Gaze and hand position effects on finger-movement related human brain activation

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Abstract

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, while 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 sub-cortical 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 mid-cingulate gyrus, left putamen, and right tempo-occipital junction with activation driven only by gaze orientation. Finally, clusters with hand position 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.
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 since misreaching can occur when one or both of these sources of information is absent or altered (Prablanc et al. 1979; Rothwell et al. 1982; Sanes et al. 1984; Bock et al. 1986; Rossetti et al. 1994; Enright 1995; McIntyre et al. 1997; Desmurget et al. 1998; Henriques et al. 1998; Bédard and Proteau 2001, 2005). 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; Mushiake et al. 1997; Boussaoud et al. 1998; Jouffrais and Boussaoud 1999; Cisek and Kalaska 2002; Pesaran et al. 2006) when monkeys reach voluntarily; the same effect has not yet been observed in primary motor cortex (M1; Mushiake et al. 1997). Neurons in the visual cortex also exhibit gaze-related modulation of spiking upon processing visual information (Trotter and Celebrini 1999; Rosenbluth and Allman 2002). In humans, neuroimaging studies have shown that gaze orientation modulates visual processing in visual areas (DeSouza et al. 2002; Andersson et al. 2006; Bédard et al. 2008) and hand movement-related activation in parietal (Baker et al. 1999; DeSouza et al. 2000; Medendorp et al. 2003; Bédard et al. 2008) 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 towards the right of the body midline for movements made with the right hand (Baker et al. 1999; DeSouza et al. 2000; Bédard et al. 2008) 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 (Lacquaniti et al. 1995; Graziano et al. 2000; Graziano 2001) and that arm configuration in the workspace modifies the activity in parietal cortex, PM and M1 upon reaching and isometric force exertion (Caminiti et al. 1990, 1991; Scott et al. 1997; Scott and Kalaska 1997; Kakei et al. 2001; Sergio and Kalaska 2003; Pesaran et al. 2006). In humans, a frontal-parietal network appears to code arm configuration since parietal cortical damage impairs the internal representation of the body’s state (Wolpert et al. 1998), and neuroimaging studies have revealed frontal-parietal activation upon updating body’s configuration to plan arm movements or to localize visual stimuli (Rushworth et al. 1997; Lloyd et al. 2003; Pellijef et al. 2006; Makin et al. 2007).

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., Simon et al. 2002; Astafiev et al. 2003; Connolly et al. 2003; Gorbet et al. 2004; Medendorp et al. 2003; Beurze et al. 2006; Bédard et al. 2008), 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; Connolly et al. 2003; Medendorp et al. 2005; Beurze et al. 2006). These studies with humans have not systematically varied both gaze and hand positions as done in monkeys studies. Therefore, knowledge is missing 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 above, 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-centered 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 non-goal 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 upon generating arm muscles commands. Building on previous work (e.g., Baker et al. 1999; DeSouza et al. 2000; Buneo et al. 2002; Bédard et al. 2008), 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 sub-cortical structures such as the cerebellum and putamen.

**Method**

*Participants, tasks and apparatus*

We recruited 15 healthy adults from the Brown University community (aged 19-34 years; 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 Institution 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), either left, center, or 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 mid-flexion 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, Inc.; 800 x 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, Scottsdale, AZ). 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 1.5T 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) = 1900 msec, echo time (TE) = 4.15 msec, inversion time = 20 msec, 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 msec, TR = 3.86 sec, field of view = 192 mm, image matrix = 64 x 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.fmriib.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 by 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 $p \leq 0.001$ 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 $p \leq 0.05$ corresponding to 12
adjacently clustered 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 $p \leq 0.05$. For these analysis, we excluded from further consideration the functional MRI signals obtained when participants fixed gaze centrally since 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 non-linear 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 sec and re-sampled it to half-TR for illustration. To localize activation to brain areas, we used the brain atlas of Duvernoy (1991), the cerebellum atlas of Schmahmann et al. (1999), and a web-based human brain atlas (www.msu.edu/~brains/brains/human/index.html).

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, less than 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 first 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 (two Hand positions by two 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 (means±SEM, 404 ± 13 and 410 ± 13, for left and right gaze, $p = 0.09$), but with the hand on the left RT were significantly slower when gazing right (407 ± 13 and 429 ± 14, $p \leq 0.001$).

**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 mid-cingulate 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 pre-central gyrus (BA4), and in the tempo-occipital junction (39, 22; labeled TOJ). In sub-cortical 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 sub-thalamic 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 (two Hand positions by two Gaze positions). We found four clusters with a significant Hand by 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 non-significant changes in activation ($p > 0.13$). Fig. 3A illustrates the location of significant activation for the clusters that exhibited a Gaze by Hand interaction. We then explored the interaction using post-hoc $t$-tests. When the hand was on the right, the activation of these clusters was higher ($p \leq 0.05$) when participants fixed gaze rightward compared to 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 ($p \leq 0.001$); otherwise we did not reject the null hypothesis of no difference in finger-movement related activation between rightward and leftward gaze. These results demonstrate that the effect of gaze orientation on movement-related activation shown in
our previous work and others (Baker et al. 1999; DeSouza et al. 2000; Bédard et al. 2008) 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 mid-cingulate 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). Fig. 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 pre-central 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 since previous work in human studied how the brain codes these movements in relation to gaze or hand position (e.g., Baker et al. 1999; DeSouza et al. 2000; Bédard et al. 2008; Wolpert et al. 1998) or how the brain integrates target location with effector choice (saccade, right or left arm; DeSouza et al. 2000; Connolly et al. 2003; Medendorp et al. 2005; Beurze et al. 2006). 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 sub-cortical regions such as SMC, SPL, ACC/SMA, primarily those previously identified as having involvement in generating hand movements, as was shown in the monkeys (Caminiti et al. 1990, 1991; Battaglia-Mayer et al. 2000, 2001; Buneo et al. 2002). 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; DeSouza et al. 2000; Medendorp et al. 2003; Bédard et al. 2008) 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 echos findings in non-human primate of combined representations for eye and hand movements (Battiglia-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), which had not been previously observed (Mushiake et al. 1997; DeSouza et al. 2000). 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 pre-motor 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. 2003; 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, though 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 mid-cingulate 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 pre-cuneus (Leichnetz 2001; Cavanna and Trimble 2006), 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 pre-cuneus/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 involvement in sensory-motor actions since many neuroimaging studies have shown activation there during hand movements (Simon et al. 2002; Astafiev et al. 2003; Diedrichsen et al. 2005; Wenderoth et al. 2005; Beurze et al. 2006). Furthermore, damage to this region yields impaired reaching (Rondot et al. 1977; Battaglia-Mayer et al. 2006). Neurons in BA5 of monkeys process visual, gaze, and hand position signals (Lacquaniti et al. 1995; Scott et al. 1997; Battaglia-Mayer et al. 2000, 2003; Graziano et al. 2000; Buneo et al. 2002) and project to frontal motor areas and sub-cortical areas (Strick and Kim 1978; Petrides and Panya, 1984; Johnson et al. 1996; Marconi et al. 2001). 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 focussed mostly on contralateral hemisphere). The cerebellum receives inputs from the parietal cortex (Middleton and Strick 1998; Glickstein 2003) and participates in eye-hand coordination and regulation of
ongoing movements (Desmurget et al. 2001; Robinson and Fuchs 2001; Miall and Reckess 2002). It may have been expected that the left SMG and right cerebellum showed these effects since 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 upon 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 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 non-goal directed hand movements. These results suggest that the brain uses a multiplicity of frame of reference for movements (Carrozzo et al. 2002; Battaglia-Myer et al. 2003; Lemay and Stelmach, 2005; Ghez et al. 2007) as opposed to a pure gaze- (McIntyre et al. 1997; Henriques et al. 1998) or a hand-centered reference frame (Soechting and Flanders 1989; Gordon et al. 1994; 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 efference copy to yield appropriate body representations that mediate effective and accurate movements.
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2002.


Figure Legends

Figure 1. Experimental design and eye position record. A: Task schematic. During each of six runs, participants gazed at one of three 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 three times with the right thumb; trial-onset-asynchronies were 3.86, 4.825, 5.79, 6.755, or 7.72 sec. 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 MRI compatible goggles that displayed visual stimuli and recorded eye positions. C: Eye positions across the experiment of two participants for the first 600 ms after the cue to tap appeared.

Figure 2. Brain activation (% MRI signal) related to finger movement. Activation presented here results from data pooled across all six conditions. Note strong activation in classically defined motor areas, such as contralateral M1, SMA, cerebellum (CR = Crus), anterior cingulate gyrus and right SMG. Table 1 lists all activated areas. CS, central sulcus.

Figure 3. A: Brain areas depicting finger movement-related activation with hand-gaze interaction effects. Values reflect the average derived from the beta-weights across the response period; CR = cerebellar crus. Legend applies to panels A, B and C. B: Brain areas with gaze-only effects. Note that all clusters except for the one in the cuneus showed more activation with the hand positioned on the right. C: Brain areas with hand-only effects. D: Evoked hemodynamic response for the cluster found in the right cerebellum (CR-VIIa) for a single participant. Each point represents the functional MRI signal interpolated to twice temporal resolution for illustration purposes. Note different legend from panels A, B, and C.
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>Max Intensity</th>
<th>Coordinates</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cortical areas</strong></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>L Sensorimotor cortex (1-4)</td>
<td>21168</td>
<td>0.24</td>
<td>0.7</td>
<td>42</td>
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<tr>
<td>L ACC/SMA (6, 24, 32)</td>
<td>1917</td>
<td>0.1</td>
<td>0.16</td>
<td>5</td>
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<tr>
<td>L Cuneus (31)</td>
<td>972</td>
<td>0.08</td>
<td>0.11</td>
<td>16</td>
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<tr>
<td>L Superior Frontal Gyrus (8)</td>
<td>648</td>
<td>-0.05</td>
<td>-0.08</td>
<td>1</td>
</tr>
<tr>
<td>R Supramarginal gyrus (40)</td>
<td>513</td>
<td>0.1</td>
<td>0.17</td>
<td>-56</td>
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<tr>
<td>R Pre-central gyrus (4)</td>
<td>459</td>
<td>-0.12</td>
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<tr>
<td>L Mid-Cingulate gyrus (24)</td>
<td>432</td>
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<td>0.1</td>
<td>12</td>
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<tr>
<td>L Pre-cuneus (5, 7)</td>
<td>405</td>
<td>-0.05</td>
<td>-0.07</td>
<td>7</td>
</tr>
<tr>
<td>R tempo-occipital junction (39, 22)</td>
<td>324</td>
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<td>0.09</td>
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<tr>
<td><strong>Sub-cortical areas</strong></td>
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</tr>
<tr>
<td>R Cerebellum (CR-V)</td>
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<td>-16</td>
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<tr>
<td>R Cerebellum (CR-VIIa)</td>
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<td>0.17</td>
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<tr>
<td>L Cerebellum (CR-VIIIb)</td>
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<td>0.08</td>
<td>0.1</td>
<td>28</td>
</tr>
<tr>
<td>L Cerebellum (CR-VI)</td>
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<td>0.11</td>
<td>17</td>
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<tr>
<td>L Putamen</td>
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<td>19</td>
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<tr>
<td>L Caudate nucleus / Thalamus</td>
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<tr>
<td>R Thalamus</td>
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<tr>
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<td>0.1</td>
<td>14</td>
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<tr>
<td>L Insula</td>
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<td>0.13</td>
<td>43</td>
</tr>
</tbody>
</table>

Cluster volume in µl with one voxel = 27 µl. *Mean Intensity* represents the average activation across all conditions and *Max Intensity* represent the maximal value within a cluster. *Coordinates* represent the center of mass of an activation cluster, with +x indicating left hemisphere.
A Run 1

Center Gaze Left Right

10 trials

Hold Tap

Tap

Variable time (TOA - 1 sec) 1 sec

B

C

Horizontal Gaze (degrees)

Hand Right Hand Left Hand Right Hand Left

Sample (n)

0 1000 2000 3000 0 1000 2000 3000

-10 10 0