td>0.16</td>
<td>15 18 9</td>
</tr>
<tr>
<td>R Thalamus</td>
<td>1026</td>
<td>0.08</td>
<td>0.11</td>
<td>-12 14 7</td>
</tr>
<tr>
<td>L Subthalamic nucleus/thalamus</td>
<td>405</td>
<td>0.08</td>
<td>0.1</td>
<td>14 18 -7</td>
</tr>
<tr>
<td>L Insula</td>
<td>1215</td>
<td>0.09</td>
<td>0.13</td>
<td>43 1 10</td>
</tr>
</tbody>
</table>

Cluster volume in $\mu l$ with one voxel $= 27 \mu l$. Mean intensity represents the average activation across all conditions and Maximum intensity represent the maximal value within a cluster. Coordinates represent the center of mass of an activation cluster, with +x indicating left hemisphere. ACC, anterior cingulate cortex; SMA, Supplementary motor area.
Movement-related activation

We found 19 clusters that exhibited finger-movement-related activation (Table 1, Fig. 2). We found activation in several regions traditionally considered as movement-related including the left sensorimotor cortex (labeled SMC in Fig. 2), that spanned left M1 (BA4) and primary somatic sensory cortex (BA1-3) in a contiguous region that encompassed the motor area of the left cingulate gyrus (Picard and Strick 2001) and the left SMA (hereafter called ACC/SMA, BA32, BA24, BA6; note $P = 0.06$), in the left midcingulate gyrus (BA24; labeled mid-ACC), a region corresponding to the anterior superior parietal lobule (BA5) and part of the left precuneus (BA7; labeled SPL), and the right supramarginal gyrus (SMG, BA40). We also found activation in the left cuneus (BA31), left superior frontal gyrus (SFG, BA8), right precentral gyrus (BA4), and in the tempo-occipital junction (39, 22; labeled TOJ). In subcortical areas, we found two activation clusters in the left cerebellum (CR-VIIIb and CR-VI) and also two clusters in the right cerebellum (CR-V and CR-VIIa). We also found two clusters in the left putamen (labeled put-1 and put-2), left insula, left subthalamic nucleus (STN), right thalamus, and in the left caudate nucleus.

Next we assessed how gaze and hand positions modulated brain activation in these aforementioned clusters with a two-way repeated-measures ANOVA (2 hand positions × 2 gaze positions). We found four clusters with a significant hand × gaze interaction that included the left SFG (BA 8), left cerebellum (CR-VIIIb), right SMG (BA 40), and left SPL (BA 5–7). We also found two clusters with a marginal interaction in the left ACC/SMA (BA 6, 24, 32; $P = 0.088$) and in the SMC ($P = 0.109$); all others clusters had nonsignificant changes in activation ($P > 0.13$). Figure 3A illustrates the location of significant activation for the clusters that exhibited a gaze × hand interaction. We then explored the interaction using post hoc t-test. When the hand was on the right, the activation of these clusters was higher ($P = 0.05$) when participants fixed gaze rightward compared with when they fixed gaze leftward, though the difference did not reach statistical significance for the left cerebellum ($P = 0.23$). However, when the hand was positioned to the left, only the cerebellum depicted gaze effects with more activation while gazing left ($P = 0.001$); otherwise we did not reject the null hypothesis of no difference in finger-movement-related activation between right- and leftward gaze. These results demonstrate that the effect of gaze orientation on movement-related activation shown in our pre-
vious work and others (Baker et al. 1999; Bédard et al. 2008; DeSouza et al. 2000) was changed by moving the hand to a different location.

The ANOVA also revealed a significant main effect of gaze position in six other clusters exhibiting finger movement-related activation (Fig. 3B); these regions included the left insula, left cuneus (BA31), left midcingulate gyrus (BA24, labeled mid-ACC), left putamen (labeled put-2), and right tempo-occipital junction (BA39-22, labeled TOJ). All these clusters but the left cuneus, depicted more activation when participants gazed right than left; the converse occurred for the left cuneus. Finally, the ANOVA revealed significant main effect of Hand position in the right cerebellum (CR-V), right cerebellum (CR-VIIA), and left cerebellum (CR-VI) with all these regions showing more activation when the hand was positioned to the left of the body (Fig. 3C). Figure 3D illustrates the evoked hemodynamic response obtained from one participant from a region in the right cerebellum (CR-VIIA) identified at the group level to exhibit a difference in activation related to eye and hand position. Clusters in which no effects were found included the left putamen (put-1), caudate nucleus/thalamus, thalamus, right precentral gyrus, and left STN/thalamus (data not shown).

**Discussion**

To generate appropriate arm motor commands, the brain identifies the initial conditions for movement and computes target location. We investigated how the brain combines gaze orientation and initial hand position to generate movements because previous work in human studied how the brain codes these movements in relation to gaze or hand position (e.g., Baker et al. 1999; Bédard et al. 2008; DeSouza et al. 2000; Wolpert et al. 1998) or how the brain integrates target location with effector choice (saccade, right or left arm) (Beurze et al. 2006; Connolly et al. 2003; DeSouza et al. 2000; Medendorp et al. 2005). We hypothesized that changing hand position would interact with gaze orientation to modulate finger-movement-related activation, restricting our analysis only to these areas showing hand-movement-related activation and found regions that exhibited combinatorial effects of gaze orientation and hand positions. We found activation that had sensitivity to both gaze and hand position in several cortical and subcortical regions such as SMC, SPL, and ACC/SMA, primarily those previously identified as having involvement in generating hand movements, as was shown in the monkeys (Battaglia-Mayer et al. 2000, 2001; Buneo et al. 2002; Caminiti et al. 1990, 1991). We also found areas like the right and left cerebellum that only used hand signals to code hand movements and others like the cuneus, mid-ACC, and putamen that only used gaze signals.

Our results replicate previous studies that found that gaze orientation modulated movement-related activation in humans (Baker et al. 1999; Bédard et al. 2008; DeSouza et al. 2000; Medendorp et al. 2003) and in monkeys (Batista et al. 1999; Buneo et al. 2002; Pesaran et al. 2006). We also found that these gaze effects were organized spatially in the workspace as shown in our previous studies with a strong preference for increased activation as gaze deviated rightward (Baker et al. 1999; Bédard et al. 2008; see also DeSouza et al. 2000; for monkeys, see Andersen and Mountcastle 1983; Boussaoud et al. 1998; Bremmer et al. 1998). However, a new finding of the current study regarding human brain organization relates to the interaction between gaze orientation and hand position that echoes findings in non-human primate of combined representations for eye and hand movements (Battaglia-Mayer et al. 2001; Ferraina et al. 2001).

Previously, we found gaze effects in M1, ACC, and SMA (Baker et al. 1999; Bédard et al. 2008) that had not been previously observed (DeSouza et al. 2000; Mushiake et al. 1997). In our earlier work, we also described augmented finger-movement-related activation (using the right hand) as gaze deviated toward the right sector of space. The current interaction, as found in several regions, add two features to interactions between hand movements and gaze position. First, alignment of gaze and the right hand to the left of the body does not necessarily yield augmented activation; we observed this only in one cluster. Second, it appears, instead, that there exists a mixture of gaze and hand signals in the ACC and SMA components of a premotor system that has anatomical projections both to M1 and to the spinal cord (Dum and Strick 1991, 1996, 2002; He et al. 1993, 1995). In M1, neuronal spiking relates to various kinematic and kinetic parameters of movement (Georgopoulos et al. 1982; Kakei et al. 2001; Paninski et al. 2004; Sergio et al. 2005), but no current evidence exists that links gaze with output from M1 (Mushiake et al. 1997).

Frontal and parietal regions, such as PMA and posterior parietal cortex, carry combined gaze and hand signals, and these areas project to M1. While it has not been definitively established that individual PMA and parietal neurons exhibit combined eye-hand signals, the overwhelming evidence points to a convergence in M1 of gaze and hand position signals (Marconi et al. 2001); these could then become used in the process that generates hand movements, although most clearly further processing is done in the spinal interneurons downstream of M1 (Yanai et al. 2008).

The current results extend prior findings of a movement-related role for the midcingulate gyrus. The activation cluster located in the ACC/SMA most likely corresponds to the ACC motor areas or rostral cingulate zone (Picard and Strick 2001), while the mid-ACC cluster likely corresponds to the caudal cingulate zone, a separate cingulate motor areas (Picard and Strick 2001). In monkey ACC and SMA, neurons code hand movements in relation to target and hand positions (Crutcher et al. 2004). Note also that the ACC and SMA have reciprocal projections with M1 (Picard and Strick 1996) and the precuneus (Cavanna and Trimble 2006; Leichnetz 2001), both of which exhibited hand-gaze interaction in the current work. Therefore our findings support a role for the human cingulate cortex for generating even simple hand movements with gaze and hand signals converging here that suggests that cingulate cortex participates in some way in transforming sensory information into movements.

Prior work has consistently suggested that the parietal cortex participates in generating hand movements using a variety of signals such as gaze and hand position (e.g., Battaglia-Mayer et al. 2000; Buneo et al. 2002) although in human the convergence of these two signals had not been shown yet. We found that the left precuneus/BA5 processed both gaze and hand signals. Note that we also found deactivation that could relate to the finger-tapping task used as opposed to goal-directed movement. This region appears to have significant involve-
ment in sensory-motor actions because many neuroimaging studies have shown activation there during hand movements (Astafiev et al. 2003; Beurze et al. 2007; Diedrichsen et al. 2005; Simon et al. 2002; Wenderoth et al. 2005). Furthermore, damage to this region yields impaired reaching (Battaglia-Mayer et al. 2006; Rondot et al. 1977). Neurons in BA5 of monkeys process visual, gaze, and hand position signals (Battaglia-Mayer et al. 2000, 2003; Buneo et al. 2002; Graziano et al. 2000; Lacquanti et al. 1995; Scott et al. 1997) and project to frontal motor areas and subcortical areas (Johnson et al. 1996; Marconi et al. 2001; Petrides and Panya 1984; Strick and Kim 1978). Thus this region seemed well positioned to participate in the sensory-motor transformations necessary to generate hand movements by transforming sensory information about target location and hand position using gaze and hand signals.

Other structures with key involvement in movement control such as the inferior portion of the parietal cortex (SMG) and cerebellum depicted movement-related activation. More importantly, our results further show that gaze and hand signals reached these regions. Baker et al. (1999) also reported gaze effects in this parietal area (but that study focused mostly on contralateral hemisphere). The cerebellum receives inputs from the parietal cortex (Glickstein 2003; Middleton and Strick 1998) and participates in eye-hand coordination and regulation of ongoing movements (Desmurget et al. 2001; Miall and Reckess 2002; Robinson and Fuchs 2001). It may have been expected that the left SMG and right cerebellum showed these effects because participants used their right hand. However, it is well recognized that portions of the ipsilateral hemisphere have involvement in hand movements. Previous work demonstrated that the left cerebellum (CR-VIIIB) has right hand-movement-related activation (Diedrichsen et al. 2005; Kawashima et al. 1998) and right IPL damage also leads to impairments in reaching (Karnath and Perenin 2005). Additionally, perturbing the right M1 with TMS alters the timing of muscle recruitment during right hand movements (Davare et al. 2007), and patients with right hemisphere stroke display motor impairments when using their right hand (Schaefer et al. 2007). Therefore our results confirm a role for the right SMG and left cerebellum even in simple hand movements with gaze and hand signals modulating its activity.

The current results show that for even simple hand movements with low spatial requirements that both gaze and hand positions exert substantial effects on brain activation. The findings may suggest an underlying fundamental aspect of brain organization for eye-hand control, even occurring in the absence of goal-directed movements. In particular, these two systems likely have a fundamental property for synergistic action when the eyes and hand have compatible spatial alignment. This conjecture may find support in behavioral evidence of coordination between the eyes and the hand during goal directed reaching (e.g., Johansson et al. 2001) and reaction time deficits occurring when visual inputs signaling manual responses cross the brain midline (e.g., Iacoboni and Zaidel 2004). Thus we suggest that the current results might represent baseline conditions for eye-hand coordination on which the brain then superimposes processing specific to goal-directed movements.

Somewhat unexpectedly, we did not find finger-movement-related activation in premotor cortex and regions of the medial intraparietal cortex that has been previously implicated in visual-motor transformations (Battaglia-Mayer et al. 2003; Cisek and Kalaska 2002; Pesaran et al. 2006). These negative results might have related to task differences, insofar as we used tapping, while most of the studies describing involvement of these areas in sensory-motor transformations used pointing; the differences in experimental design across studies might suggest that these regions have specific spatial requirements for exhibiting movement-related activation. For example, the task we employed entailed static gaze and arm position for long periods of time, both of which could modify the way brain circuits respond to movements and thus modify the functional MRI signal (e.g., Cisek and Kalaska 2002; Peseran et al. 2006).

We showed here that in humans, the brain combines gaze orientation with the hand position to generate simple and nongaze-directed hand movements. These results suggest that the brain uses a multiplicity of frame of reference for movements (Battaglia-Myer et al. 2003; Carrozzo et al. 2002; Ghez et al. 2007; Lemay and Stelmach 2005) as opposed to a pure gaze- (Henriques et al. 1998; McIntyre et al. 1997) or a hand-centered reference frame (Gordon et al. 1994; Soechting and Flanders 1989; Vindras and Viviani 1998). Much remains to be discovered concerning how different brain areas select a reference frame and under which conditions. Future studies that will merge different fields of research such as robotics with that of neuroscience have the potential to gain further insight into how the brain mediates sensory-motor transformations (Souères et al. 2007). The regions that we identified probably also integrate other signals about the body configuration and the external world via visual, proprioceptive, auditory information, and eff erence copy to yield appropriate body representations that mediate effective and accurate movements.

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REFERENCES


