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Force related activations in rhythmic sequence production

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Brain imaging studies have implicated the basal ganglia in the scaling of movement velocity. Basal ganglia activation has also been reported for movement timing. We investigated the neural correlates of scaling of force and time in the production of rhythmic motor sequences using functional magnetic resonance imaging (fMRI) of the human brain. Participants (N = 13) were imaged while squeezing a rigid force transducer in a near isometric manner between thumb and index finger, to reproduce four different rhythmic sequences. The responses were separated by either equal (600 ms) or alternating (400, 800 ms) intervals, and produced with either equal (12 N) or alternating (8, 16 N) forces pulses. Intervals and force levels were balanced across each condition. The primary motor cortex (M1), supplementary motor area (SMA), basal ganglia, thalamus, and cerebellum were activated during the production of sequences marked by equal interval and force. There was no reliable main effect of alternating interval. In contrast, greater activation of these regions was associated with the extra demands of responding with alternating force pulses. We interpret the data as identifying a significant role of the BG in the control of force. In addition, the results indicate the importance of monitoring force when studying brain activation associated with motor timing.

Keywords: Force production; Rhythm; Basal ganglia; Functional magnetic resonance imaging

Introduction

The level of force used and the timing of forces are critical parameters in the control of movement. In this study, we have explored changes in cerebral activation during the production of force pulses in rhythms that required scaling of level and timing of force. Turner et al. (2003a) proposed that a subset of brain regions, including basal ganglia (BG), cerebellum and sensory motor cortex (SMC), contribute to the setting of parameters that scale motor output to task demands. They found rCBF in these structures directly related to movement velocities and extents in a pursuit tracking task performed under different control-display gains. Moreover, bilateral BG activation has been reported in the early stage of adapting to visuomotor gain changes that required scaling of the velocity and extent of movements (Krakauer et al., 2004).

The link between the BG and scaling of motor output is appealing, as studies of non-human primates (Turner and Anderson, 1997) and clinical disorders associated with BG dysfunction (Berardelli et al., 2001; Turner et al., 2003b; Desmurget et al., 2004a) have implicated the BG in scaling upper limb movement velocity and extent. In demonstrating a link between BG activation and motor output, it is interesting to ask whether force might be a contributing variable, given that force and velocity are coupled through acceleration. Moreover, deficits in force control have been noted in Parkinson's disease, a neurological disorder affecting the BG (Hallett and Khoshbin, 1980; Wing, 1988; Jordan et al., 1992; Kunesch et al., 1995).

A number of imaging studies have examined brain activation related to force. For instance, depression of a Morse key at 1 Hz with the right index finger resulted in increases in fMRI and PET activation with force in MI and SMA (Dettmers et al., 1995, 1996a). Activation of sensory motor cortex (SMC) in a finger flexion force production task was observed to be greater in repetitive squeezing than in steady contraction (Thickbroom et al., 1999). In thumb-finger squeezing movements, increases in activation with force have been noted in MI (Cramer et al., 2002), SMA, PMC and cerebellum (Dai et al., 2001).

The above studies of force production did not report on the BG. Yet, BG activation was reported in the production of static force (depression of a Morse key for several minutes), but not dynamic force (repeated key depression; Dettmers et al., 1996b). More recently, bilateral BG activation was observed in producing controlled thumb-finger pinch grip force (Vaillancourt et al., 2004). This study included four conditions varying in rate of force development to attain a fixed force level of 25% maximum voluntary contraction. Region of interest analysis revealed condition effects across several motor structures including a parametric relation between rate of force development and bilateral activation of the internal segment of the globus pallidus. In another study that focused on coordination of thumb-finger grip force to maintain stable grasp while producing a lifting force on a fixed manipulandum, activation compared to rest included bilateral putamen (Ehrsson et al., 2003). A contrast between the coordinated and isolated grip and lift conditions revealed activation of right

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intraparietal cortex but not putamen. This suggests that the BG involvement was related to grip force generation, whereas the intraparietal region was key to coordination. However, in another study, activation of ipsilateral caudate nucleus as well as ipsilateral posterior cerebellum and frontal association regions was associated with predictive force coupling, over and above activity associated with isolated grip or pull (Boecker et al., 2005).

Coordination of arm and hand in grip and lift or pull tasks requires accurate relative timing. In this paper, we were interested in examining whether timed modulation of force in repetitive thumb-finger squeezes would activate BG and whether this activation would increase with controlled variation in timing. Previous studies of repetitive movement have identified BG activation with movement timing demands (Rao et al., 1997; Harrington and Haaland, 1999) and it may be noted that the conditions in the Vaillancourt et al. (2004) study included timing as well as force demands. We therefore sought to compare the effect of timing constraints on modulating force and vice versa in a rhythm production task that allowed comparison of the separate and combined effects of force and time. There have been a number of studies of brain activation associated with motor timing (for reviews, see Lewis and Miall, 2003; Ivry and Spencer, 2004). A few of these included patterned variation of inter-response intervals to investigate structures involved in rhythm (Penhune et al., 1998; Lewis et al., 2004), but no study that we are aware of has manipulated force as part of rhythm. In practiced performance, parametric variation in rhythm complexity (defined by the number of different intervals) related to activation levels in cerebellum, BG, and also to cortical regions, but only in the initial synchronization phase of each trial and not during unpaced responding (Lewis et al., 2004).

The involvement of subcortical structures in rhythmic timing is consistent with neuropsychological studies linking motor timing deficits to both cerebellar (Ivry and Keele, 1989; Ivry et al., 1988) and basal ganglia (Wing et al., 1984; Harrington et al., 1998) lesions. However, these studies were limited to the production of equal intervals and force was not recorded or controlled. In the present study, we examined effects of force modulation by including conditions in which successive force pulses alternated between two levels or were fixed at an intermediate level. We were interested in the effects of time constraints on force production and so crossed the force conditions with complementary alternating and equal interval conditions. In our study, activation measures were taken in unpaced responding. Extrapolating from our earlier study (Lewis et al., 2004) which did not control force, we expected that while alternating force levels might activate basal ganglia compared to equal force conditions, there would be no differential activation for alternating response intervals compared to equal interval conditions.

Materials and methods

Participants

A total of 9 male and 4 female participants with no history of neurological disorders took part in the study (mean age 28.4 years, standard deviation 4.9 years, range 21–40 years). All participants were strongly right-handed as assessed by the Edinburgh handedness scale (mean laterality quotient = 0.9; range = 0.4–1; Oldfield, 1971). The study was approved by the research ethics committee of Central Oxfordshire, and all participants gave informed consent after receiving an explanation of the study.

Behavioural task

A single block lasted 30 s and included presentation of one of four rhythms (Fig. 1), each defined by auditory tones (100 ms) of either equal (1250 Hz) or alternating (500, 1600 Hz) frequency that were presented at either equal (600 ms) or alternating (400, 800 ms) intervals. Participants were instructed to squeeze an MR-compatible load cell (Novatech Measurements Ltd., Hastings, UK.) between the right thumb and index finger, so that a force pulse was synchronized with each tone, squeezing with equal force to tones of equal pitch, or alternating force to tones of alternating pitch (Fig. 2). After 6 s, the pacing tones stopped, but participants continued to respond at the same rate and with the required force pattern for a further 24 s. Mean force was displayed visually at the end of each block. 6 s of rest separated each block, and 24 s of rest separated every fourth block. During rest conditions, no motor activity was performed by participants. A single scan session included 20 blocks (5 blocks × 4 rhythms). The presentation of rhythms within each session was randomized. To control for the two possible combinations of producing two-element patterns alternating in both interval and force, the experiment was run in two sessions. The short–long intervals were combined with hard–

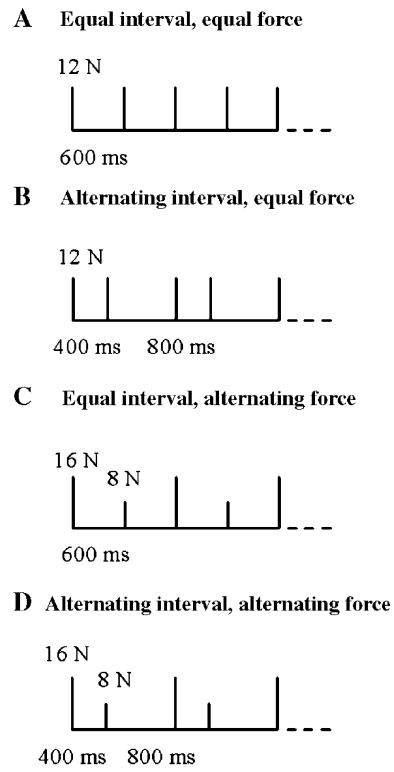

Fig. 1. In the equal interval, equal force condition (A), participants reproduced responses with equal force (12 N), each separated by an equal interval (600 ms). In condition B, responses were made with equal force (12 N), each separated by alternating intervals (400 ms and 800 ms). Condition C required the production of alternating force pulses (16 N and 8 N), each separated by an equal interval (600 ms). Lastly, condition D required the reproduction of alternating force pulses (16 N and 8 N), each separated by alternating intervals (400 ms and 800 ms). The combination of alternating force and interval in condition D was balanced across the two scan sessions.

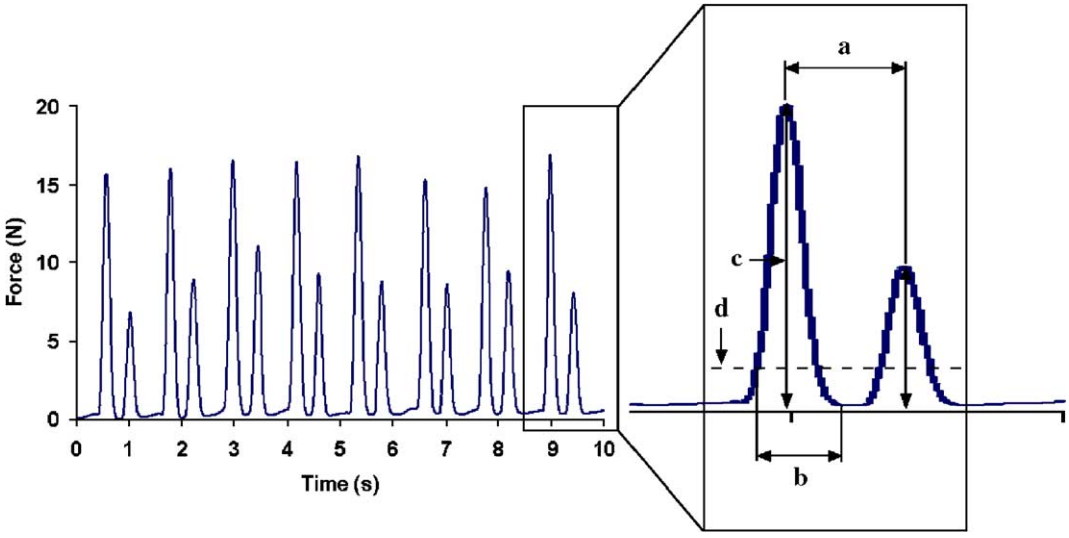

Fig. 2. Illustrative force signal showing hard and soft responses separated by short and long intervals (Left). On the right, pulse duration (b) was quantified as the interval between response threshold crossing (d) and the following force minimum. A duration of a time interval (a) and force maximum value (c) is also shown.

soft squeezes in one session, and with soft–hard squeezes in the other. The order of the two sessions was randomized across participants. The duration of each session was 13 min and 32 s. There was a 2 min pause between sessions. All participants practiced the experiment the day before scanning, producing 16 successive blocks in which responses were produced with equal force, and 16 successive blocks in which responses alternated between two levels.

Data collection

The presentation of auditory pacing stimuli, force feedback and the recording of responses (200 Hz sampling rate) were controlled under LabVIEW (National Instruments) running on a laptop computer. The amplified signal from the load cell was digitized by a 12-bit A/D converter PC card (DAQ-1200, National Instruments) and calibrated with standard weights at the start of each session. Peak force was measured as the peak output voltage from the load cell. Auditory stimuli were presented through an MR-compatible headphone system (MRC Institute of Hearing Research, Nottingham, UK), with an amplitude well above the background scanner noise (~100 dB sound pressure level [SPL]). End of block visual feedback and a within-block center fixation point were presented using a back-projection screen which the participant viewed from inside the magnet bore with 90° prism glasses.

Imaging procedure

Echoplanar imaging (EPI) was performed on a 3-T Siemens-Varian scanner (Siemens Medical Systems GmbH, Erlangen, Germany). Foam padding and a Velcro® strap limited head motion within the coil. Pulse sequence parameters were as follows: T2-weighted gradient echo modulated BEST sequence (TE, 30 ms; TR, 3 s; 90° flip angle, FOV, 256 × 256 mm; resolution, 64 × 64 matrix size). Whole-brain coverage was achieved using 25 contiguous horizontal slices (6 mm thick). A total of 540 volumes were acquired for both sessions. An additional 4 volumes (12 s) was collected at the beginning of each scan session to allow the MR signal to reach equilibrium, and was discarded from subsequent analysis. Scanning was synchronized with the onset of the test paradigm. For anatomical localization and co-registration a high-resolution scan of the entire brain was acquired after completion of testing using the following parameters: T1-weighted EPI TURBO-FLASH sequence with inversion pulse 500 ms, 64 contiguous slices, 1 × 1 × 3 mm each.

fMRI data analysis

The MRI data were converted into ANALYZE format and processed using FEAT (FMRI Expert Analysis Tool) version 5.1 (http://www.fmrib.ox.ac.uk/fsl). Pre-statistical processing included head motion correction using MCFLIRT (Jenkinson and Smith, 2001) to correct for rigid-body motion by realigning images on the central volume, spatial smoothing on every volume with a 5-mm Gaussian full-width half-maximum filter, and high-pass temporal filtering with a cutoff period of 120 s (set to the maximum stimulation period).

Statistical analysis was based on the general linear model approach, whereby the input stimulation timing for the continuation phase of each condition was convolved with a Gaussian kernel to simulate hemodynamics. To test hypotheses about regional specific condition effects, we defined a design matrix, contrasting the continuation phase of each rhythm (conditions A–D in Fig. 1) with the unmodeled rest. Additional contrasts in our design matrix included tests for main effects of increasing (positive) and decreasing (negative) activity with alternating intervals ($B + D > A + C$, $B + D < A + C$) and alternating force levels ($C + D > A + B$, $C + D < A + B$), together with positive and negative interactions between interval and force ($A + D > B + C$, $A + D < B + C$).

Statistical images of Z values from each participant were co-registered with their (brain-extracted) high-resolution structural image and transformed into a standard stereotaxic space corresponding to the MNI-305 template provided by the Montreal Neurological Institute using the linear image registration tool FLIRT (Jenkinson and Smith, 2001). Fixed effects analyses were

then carried out on the statistical maps using clusters determined by $Z > 2.96$ and a (corrected) cluster significance threshold of $P < 0.01$, using the theory of statistical parametric mapping (Worsley et al., 1992; Friston et al., 1992). Final results are presented in MNI coordinate space. Locations of both cluster and local maxima are reported. Identification of maxima was examined in the axial images of subjects' brains by reference to the automated anatomical map of Tzourio-Mazoyer et al. (2002).

Analysis of behavioural data

Performance data comprised force maxima and time intervals produced in the continuation phase for each rhythm, collapsed across both sessions. To remove scanner-related artifacts in the force signal acquired during the two scanning sessions (while preserving behavioural responses), two band-stop filters (0.36–0.49 and 1.18–1.34 Hz) were used to remove the power at frequencies associated with volume acquisition. Data sets acquired during scanning were also conditioned with a 2nd-order Butterworth low-pass filter (cutoff frequency = 10 Hz). Timing was extracted from the filtered force signal by measuring the interval between force pulse maxima. The amplitude of each pulse was taken as the peak force relative to zero force (see Fig. 2). Pulse duration was quantified as the interval between response threshold crossing and the following force minimum. Time and force accuracies for each condition were calculated as the percent error relative to the target interval and target force, respectively. The variabilities of the intervals and forces about their respective means were calculated for each condition as the coefficient of variation ([CV] expressed as a percentage). Accuracies and CVs for interval and force were analyzed separately with ANOVA performed in SPSS using a 2 × 2 design with repeated measures factors of Time (Equal vs. Alternating) and Force (Equal vs. Alternating). All post hoc tests were corrected for multiple comparisons using the Bonferroni method.

Results

Behavioural findings

Group average results for the mean and variance of time intervals and forces are shown in Fig. 3. The mean interval and force was close to target in all conditions. Occasionally, participants adopted the incorrect pattern of responding for a particular rhythm and the scanning data on these trials (less than 4% of the total) were excluded from analysis. Brain volumes corresponding to these data were not modeled.

Timing

The analysis of timing accuracy demonstrated main effects of Time $F(1,12) = 54.47$, $P < 0.001$ and Force, $F(1,12) = 6.87$, $P <$

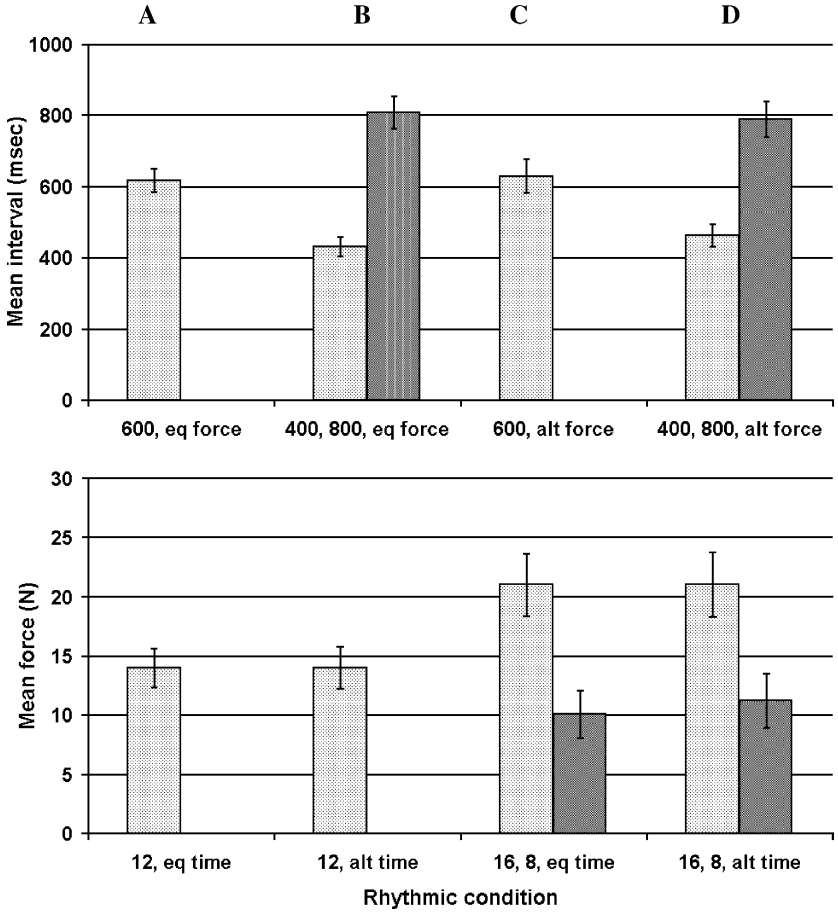

Fig. 3. Behavioural results for the production of equal (eq) and alternating (alt) intervals (upper) and forces (lower) acquired during scanning. Capital letters refer to the rhythm conditions detailed in Fig. 1. Error bars indicate the standard deviation for each condition.

0.05. Timing was more accurate when responses were separated by equal compared with alternating intervals (4.40% vs. 8.42%), and when responses were produced with equal compared with alternating forces (5.37% vs. 7.47%). There was no significant interaction.

The analysis of timing variability demonstrated a main effect of Force, $F(1,12) = 9.18$, $P < 0.01$. Timing was less variable when responses were produced with equal, compared with alternating force levels (5.55% vs. 6.50%). A Time × Force interaction was close to significance, $F(1,12) = 4.48$, $P < 0.06$ (Fig. 4). Analysis of the interaction revealed that timing variability was greater with alternating interval in B (5.85%) or force in C (6.53%) compared with equal interval and force in A (5.25%). These results suggest that alternation of either interval or force affect timing variability.

We also considered the possibility that the duration of force pulses differed between rhythmic conditions. To investigate this, we analyzed pulse duration in each condition according to the same 2 × 2 design outlined above. We observed no significant main effects or interaction. This result suggests that there are no systematic differences in pulse duration between conditions that would otherwise confound an interpretation of imaging data. Furthermore, analysis of a subset of data acquired during training showed that the average rate of change of force production over each rhythm was similar between conditions.

Force control

The analysis of force accuracy demonstrated a main effect of Time, $F(1,12) = 5.64$, $P < 0.05$. Force production was more accurate when responses were separated by equal compared with alternating intervals (24.97% vs. 35.55%). A significant Time × Force interaction, $F(1,12) = 5.53$, $P < 0.05$ was also observed. Force accuracy was more similar in conditions where timing was equal (26.04% vs. 23.89%), than when intervals alternated (32.44% vs. 38.65%).

The analysis of force variability demonstrated main effects of Time, $F(1,12) = 26.56$, $P < 0.001$ and Force, $F(1,12) = 8.16$, $P < 0.05$ (Fig. 4). Force was less variable when responses were separated by equal compared with alternating intervals (12.69% vs. 16.95%), and when responses were produced with equal compared with alternating forces (14.37% vs. 15.28%). There was no significant interaction.

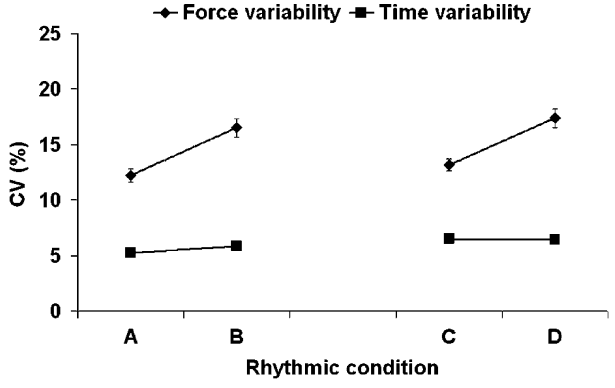

Fig. 4. The deviation of intervals and forces from their respective means (Coefficient of variation [CV] expressed as a percentage). Capital letters refer to the rhythm conditions detailed in Fig. 1. Error bars indicate the standard error of the mean (SEM).

Overall, the production of time intervals was more accurate and less variable than the production of force. Nonetheless, in the mean, both variables were produced relatively accurately so that the average values in the alternating condition matched the value in the constant condition (see Fig. 3).

Functional imaging findings

Table 1 shows the cluster size (cc), peak intensity (maximum Z score), MNI coordinates and anatomical location demonstrating clusters that were significant at $P < 0.01$ for direct contrasts between the four rhythmic conditions relative to rest. Clusters are rendered as color images onto averaged axial anatomical (T1) scans. All four rhythms showed a pattern of activity that included the primary motor cortex (M1), premotor cortex (PMC), supplementary motor area (SMA), somatosensory cortex (S1), basal ganglia, thalamus and cerebellum (see Fig. 5). It is clear from this figure that the magnitude of activation in the SMA, basal ganglia and the cerebellum is greater for the two conditions where force pulses alternate between two levels, compared with the two conditions where force production was equal. This is demonstrated by an increased number of activated voxels (cluster size [cc]) between such conditions, located within the basal ganglia, in the vicinity of the caudate and putamen, and within the anterior lobe of the cerebellum, located in the vicinity of lobules HVI and VIII (see Table 1, parts a–d). Activity within these regions was also bilateral.

A contrast testing for a main effect of alternating interval was not significant, indicating that brain regions activated in the two conditions where intervals were equal (A and C), were not more activated in the two conditions where intervals alternated (B and D). Reducing the Z value threshold of statistical maps from 2.96 to 2.3 failed also to reveal timing activity. Selecting a Z value of 1.8 failed to show even a trend towards a significant effect of time.

However, the main effect of alternating force was significant (Fig. 6) due to bilateral activations for thalamus, basal ganglia and cerebellar sites, and contralateral M1 and SMA regions. There was extra brain activity for producing a sequence with force levels alternating between two levels, compared with producing an equal force sequence. Additional activity seen within all four conditions (especially when reducing the Z value threshold from 2.96 to 2.3) included the superior temporal gyrus (STG), which was predominantly bilateral, together with bilateral BG activity in all four conditions. We observed no significant inverse effects. A positive interaction between time and force was close to significance ($Z = 1.8$ [$P = 0.05$]), which revealed posterior parietal cortex activity limited to the right side for the control of a sequence marked by both alternating interval and force (double alternation), compared with alternation on a single dimension of either time or force.

Discussion

In this study, we asked what brain structures are involved in accurately scaling force pulses produced during near isometric repetitive squeezing of the right thumb and index finger? In order to control for motor timing effects, we used a rhythm production task with alternating or equal force targets combined with alternating or equal interval targets. Previous functional imaging studies have shown a positive linear relationship between tapping

Table 1
Significant clusters and MNI coordinates for local maxima of blood oxygen level dependent (BOLD) activity for each rhythm condition, and the main effect of force

Cluster size (cc)	Cluster P (nmax $\geq k$)	Max Z score	Peak x mm	Peak y mm	Peak z mm	Anatomical location	BA
(a) Equal interval and equal force condition							
11.96	<0.00001	4.76	−34	−16	66	L precentral (PMC)	6
		4.75	−50	−20	50	L postcentral (S1)	3
		4.17	−32	−28	60	L precentral (M1)	4
2.59	0.000859	4.49	−4	−6	72	L precentral (SMA)	6
3.24	0.000164	4.08	−52	16	−16	L sup. temporal pole	38
4.45	<0.00001	4.14	−28	−2	−12	L putamen	
2.46	0.00121	3.74	−12	−20	−4	L thalamus	
6.36	<0.00001	4.29	14	−56	−22	R cerebellum HVI	
(b) Alternating interval and equal force condition							
14.6	<0.00001	5.02	−50	−20	52	L postcentral (S1)	3
		4.91	−34	−16	66	L precentral (PMC)	6
		4.39	−38	−18	62	L precentral (M1)	4
4.6	<0.00001	4.37	−4	−6	72	L precentral (SMA)	6
14.7	<0.00001	4.65	−26	−8	−8	L putamen	
		4.33	−20	−6	20	L caudate	
		4.2	−12	−20	−4	L thalamus	
6.4	<0.00001	4.58	12	6	16	R caudate	
		3.95	28	−6	6	R putamen	
10.3	<0.00001	4.56	6	−60	−26	R vermis VIII	
		4.53	16	−54	−24	R cerebellum HVI	
(c) Equal interval and alternating force condition							
93.4	<0.00001	5.12	−50	−20	52	L postcentral (S1)	3
		4.96	−8	−2	50	L precentral (SMA)	6
		4.87	−36	−14	66	L precentral (PMC)	6
		4.47	−38	−18	62	L precentral (M1)	4
		4.19	−52	16	−16	L sup. temporal pole	38
		4.75	−12	12	14	L caudate	
		4.47	10	6	16	R caudate	
		4.66	−22	−2	8	L putamen	
		4.17	28	4	−6	R putamen	
		4.27	−12	−10	0	L thalamus	
		4.2	6	−10	0	R thalamus	
20.3	<0.00001	5.28	18	−54	−24	R cerebellum HVI	
		5.04	10	−64	−36	R cerebellum HVIII	
		4.29	−20	−54	−40	L cerebellum HVIII	
2.6	0.000745	4.31	56	−30	4	R sup. temporal	22
(d) Alternating interval and alternating force condition							
29.8	<0.00001	5.3	−50	−20	52	L postcentral (S1)	3
		4.86	−32	−16	66	L precentral (PMC)	6
		4.6	−6	0	50	L precentral (SMA)	6
		4.54	−32	−28	60	L precentral (M1)	4
51.8	<0.00001	4.6	−52	16	−16	L sup. temporal pole	38
		4.05	50	10	−12	R sup. temporal pole	38
		4.51	−12	12	14	L caudate	
		4.02	16	16	14	R caudate	
		4.17	−24	0	4	L putamen	
		4.11	28	2	−4	R putamen	
		4.41	−12	−20	−4	L thalamus	
		4.58	10	−10	−10	R thalamus	
20.4	<0.00001	5.29	18	−54	−24	R cerebellum HVI	
		5.03	8	−60	−30	R cerebellum HVIII	
		4.18	−20	−52	−42	L cerebellum HVIII	
		3.99	−18	−62	−32	L cerebellum HVI	

Table 1 (*continued*)

Cluster size (cc)	Cluster P (nmax $\geq k$)	Max Z score	Peak x mm	Peak y mm	Peak z mm	Anatomical location	BA
(e) Main effect of alternating force							
45.78	1.22E−33	5.79	−28	−6	62	L sup. frontal	6
		5.6	−8	4	50	L precentral (SMA)	6
		5.25	34	−12	60	R precentral	6
		4.84	−40	−10	58	L precentral	6
		4.75	−26	−42	74	L sup. parietal	1
36.03	1.46E−28	5.5	22	−58	−24	R cerebellum HVI	
		5.44	−18	−62	−26	L cerebellum HVI	
23.67	2.15E−21	4.82	−60	4	18	L postcentral	6
		4.52	−12	−20	4	L thalamus	
		4.44	−56	8	−2	L sup. temporal pole	38
		4.41	−26	−2	8	L putamen	
22.28	1.62E−20	5.2	56	10	−4	R sup. temporal pole	38
		4.64	12	−18	4	R thalamus	
		4.2	28	−2	−2	R putamen	
13.40	2.12E−14	4.59	46	−42	60	R sup. parietal	2
		4.34	58	−2	42	R precentral	4
		4.22	46	−36	50	R inferior parietal	2
		4.18	44	−36	44	R sup. margin	3
		4.18	40	−36	58	R postcentral	4
2.56	0.000299	4.36	66	−38	−4	R mid temporal	21
		3.67	62	−32	10	R sup. temporal	22

rate and the spread of cortical activity for movement rates between 1 Hz and 5 Hz (Rao et al., 1996), and between force level and the amplitude of the measured fMRI signal, for forces between 20% and 65% of maximum (Dai et al., 2001). We controlled for these effects of rate and force level by setting the target time interval and force for the equal conditions to be the average of the values used in the alternating conditions.

Our analyses focused on data produced in each trial during steady-state, free responding following an initial paced phase. The behavioural results indicated successful performance of the various conditions with force and interval in the alternating conditions relatively accurately spaced on either side of the values in the alternating conditions. The imaging results showed a clear pattern of activation compared to rest that included M1, PMC, SMA, S1, BG, thalamus and cerebellum. A main effect of force alternation revealed bilateral PMC, BG and cerebellum and contralateral M1 and SMA. There was no main effect of alternating interval, but an interaction between time and force that was close to significance revealed right-sided posterior parietal activity.

Previous research has implicated the BG in modulation of force. Bilateral activation of putamen (Ehrsson et al., 2003) and ipsilateral activation of the caudate (Boecker et al., 2005) was reported in a thumb-finger squeezing task. Bilateral activation of BG, as well as many other motor structures, was noted in a task requiring the production of a controlled change and/or level of grip force (Vaillancourt et al., 2004). The latter study included four conditions varying in force rate and in the duration over which force changed. A region of interest analysis revealed systematic increase in activation with force rate in internal (but not external) globus pallidus. In the present study, the rate of force development was not controlled and co-varied with change in peak force; force rate for a hard response was double that of a soft response in both rhythms C and D. Moreover, both force and force rate were constant across rhythms A and B. Thus, in the present study, it was not possible to determine whether the effects obtained related to force per se or to rate of change of force. Nonetheless, we also show for the first time that effects related to force extend to force impulse production and that these effects are independent of timing, in the sense that there is no significant interaction involving time and force. However, an interaction between time and force that was close to significance revealed right-sided posterior parietal activity. This result is consistent with that of Ehrsson et al. (2003) and Boecker et al. (2005) who reported BG activity for coordinating load and grip force changes in a precision grip between the thumb and index finger.

It is interesting to relate our observations of force-related BG activation to previous studies indicating a relation between activity in the BG and the speed of arm movement (Taniwaki et al., 2003; Turner et al., 2003a,b) and control of speech volume (Liotti et al., 2003). Taken with results from non-human primate studies using single cell recording (Georgopoulos et al., 1983; Turner and Anderson, 1997), neuronal inactivation (Alamy et al., 1995; Inase et al., 1996; Mink and Thach, 1991) and electrical stimulation (Horak and Anderson, 1984), this supports the hypothesis that the BG contribute to the control of movement scale. Impairments in control of scaling of movement amplitude observed in BG disorders such as Parkinson's disease (Berardelli et al., 2001; Desmurget et al., 2004b; Godaux et al., 1992) and Huntington's disease (Berardelli et al., 1999; Thompson et al., 1988) lend additional support to the suggestion that BG activation is related to movement intensity.

What functions might the BG serve in controlling movement intensity? One possibility is that BG BOLD signal reflects an inhibitory process leading to muscle relaxation to a specific level of force (or force rate). The force alternation effect in the BG might then reflect a gain switch or amplification parameter acting on successive responses. Another possibility is that the alternation effect in the BG might reflect a process of selection between different responses. Animal work by Mink (1996) and Boraud et al. (2002) has implicated the BG in response selection. Response selection deficits are also evident in work with PD patients, who find it difficult to inhibit competing response alternatives and to initiate a correct response (Praamstra and Plat, 2001; Turner et al., 2003a; Desmurget et al., 2004a). Such selection deficits may

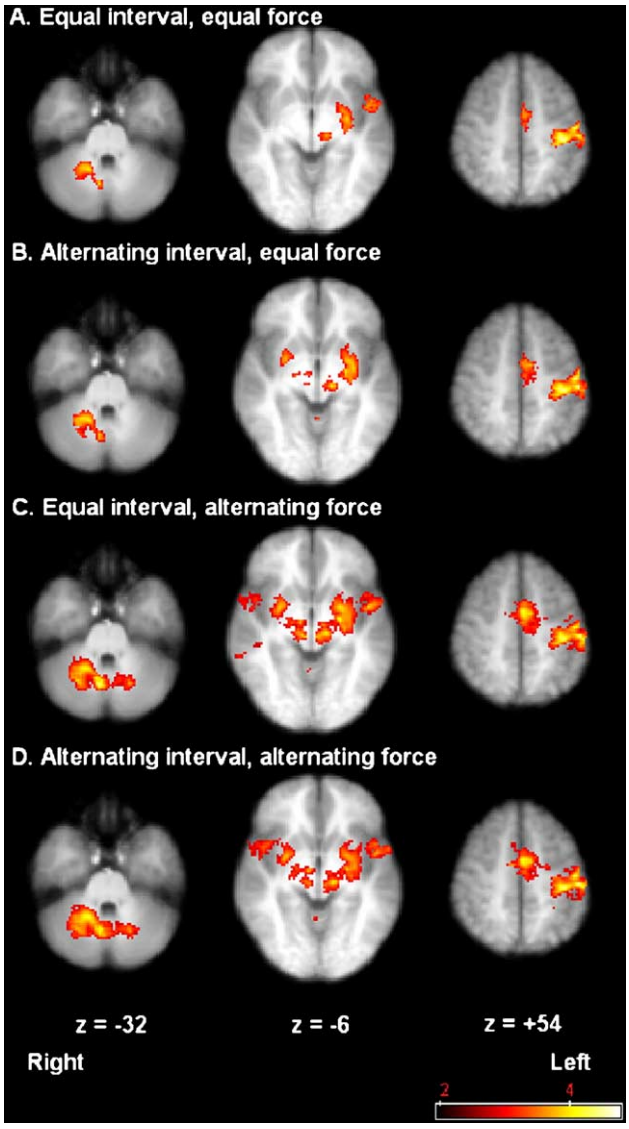

Fig. 5. Brain regions demonstrating significantly increased MR signal intensity changes for all four rhythm conditions relative to rest. *Z* indicates distance in millimeters above (+) or below (−) the anterior–posterior commissure line. Functional activity is overlaid on averaged axial anatomical (T1) scans. The right side of the figure corresponds to the left of the brain.

underlie problems in performing sequential movements in PD patients (Benecke et al., 1987).

Our study revealed bilateral activation of the cerebellum. The involvement of the cerebellum in the control of scale-related parameters of movement is well established. Non-human primate recording studies have demonstrated relations between cerebellar single unit discharge and motor parameters such as velocity (Coltz et al., 1999) and extent (Fu et al., 1997). Functional imaging studies have identified the cerebellum in the regulation of velocity and extent of movement (Turner et al., 2003a). However, in these studies, interaction torques may have played a significant role, especially given that altered control of interaction torques underlies impaired multijoint reaching movements observed in cerebellar disease (Bastian et al., 1996). However, in the near isometric conditions of the present study, no such torques arise, which identifies the cerebellar activation with pure force control, although this may have included monitoring of force either through efferent or afferent signals.

Our study included conditions requiring temporal control in the production of equal and alternating (rhythmic) inter-response intervals. However, we observed no reliable activity for conditions where responses were separated by alternating compared with equal intervals—there was no main effect of alternating interval. Other imaging studies have reported reliable activation of a number of structures including BG and cerebellum in a comparison of alternating and equal interval production in an evaluation of learning (Doyon et al., 2003) and in a parametric analysis of rhythm complexity in well-learned performance (Lewis et al., 2004). However, in the former, the differential subcortical activation dissipated in well-practiced performance and in the latter, parametric subcortical activation effects were limited to initial preparation and synchronization phases of each trial and were not present during unpaced responding. Thus, the lack of time-related activation in the present study is not inconsistent with the earlier work.

There was a marked contrast between the pattern of activation we obtained for force alternation and the lack of activation observed in alternation of the time intervals between force pulses. Our behavioural data showed relatively greater variability (in terms of CV) in the control of force than in the control of time interval. This was most likely due to the differential information provided in the initial pacing phase in that time errors were available on each response in terms of the asynchrony between the pacing tone and feedback from the force pulse. There was no corresponding feedback to indicate discrepancy between produced force and target force, although some attempt was made to redress the balance by providing objective information about force level(s) at the end of each trial. This raises the question whether our results might be due to differential difficulty? In previous timing studies, the possibility of differential difficulty across conditions has been an issue because observed effects might be attributed to processes responsible for allocation of attention rather than to greater involvement of the process itself. For instance, Lewis et al. (2004) noted increased fronto-parietal involvement with more complex rhythms and this could have reflected either greater demands on brain regions responsible for timing or increased demand on attentional circuits. However, in the present study, it seems less likely that the subcortical foci of activation associated with alternation of force but not interval should be

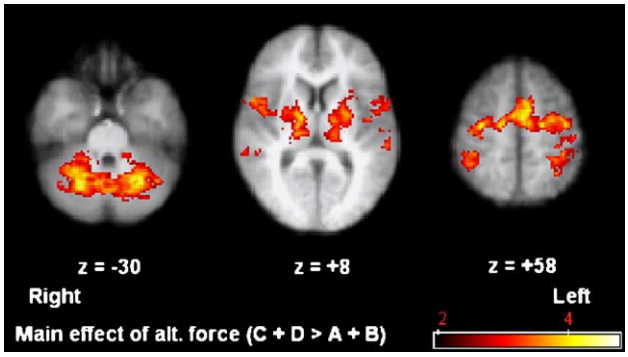

Fig. 6. Brain regions demonstrating significantly increased MR signal intensity changes for a positive main effect of alternating force (C + D > A + B).

identified with attention control and we therefore suppose the activated regions directly reflect the control of force.

Conclusion

Previous studies of motor timing have identified various cortical and subcortical regions that contribute to the control of interval production. Yet, very little is known about the control of force. Indeed, many studies of motor timing have not included an investigation of rhythm, where both time and force vary. The current findings are among the first to report an effect of force modulation, using a paradigm in which timing was controlled. These findings establish a network of brain regions involved in rhythm production, including; M1, PMC, SMA, thalamus, basal ganglia and the cerebellum. The increased demands of responding with two different force levels (compared with an equal force) resulted in greater activation of cortical regions, and included bilateral basal ganglia and cerebellar activity. Rhythms marked with two intervals (compared with an equal interval) made no additional demands upon these regions. These results suggest that the basal ganglia mediate the control of force, most likely the transition between successive force pulses, rather than interval timing per se. Identifying such activity associated with alternating force levels, but not with alternating interval, indicates the importance of monitoring force when studying brain activity correlating with motor timing.

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