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Movement Quantity and Frequency Coding in Human Motor Areas

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Kim, Jennifer A., James C. Eliassen, and Jerome N. Sanes. Movement quantity and frequency coding in human motor areas. *J Neurophysiol* 94: 2504–2511, 2005. First published June 8, 2005; doi:10.1152/jn.01047.2004. Studies of movement coding have indicated a relationship between functional MRI signals and increasing frequency of movement in primary motor cortex and other motor-related structures. However, prior work has typically used block-designs and fixed-time intervals across the varying movements frequencies that may prevent ready distinction of brain mechanisms related to movement quantity and, especially, movement frequency. Here, we obtained functional MRI signals from humans working in an event-related design to extract independent activation related to movement quantity or movement frequency. Participants tapped once, twice, or thrice at 1, 2, or 3 Hz, and the tapping evoked activation related to movement quantity in the precentral and postcentral gyri, supplementary motor area, cerebellum, putamen, and thalamus. Increasing movement frequency failed to yield activation in these motor-related areas, although linear movement frequency effects occurred in nonmotor regions of cortex and subcortex. Our results do not replicate prior data suggesting movement frequency encoding in motor-related areas; instead we observed movement quantity coding in motor-related brain areas. The discrepancy between prior studies and this study likely relates to methodology concerns. We suggest that the movement quantity relationships in human motor areas and encoding of movement frequency in nonmotor areas may reflect a functional anatomical substrate for mediating distinct movement parameters.

INTRODUCTION

Human voluntary movements have many attributes, including amplitude, direction, speed, and, for sequences, number of segments, and considerable evidence has accrued indicating that various brain regions support the various aspects of voluntary movement. Early neurophysiology studies focused on simple movement features, such as position and force (Evarts 1968; Evarts et al. 1983; Thach 1978), indicating that neurons in primary motor cortex (M1) and other brain areas had rough correspondence with exerted force and static limb position. Subsequent studies provided evidence for more complex relationships among a variety of kinematic variables in M1 and Brodmann area 5 (e.g., Ashe and Georgopoulos 1994). Recognizing that purposeful actions combine elemental aspects of motor control, Georgopoulos et al. (1982) determined that M1 neural activity had broad movement directional tuning. Subsequent studies have indicated that many motor-related brain areas in neocortex and subcortex, including M1, premotor area (PMA), supplementary motor area (SMA), cerebellum, and basal ganglia structures, exhibit directional tuning for reaching and that neural population vectors combine movement direc-

tion, amplitude, and velocity (Amirikian and Georgopoulos 2000; Fu et al. 1993, 1995, 1997; Schwartz and Moran 2000). From this work, it appears that both simple and complex attributes of voluntary movement have representations in many brain regions and that neurons within a particular brain region can provide neural codes for different movement features.

Neuroimaging methods have also provided evidence of movement coding in a number of brain structures, including relationships to force (Dai et al. 2001; Dettmers et al. 1995, 1996), flexor-extensor hand muscle activity (Yue et al. 2000), and movement velocity (Turner et al. 1998, 2003). Additionally, several studies have described movement frequency coding in M1, other neocortical motor-related areas, basal ganglia, and cerebellum (e.g., Agnew et al. 2004; Jancke et al. 1998a,b; Khushu et al. 2001; Rao et al. 1996; Schlaug et al. 1996; Taniwaki et al. 2003). Most commonly, movements were performed without benefit of pacing by an external stimulus, although movement frequency also modulates brain activation patterns when auditory (Riecker et al. 2003) or visual (Agnew et al. 2004) stimuli pace repetitive movements. Collectively, this work argues that M1, other neocortical motor-related areas, and cerebellum exhibit a roughly linear increase in activation from low to higher frequency movements, at least up to certain movement frequencies. Different groups have found activation saturation at different frequencies ranging from 2 (Khushu et al. 2001) to 6 Hz (Riecker et al. 2003), differences that likely are related to differing instrumentation and experimental designs. Other variables of movement control, such as limb position and movement direction, have not been extensively studied (but see Lloyd et al. 2003), perhaps reflecting difficulty of current brain imaging methods and data analysis approaches to reveal distributed representations for various features of voluntary action.

Despite the preponderance of evidence finding movement frequency-related effects in M1 and other motor-related areas in the human brain with neuroimaging methods, prior studies appear to share a potentially significant methodological flaw. That is, the experimental designs in these studies commonly used equivalent duration epochs while varying movement frequency (see Agnew et al. 2004; Jancke et al. 1998a,b; Schlaug et al. 1996). Hence, an alternative explanation of the obtained results is that the increasing number of movements contributed to the observed activation patterns instead of actual frequency. Because the signals of blood-based neuroimaging methods, especially for functional MRI (fMRI), tend to rise and saturate at a steady-state level, and stimulus duration does yield longer fMRI signal responses (Rosen et al. 1997), movement quantity instead of frequency may have been the salient

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variable in the observed activation patterns. While assessing the linearity of fMRI signals, Birn et al. (2001) observed increased labeling of M1 related to greater number of finger taps. However, Birn et al. (2001) did not systematically compare brain activation related to movement frequency and quantity. The tendency of many prior investigators to analyze fMRI data with block-design methods (e.g., Agnew et al. 2004; Jancke et al. 1998a,b; Schlaug et al. 1996) may also have factored into the difficulty in distinguishing movement frequency from movement quantity effects. With block-design methods, one cannot readily assess the relationship of fMRI signals to individual or closely spaced events. To address these issues, we used event-related fMRI methods that dissociated movement frequency and quantity. For visually paced movements, we found that movement quantity best described the activation patterns observed in motor-related areas of neocortex and subcortex, whereas other neocortical areas not typically thought to have motor functions exhibited activation related to movement frequency. These results have been presented in abstract form (Sanes et al. 2002, 2003).

METHODS

Participants

Fourteen healthy participants (age, 19–31 yr; 8 women and 6 men) were recruited from the Brown University community. All participants gave written informed consent before performing the study. The consent was acquired according to established institutional guidelines, and the study had institutional ethical approval from Brown University and the Memorial Hospital of Rhode Island. All 14 participants were right-handed, with laterality quotients ranging from 63 to 100%, as determined by a modified Edinburgh Handedness inventory (Eliassen et al. 2001; Oldfield 1971). Participants were screened for ferromagnetic implanted devices and asked to remove any ferromagnetic objects before continuing the study. Before MRI acquisition, participants were given instructions and practiced the task to be performed in the MR environment for between 5 and 10 min until the experimenter determined that a participant performed the tapping tasks reliably, automatically, and stereotypically. We provided modest monetary compensation for participation.

Task procedure

In this event-related fMRI experiment, participants performed a discrete tapping task with the right thumb in which a visual stimulus indicated the required number and frequency of the finger taps (see Fig. 1*B*). The right thumb of an individual rested atop a button of a hand-held optical switch (see *Apparatus*). The tapping movement(s) consisted of a brief (<0.5 s), pulsatile combination of flexion-extension of the distal-most portion of the thumb and forward-flexion and then backward-extension of the entire thumb. In most cases, the thumb became slightly elevated off the button after each press. (We did not observe or monitor the actual joint angles during the MRI; the above description derives from observations of tapping practice before MR imaging.) The total movement extent did not commonly exceed 2 cm and had a rhythmic aspect to it for tap quantities >1. While we did not measure force or EMG in the MRI or non-MRI environment, the simplicity of the apparatus and the task yielded roughly similar movement performance within and between participants.

Figure 1 shows key components of the task design that comprised runs, blocks, and trials. Briefly, participants performed four essentially identical runs during which three blocks each of tapping and no-tapping alternated (Fig. 1*A₁*). Participants performed 10 trials for

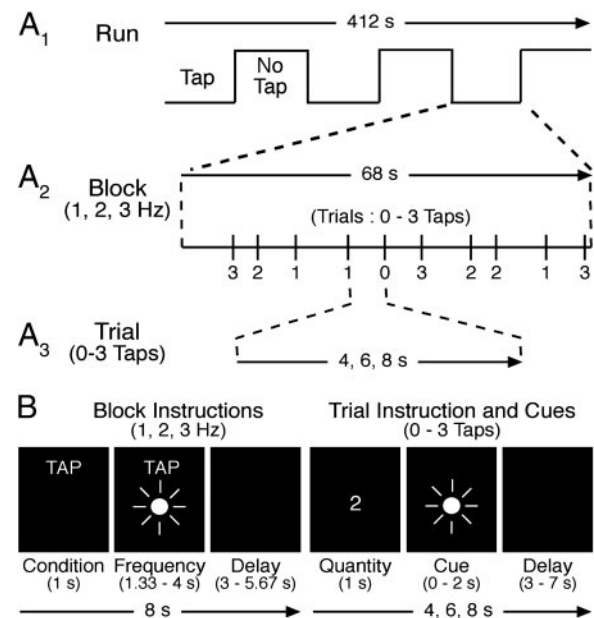


FIG. 1. Experimental design and visual stimuli presentation. *A₁*: run design. Each participant performed 4 412-s runs with each run comprised of 3 tapping and 3 no-tapping blocks, occurring in alternating fashion. Two runs began with a tapping block, and 2 runs began with a no-tapping block. *A₂*: block design. Each of the 6 blocks in a run began with a visual instruction indicating whether the 68-s block required tapping (Tap, as shown by the left panel in *B*) or no-tapping (No Tap). Each block consisted of 10 trials with an exemplar set of trials indicated in the figure. *A₃*: trial design. During tapping blocks, participants tapped the requisite quantity of taps as indicated by a visual cue (see *B*). *B*: visual instructions and cues. Left 3 panels show exemplar images observed at the beginning of a block. A Tap or No Tap instruction appeared initially followed 1 s later by 5 white circular flashes at the pacing frequency to be performed (or observed as for the no-tapping condition) for the given block. Right 3 panels show an exemplar trial, 2 taps in this case. A number appeared to indicate the quantity of taps followed 1 s later by the pacing cue.

blocks requiring tapping (Fig. 1*A₂*) and simply attended to the visual display during no-tapping blocks. We used four runs to generate sufficient tapping events for purposes of statistical power within an event-related fMRI design. Participants received instructions and movement cues from video signals displayed on a rear projection screen (see Fig. 1*B* for general features and *Apparatus*). Each 6 min, a 52-s run began with a 4-s delay period without any visible information. The delay period occurred simply for synchronization purposes of the task with the MR imaging. Thereafter, the runs comprised six successive 68-s blocks that alternated between tapping and no-tapping periods: two runs (1st and 3rd) began with a tapping block and two runs (2nd and 4th) began with a no-tapping block. During the initial 8 s of each block, a visual instruction, either No Tap or Tap, indicated whether the participant should perform movements (Tap condition) or simply attend to the visual stimuli without responding (No-Tap condition). After 1 s, a movement frequency cue appeared in the form of a flashing white circle, which flashed five times at the selected rate for that block of trials (Fig. 1*B*). The movement frequency was set at 1, 2, or 3 Hz for the entire 68-s block, each rate performed in separate blocks. After the movement frequency instruction, a blank screen filled the remainder of the initial 8-s block-instruction epoch before the trial sequence began. Figure 1, *A₂* and *B*, depicts trials events. Ten trials occurred for either the Tap or No-Tap blocks; participants responded to the movement cues during the Tap blocks and simply viewed the stimuli during the No-Tap blocks. At the beginning of each trial, the number 0, 1, 2, or 3 appeared on the video display for 1 s to indicate the required number of taps for each individual trial. For all but the 0 tap condition, a white circle flashed the specified number of times at the frequency specified by the

instruction stimulus for that block. No flashes occurred for the zero tap trials with the screen becoming blank after 1 s. Thereafter, the screen blanked for the remainder of the trial period. Because of prior practice outside the MRI environment, participants performed the tapping task essentially automatically and roughly in phase with the flashing pacing stimulus. In total, each block had 10 trials of zero to three taps performed at the instructed frequency, three each of one, two, and three taps, and one no-tap event (Fig. 1A₂, 0). A Latin-square design randomized the trial-to-trial onsets of 4, 6, and 8 s, with a 6-s trial-to-trial onset after all zero tap events. Within a block, the different quantities of taps were randomized according to Latin-square design with the exception that the zero tap trials occurred in the middle of the block as the fifth event.

Apparatus

In the bore of the MRI system, participants viewed the stimuli on a back projection screen at the foot of the MR transport. The screen was visible through an angled mirror mounted on top of the head coil at a distance of ~2.4 m from a participant's eyes. The mirror was adjusted for each participant so that images appeared in central gaze. Video images were projected with an Epson LCD projector and generated from an Apple G3 Powerbook computer (Cupertino, CA). We used Psychtoolbox (Brainard 1997) running under Matlab 5.3 (Mathworks, Natick, MA) to control stimulus delivery and timing. The tapping movements were monitored by a custom-built, fiber optical button (Bull Electronics, Rehoboth, MA) held in the right hand and depressed using the thumb. Responses were monitored visually for accuracy to ensure that participants made synchronous rather than reactive movements, but responses were not recorded.

MRI parameters

We used a 1.5T Siemens Medical Systems Symphony MR system equipped with Quantum gradients, a circularly polarized quadrature head-coil for radio-frequency reception and a body-coil for radio-frequency transmission to acquire MR images. Mild cushioning was used to minimize head movements. Each MR experiment entailed acquiring a high-resolution T1-weighted anatomical volume and several hundred T2*-weighted echo planar images (EPIs) sensitive to the intrinsic blood oxygenation level-dependent (BOLD) contrast mechanism (Kwong et al. 1992; Ogawa et al. 1992). High-resolution, three-dimensional anatomical data sets were collected as $160 \times 1 \times 1$ -mm resolution slices (Siemens MPRAGE sequence, TR = 1,900 ms, TI = 1,100, TE = 4.1 ms, 256×256 matrix, 256 mm field-of-view). EPIs were acquired in tilted axial planes (0 – 36°) to maximize neocortical and cerebellar coverage in 25 slices. The EPI data were acquired into 5-mm-thick slices with a 64×64 matrix with a 192-mm field-of-view for an in-plane resolution of 3 mm (TE = 40 ms, TR = 2,000 ms). A total of 824 EPI volumes were acquired in groups of 206 volumes obtained continuously throughout each of four runs. Four EPI MR volumes at the beginning of each block were removed from analysis because of TI saturation effects.

Data analysis

For image analysis and visualization, we used Unix workstations running the AFNI (Analysis of Functional NeuroImages) software package (Cox 1996; Cox and Hyde 1997). Preprocessing of the raw functional MR images from each participant entailed a six-parameter rigid body motion correction procedure (Cox and Jesmanowicz 1999), smoothing, normalization to a standard space (Talairach and Tournoux 1988), and extraction of the event-related hemodynamic response through a deconvolution procedure. For each participant, the 808 EPI acquisitions were deconvolved on a voxel-by-voxel basis to estimate the average and linear drift and to remove any residual contributions from the resultant parameters of the motion correction

procedures, all designated as covariates of no interest. The deconvolution procedure modeled the hemodynamic responses for each tapping event-type (0, 1, 2, or 3, at each of the relevant frequencies) and for no-tapping by generating fit coefficients at 2-s intervals, from 2 to 10 s (5 time-points) after visual presentation of the number indicating how many taps to perform. The fit coefficients were normalized to the average EPI signal from the deconvolution to create percent change scores for subsequent statistical analysis of evoked brain activation. Thus these fit coefficients specified the shape of the hemodynamic response function (HRF) in 2-s increments.

The percent change scores at each lag were statistically compared across the group using linear regression methods to determine brain regions having linear trends in activation related to tapping frequency or number of taps. We also performed additional ANOVAs to test for interactions between tapping frequency and tap quantity. Activation maps became thresholded at $P < 0.001$ at the voxel level and at $P < 0.01$ at the cluster level using Monte Carlo simulation tools in AFNI. The anatomical location of the activation clusters was determined from the Talairach tools provided in AFNI (Lancaster et al. 2000) and brain atlases (Duvernoy 1991; Schmahmann et al. 1999; Talairach and Tournoux 1988). For illustrative purposes, we also generated average time courses of functional MRI signal obtained during movement from each of several activation clusters. The data for the time-course illustrations derived only from voxels (and the ensuing clusters) passing through the two-stage inferential analysis just described. We first defined a region from which to extract the fMRI signal time series by creating an anatomical mask; the mask became established either by demarcating isolated activation clusters, for example, the SMA (Fig. 2A) or by dividing a cluster spanning cortical fields and demar-

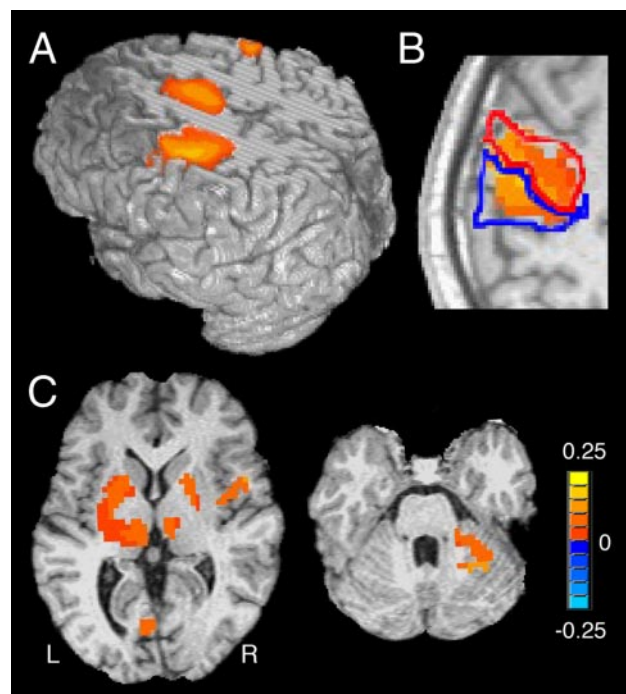


FIG. 2. Brain activation related to movement quantity. A: 3-dimensional rendering of cortical activation obtained from analysis of the main effect for quantity. Shown are areas exhibiting cortical activation with increasing quantity of finger tapping: precentral gyrus, postcentral gyrus, and SMA. B: depiction of masking technique used to determine regions of interest for the time series. Time series were constructed from the functional MRI signal obtained from voxel in these regions of interest. C and D: axial slices ($z = +5$, -24) show subcortical and cerebellar regions showing activation related to increasing quantity of finger tapping. Colored labeling on the rendered brain and slices represent functional overlays of average activation of 14 participants on 1 participant's anatomical T1 underlay. Calibration reflects percent signal change from a calculated global mean.

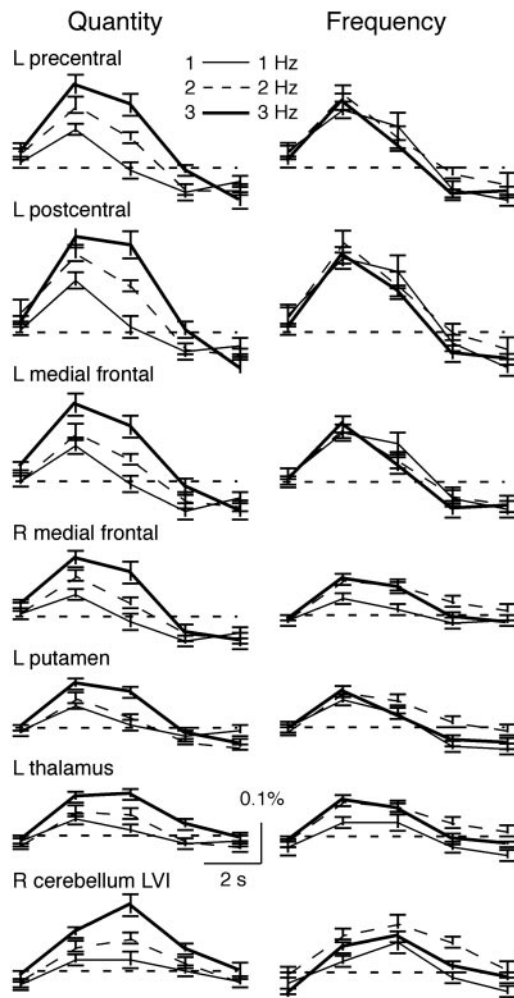


FIG. 3. Evoked hemodynamic responses related to movement quantity. Each record represents the time series of functional MRI signal obtained during the quantity or frequency components of the finger tapping task in each of the noted brain regions. Time series were obtained from identical voxels in each region of interest for both tasks. Note that the time series for depicted motor-related areas all exhibit a quantity, but not a frequency, effect. Functional MRI labeling indicated in percent change referenced to a global mean.

cating its subregions, for example, M1 and somatic sensory (S1) cortex (Fig. 2*B*), according to gyral and sulcal landmarks using the same tools noted above. For each participant, we next averaged the percentage change signal obtained from each time-point (2–10 s poststimulus) for each voxel within the defined region. Note that because of the morphological normalization procedures, the individual time series data were assumed to derive from the same brain area. The individual participant data obtained in this manner were averaged to create a grouped fMRI time series for each region (Fig. 3).

RESULTS

The regression analysis revealed that the quantity of taps modulated activation in several brain regions (Table 1). Linearly increasing activation corresponding to a greater number of movements occurred in the left precentral gyrus, left postcentral gyrus, bilateral SMA, right cerebellum, left putamen, and left thalamus (Fig. 2); these regions and others commonly exhibiting physiological responses to motor actions have become classified as motor-related areas. In contrast to the quantity effects, we failed to identify a motor-related brain

region having significant activation modulation related to tapping frequency or any regions having an interaction between the tapping frequency and quantity. To study whether the inclusion in the analysis of three closely spaced movement rates (1, 2, and 3 Hz) prevented uncovering of significant movement frequency effects, we implemented a categorical analysis (ANOVA) to test the null hypothesis of no activation differences between 1 and 3 Hz; however, we failed to reject this null hypotheses, thereby finding no evidence for activation differences related to movement frequency in the motor-related areas assessed. To study further the possibility of a movement frequency effect in motor-related brain areas, we implemented a three-way ANOVA using quantity, frequency, and time-point as nominal variables to contrast fMRI signals obtained during the 3- and 1-Hz conditions, collapsed across the movement quantity conditions. This analysis revealed no significant frequency-related activation in motor-related regions in neocortex and subcortex.

Figure 3 shows time-courses of the BOLD signal obtained from the significantly activated voxels in each of the activated brain regions across movement quantity (*left*) and movement frequency (*right*). The shown data clearly indicate a graded effect of movement quantity across several brain regions (see Table 1 for full details) and an absence, in these same regions, of any indication of a movement frequency-related effect. The absence of a movement frequency effect was not likely related to statistical power issues, because relaxation of the statistical threshold did not reveal frequency-related activation.

An alternative explanation for the observed effect of movement quantity could have related to the fact that for a movement frequency one needs more time to perform more movements. Thus the quantity effect might relate to the longer time needed to perform three movements compared with one movement. To address this possibility, we performed two additional analyses. First, we compared fMR signals obtained when participants tapped twice at 1 Hz with MR signals for three taps performed at 2 Hz, each condition lasting 1 s from the first to the last movement. If movement duration explains the observed quantity effects, the functional MR labeling for these two conditions should not differ. The results indicated no statistical difference between the activation resulting from the two taps at 1 Hz and three taps at 2 Hz in the regions of interest (ROIs) exhibiting quantity-related activation. (We do recognize that one cannot accept H_0 ; it also should be noted that we tested this hypothesis in motor-related areas of the cerebral cortex.) Second, we compared two taps at 1 Hz (1-s duration) with three taps at 3 Hz (0.667-s duration). If duration alone can affect brain activation, two taps at 1 Hz would be expected to show greater activation than three taps at 3 Hz. The contrast of two taps at 1 Hz and three taps at 3 Hz also yielded no significant differences in the brain regions with quantity effects. In general, these comparisons could suffer from a lack of statistical power; however, as best we can address this concern, our data suggest that movement quantity rather than movement duration explains the increasing brain activation with increasing number of movements.

Although motor-related brain regions did not exhibit activation having linear relationships with tapping frequency, post hoc analyses revealed that activation in some non-motor-related areas and sensory-motor neocortical areas ipsilateral to the moving finger showed linear frequency effects (Fig. 4).

TABLE 1. Total volume and maximum intensity Talairach coordinates for activation clusters related to finger tapping quantity and frequency

Area, BA	Volume, μ l	Intensity, % Δ	Coordinates		
			x	y	z
Quantity effect					
L/R superior frontal gyrus (6)	13,041	0.11	-1.5	-7.5	62.5
L pre/postcentral (6, 1, 2, 3, 4)	18,441	0.19	-31.5	-28.5	68.5
R precentral (6)	1,377	0.11	46.5	-1.5	44.5
R precentral/insula (9)	2,025	0.08	49.5	7.5	5.5
R inferior parietal (40, 2)	3,213	0.08	61.5	-25.5	26.5
L lingual/cuneus (18 19)	1,998	0.08	-4.5	-70.5	5.5
R lingual/cuneus (18 19)	1,215	0.06	7.5	-73.5	8.5
Thalamus/Putamen	17,253	0.07	-1.5	-16.5	2.5
L putamen		0.06	-16	8	10
L thalamus		0.06	-4	-22	1
R putamen		0.05	18	5	9
R thalamus		0.06	5	-19	6
L cerebellum (LVI)	540	0.06	-7.5	-58.5	-6.5
R cerebellum (LVI)	4,644	0.09	31.5	-55.5	-24.5
Frequency effect					
R inferior frontal gyrus (13)	1,971	0.11	43.5	25.5	5.5
R precentral gyrus	783	0.20	28.5	-28.5	68.5
L superior temporal gyrus (38)	2,322	0.06	-31.5	4.5	-15.5
R superior temporal gyrus (22)	1,242	0.11	61.5	-52.5	14.5
R middle temporal gyrus (39)	1,485	0.13	52.5	-70.5	14.5
L/R posterior cingulate	1,863	0.10	-1.5	-52.5	8.5
R cuneus (23)	6,102	0.06	7.5	-73.5	14.5
L middle occipital gyrus (19)	729	0.16	-37.5	-91.5	17.5
L parahippocampal gyrus (35)	3,321	0.06	-19.5	-22.5	-9.5
R insula	432	0.04	37.5	-16.5	-0.5
R culmen	1,026	0.07	13.5	-31.5	-12.5

These areas included the right precentral gyrus, postcentral gyrus, superior temporal, middle temporal, posterior cingulate, and cuneus. Time-courses of these regions of activation display these significant trends over time for movement frequency (Fig. 5). None of these areas exhibited significant activation effects related to movement quantity.

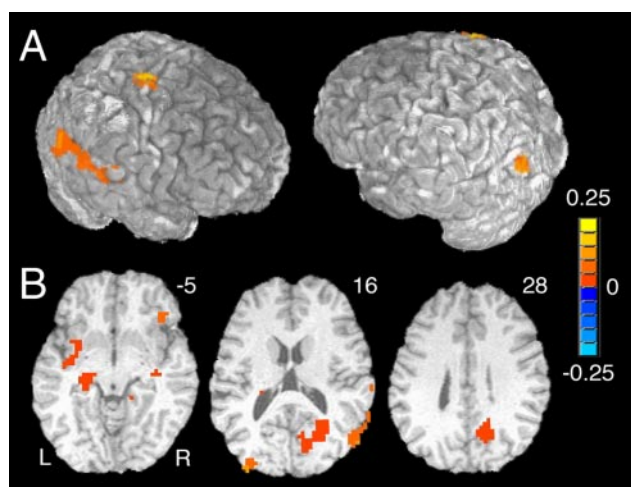


FIG. 4. Brain activation related to movement frequency. Nonmotor regions with increased activation linearly correlated to increasing frequency. *A*: 3-dimensional rendering of cortical activation obtained from analysis of the main effect for movement frequency. *B*: axial slices ($z = -5, +16, +28$) displaying other regions with activation related to increasing frequency of finger tapping. Both rendering and slices are functional overlays of average activation of 14 participants on an individual participant's anatomical T1 underlay. Calibration as in Fig. 2.

DISCUSSION

The results of this study indicate that the quantity of right thumb tapping is reflected by increasing cortical activation in many motor-related areas including the left precentral gyrus, left postcentral gyrus, bilateral SMA, right cerebellum, left putamen, and left thalamus. Contrary to previous reports, motor-related neocortical regions did not exhibit activation correlated with movement frequency. However, we did find frequency-related activation in frontal, temporal, and occipital structures likely engaged in premotor visual processing of stimuli that paced the repetitive movements. Furthermore, no interaction between frequency and quantity activation effects became apparent, suggesting that the increased fMRI labeling has relation to increasing quantity of finger tapping and not to stimulus duration. Thus in this event-related fMRI study, the increased activation in motor-related regions of the brain had a close relationship to increasing numbers of movements.

Previous studies using block-design methods have shown increasing neocortical fMRI signals that correlate with increasing frequency of finger tapping (e.g., Agnew et al. 2004; Jancke et al. 1998a,b; Schlaug et al. 1996). In contrast, these results provide no evidence for movement frequency effects in neocortical or subcortical motor-related areas. However, these motor-related areas ubiquitously exhibited activation related to the increasing *quantity* of finger taps. An explanation for the discrepancy between prior results and these data likely relates to methodological differences. To our knowledge, most if not all prior studies concerned with fMRI correlates of movement rate have varied movement frequency while holding the movement interval constant (cf., Riecker et al. 2003; Sadato et al.

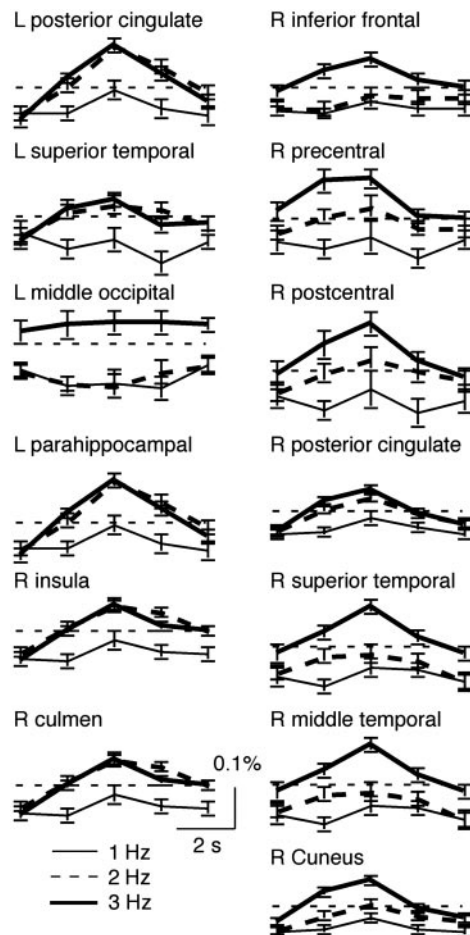


FIG. 5. Evoked hemodynamic responses related to movement frequency. Each record represents the time series of functional MRI signal obtained during the frequency components of the finger tapping task in each of the noted brain regions. These areas did not exhibit any significant trend in activation pattern related to movement quantity (data not shown). Calibration as in Fig. 3.

1997). Necessarily, the total number of movements varies when movement frequency changes while holding the movement epoch constant. In this study, we used event-related fMRI methods that effectively dissociated movement frequency from movement quantity, thereby allowing unfettered assessment of the relationship between fMRI signal and movement parameters. The resulting data unequivocally showed an absence of a movement frequency effect and a presence of a movement quantity effect in brain regions having clear relations with movement performance, such as M1, the motor cerebellum, and the putamen.

Movements performed at different frequencies necessarily imply performance occurring at varying rates. Thus we also considered whether movement velocity may have accounted for some of the observed effects, especially because prior neuroimaging work with PET methods has indeed correlated brain responses with movement velocity (Siebner et al. 2001; Turner et al. 1998). These studies consistently found velocity-related activation in the same motor-related structures (e.g., M1, putamen, anterior cerebellum) for which we found movement quantity effects and no apparent activation in brain regions not commonly classified as motor-related (e.g., inferior frontal gyrus, superior temporal gyrus, cuneus). How can this apparent discrepancy have occurred? We note that participants

in this study did not likely modulate the velocity of individual movements when performing tapping bouts at different frequencies. Instead, as described in METHODS, the individual movements within a bout had a stereotypical pulsatile characteristic. The movements did, however, differ in the density per unit time (frequency or rate) or quantity. With this in mind, we feel that velocity, per se, did not represent a significant factor in the observed activation, although clearly does represent an important variable for motor control physiology (Anderson and Turner 1991; Siebner et al. 2001; Turner et al. 1998, 2003).

Movement force may also have factored in these results, especially because several investigators have found relationships between exerted voluntary force and fMRI or PET signals (Dai et al. 2001; Dettmers et al. 1995, 1996). It seems unlikely that exerted force, at least that occurring tap-to-tap, accounted for differences in fMRI signal across the tapping frequencies and quantities examined in this study. Independent of the requested tapping frequency or quantity, participants performed discrete tapping movements using a minimally compliant button that likely yielded roughly comparable exerted forces. Despite the likely absence of substantial tap-to-tap force variation, cumulative motor output had a substantive role in the observed results.

These results potentially bear on the relationship between the BOLD response and increased stimulus or, as in this case, movement duration. Specifically, we observed predominantly linear increases in the fMRI BOLD response across several neocortical and subcortical motor-related areas; while not documented in this report, we tested and found little of remark regarding nonlinear fMRI labeling related either to movement quantity or frequency. Indeed, others have suggested that steady-state fMRI response observed in block-design experiments occurs because of summation of transient responses to each successively occurring event (e.g., Miezin et al. 2000). The observed linear increase in BOLD signal related to movement quantity finds support in other studies showing linear summation of fMRI labeling with increased stimulus duration (e.g., Dale and Buckner 1997; Logothetis et al. 2001). However, others have reported predominantly nonlinear fMRI responses to unitary events (e.g., Birn et al. 2001; Liu and Gao 2000). While we predominantly found evidence for linear relationships between the number of taps and the BOLD response, our experimental design and analysis strategy did not directly address the fundamental nature of the BOLD response or its relationship to neural activity. Thus while our results might suggest linear summation of the BOLD response, they do not provide direct support for or against the argument on the BOLD response profile.

We note that one requires more time to generate increasingly numerous finger taps; therefore one alternative explanation of these results might simply pertain to summation of evoked BOLD responses that follow closely spaced events, such as the 1- to 3-Hz movements of this experiment. In particular, Birn et al. (2001) found that duration of the evoking stimulus or event affected the BOLD response; increases in stimulus duration, either through visual stimulation or motor responding, yielded commensurately increased BOLD responses. Thus one might suggest that the resulting increase in cortical BOLD response observed in this study occurred simply because of increasingly longer movement durations as the tap quantity increased. The initial observation in which frequency did not affect cortical

BOLD responses in this experiment served as an argument against this hypothesis, because increasing frequency of finger tapping decreases stimulus duration. Thus if it were a stimulus duration effect, a decreasing BOLD response would be correlated with increasing frequency. However, no such trend was found in the analysis of the main effect of frequency for tapping in motor-related areas of neocortex or in subcortical structures. Second, to confirm this result, an analysis of the interaction between the effects of frequency and quantity was made. Again, no interaction between these two effects was found, thereby providing additional evidence against the hypothesis that stimulus duration mediated the observation of BOLD effects related to movement quantity. Third and relatedly, we conducted additional analyses to examine further the hypothesis that movement duration alone mediated the BOLD effect with the results indicating no support for a movement duration-related effect.

Movement frequency-related encoding was observed in right hemisphere homologues of precentral and postcentral regions as well as other nonmotor areas. Although this study did not observe frequency-related activation in "classical" motor areas, frequency encoding was observed in nonmotor regions of the brain. Such activation may indicate a more stimulus-specific encoding of frequency, whereas motor output areas are primarily concerned with the ensuring proper quantity movement coding. These results might suggest that nonmotor structures in the visual-to-motor stream might participate in forming motor plans for abstract parameters of movement, such as the overall rate. We note that the experimental situation required substantial visually based vigilance; a possible explanation why visual-related structures such as the cuneus and middle occipital gyrus exhibited movement frequency effects. The results also suggest that fundamental parameters of movement—in this case frequency and duration—might be processed in separate information channels. Prior results have indeed indicated separate processing streams for movement parameters in behavior (Bhat and Sanes 1998; Krakauer et al. 2000) and brain (Krakauer et al. 2004; Turner et al. 2003) processing. Whether movement quantity and frequency truly represent separable motor channels that also have distinctive neural circuits requires additional study. In summary, we confirmed our objective to determine independent contributions of the effect of frequency and quantity in movement tapping. Cortical and subcortical motor-related areas exhibited activation related to quantity of finger tapping rather than its frequency. This effect contradicts previous studies, and the discrepancy may be caused by our use of an event-related paradigm rather than a block paradigm that fixed the duration of the observation period. Through analysis of the frequency effect and the interaction between the quantity and frequency effects, it was found that the increase in cortical activation was caused by the increasing quantity of finger tapping rather than increasing stimulus duration. Thus this study may be the first to provide evidence for the linear correlation between quantity of finger taps and increasing neocortical activation.

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