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Neural Networks for the Coordination of the Hands in Time

FREDRIK ULLÉN, HANS FORSSBERG, AND H. HENRIK EHRSSON
Neuropediatric Research Unit, Department of Woman and Child Health, Karolinska Institutet, SE-171 76 Stockholm, Sweden

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Ullén, Fredrik, Hans Forssberg, and H. Henrik Ehrsson. Neural networks for the coordination of the hands in time. *J Neurophysiol* 89: 1126–1135, 2003. First published October 23, 2002; 10.1152/jn.00775.2002. Without practice, bimanual movements can typically be performed either in phase or in antiphase. Complex temporal coordination, e.g., during movements at different frequencies with a noninteger ratio (polyrhythms), requires training. Here, we investigate the organization of the neural control systems for in-phase, antiphase, and polyrhythmic coordination using functional magnetic resonance imaging (fMRI). Brisk rhythmic tapping with the index fingers was used as a model behavior. We demonstrate different patterns of brain activity during in-phase and antiphase coordination. In-phase coordination was characterized by activation of the right anterior cerebellum and cingulate motor area (CMA). Antiphase coordination was accompanied by extensive fronto-parieto-temporal activations, including the supplementary motor area (SMA), the preSMA, and the bilateral inferior parietal gyri, premotor cortex, and superior temporal gyri. When contrasting polyrhythmic tapping with in-phase tapping, activity was seen in the same set of brain regions, and in the posterior cerebellum and the CMA. Antiphase and polyrhythmic coordination may thus to a large extent use common neural control circuitry. In a separate experiment, we analyzed the neural control of the rhythmic structure and the serial order of finger movements during polyrhythmic tapping. Polyrhythmic tapping was compared with an isochronous coordination pattern that retained the same serial order of finger movements as the polyrhythm. This experiment showed that the preSMA and the bilateral superior temporal gyri may be crucial for the rhythmic control of polyrhythmic tapping, while the cerebellum, the CMA, and the premotor cortices presumably are more involved in the ordinal control of the sequence of finger movements.

INTRODUCTION

The behavioral characteristics of different patterns of temporal coordination of the hands have been a major topic in human motor control research. A consistent finding in these studies is the preference for in-phase (synchronous) or antiphase (alternating) coordination of the hands, during continuous movements, e.g., wrist rotations (Lee et al. 1996) and finger oscillations (Kelso 1984) as well as during tasks involving repetitive brisk movements, such as rhythmic finger tapping (Tuller and Kelso 1989; Yamanishi et al. 1980). In-phase coordination is performed with higher accuracy, i.e., lower variance in the phase difference between the hands (Yamanishi et al. 1980), less sensitivity to perturbations (Scholz et al. 1987), and larger persistence over frequency changes than antiphase coordination (Amazeen et al. 1998; Kelso 1984; Kelso et al. 1988). Patterns with intermediate phase-relations (Semjen and Ivry 2001; Yamanishi et al. 1980) or polyrhythms, where the limbs move at different frequencies with a noninteger ratio (Deutsch 1983), are common, e.g., in musical performance and dance. These are more variable and require training (Peper and Beek 1998; Summers et al. 1993a,b).

The functional organization of the neural control systems for temporal coordination has, however, remained poorly understood. Neurobiological studies of bimanual movements have largely focused on the spatial coordination of continuous movement trajectories (see e.g., Sadato et al. 1997; Stephan et al. 1999a,b; Toyokura et al. 1999). To specifically study temporal coordination, it is important to use rhythmic tasks with brisk discrete movements, where spatial coordination demands are minimized. Interestingly, Kennerley et al. (2002) in a recent study on callosotomy patients, provided evidence for that repetitive brisk finger movements can be synchronized by subcortical structures. Whether antiphase coordination and more complex temporal coordination patterns can also be accurately performed by split-brain patients has not been investigated using this type of tasks. Lang et al. (1990), using electroencephalographic (EEG) recordings, found larger activity over the medial wall motor areas during polyrhythmic (3:2) tapping than during in-phase tapping. Increased activity in the supplementary motor area (SMA), and in a number of other brain regions, has also been reported in studies on unimanual motor tasks requiring explicit timing. Using functional magnetic resonance imaging (fMRI), Rao et al. (1997) found increased activity in the SMA, the cerebellum, the thalamus, the putamen, the superior temporal gyrus, and the inferior frontal gyrus during self-paced finger tapping. Involvement of the cerebellum, the basal ganglia, the SMA, and the premotor cortex in rhythmic sequence control has been shown in several studies (Penhune et al. 1998; Ramnani and Passingham 2001; Sakai et al. 1999; Ullén et al. 2001).

Here, we utilized fMRI to address some fundamental questions regarding the neural organization of the control systems for bimanual temporal coordination. First, we compared the brain activity during in-phase and antiphase coordination. We hypothesized that in-phase coordination, as suggested by data from callosotomy patients (Ivry and Hazeltine 1999; Kennerley et al. 2002), would rely less on cortical mechanisms than antiphase coordination, which requires that precisely timed motor commands are sent, in an alternating manner, to the muscles of the two hands. Second, we mapped brain areas specifically involved in the control of complex, learned coordination by comparing the brain activity during polyrhythmic

Address reprint requests to F. Ullén: (E-mail: Fredrik.Ullen@neuro.ki.se).

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tapping with that during in-phase and antiphase tapping. This revealed a network of different brain regions. Recent behavioral data has suggested that different brain mechanisms may be involved in the control of the rhythmic and ordinal (i.e., serial order of movements) structure of learned movement sequences (Bengtsson and Ullén 2002). We therefore investigated whether some of the brain regions seen when contrasting polyrhythmic tapping with in-phase tapping are specifically important for rhythm control, while others are more involved in the control of the serial order of finger movements. For this purpose, polyrhythmic tapping was compared with the tapping of another learned bimanual coordination pattern, that retained the same serial order of finger movements as the polyrhythm but was isochronous.

METHODS

Subjects

All experimental procedures were ethically approved by the Karolinska Institutet Ethical Committee (KI Forskningsetikkommitté Nord; Dnr 99-291). Fourteen healthy, right-handed (Oldfield 1971) male subjects (21–27 yr) participated in the study. No subjects were professional musicians or music students. Each subject practiced all tasks (see following text) in one 1-h rehearsal session 1–3 days before the experiment. During the training, the subjects received only auditory instruction. The finger sequence of the polyrhythmic tasks and isochronous sequence (isoseq; see following text) was presented verbally, while the temporal sequence was presented through head phones as a recorded sequence of drum beats. Only subjects that after the training session were able to perform all tasks robustly while simultaneously maintaining a conversation with the experimentor were used for fMRI recordings: six subjects for the main experiment and three subjects for the control experiment. One additional shorter (30 min) rehearsal was performed immediately before the MR recording. All tasks were rehearsed an equal amount of time. No subjects participated in both experiments.

Behavioral tasks

The subjects performed bimanual and unimanual rhythmic brisk tapping movements with the index fingers; results from the unimanual tasks will be presented in an independent study. Subjects rested comfortably in a supine position in the MR scanner, with the arms extended parallel to the trunk, so that they could comfortably tap on two nonmagnetic optic force transducers with the index fingers. The vertical tap forces were acquired, displayed on-line, and recorded on a PC computer using the SC/ZOOM data acquisition system (Dept of Physiology, University of Umeå) with a sampling frequency of 0.8 kHz.

In the main experiment, all tasks were performed in epochs lasting 36 s, using a continuation paradigm: during the first 6 s of each epoch, the subjects were given a verbal instruction on which task to perform, followed by five beats of an auditory metronome at 80 beats per minute. The subjects started to tap in phase with the metronome and thereafter continued with self-paced tapping for the remaining 30 s of the epoch. Data from this period was used in the subsequent analysis. Four bimanual tasks were used (see Fig. 1*A* and RESULTS): in-phase (In-phase), antiphase coordination (Antiphase), and two polyrhythmic tasks (3:2 and 2:3). A rest condition, where subjects relaxed without any active movements, was used as control (Rest). To ensure that the tasks were correctly performed, behavioral records from all epochs were inspected qualitatively. Behavioral data from the four first and the last epoch of all subjects was analyzed quantitatively (see Fig. 1, *B–D*, and RESULTS). To reduce possible time and order effects, five

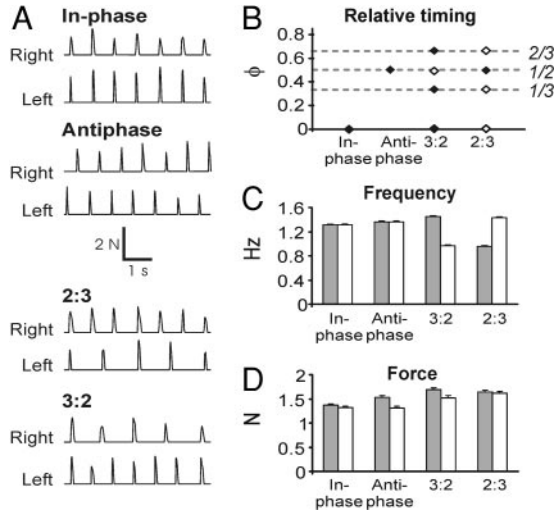

FIG. 1. Recordings of tapping forces during the functional magnetic resonance imaging (fMRI) scans. *A*: typical examples of tapping force recordings for the different conditions from a single subject. *B–D*: mean values for all subjects; error bars indicate standard error of the mean. *B*: relative timing between the hands. ◆, the phase of the right-hand taps in the left-hand cycle; ◇, the phase of the left-hand taps. - - -, ideal phase values (1/2 for antiphase; 1/3, 2/3 and 1/2 for 3:2 and 2:3). *C*: tapping frequency for the left (□) and right (■) hand. *D*: tapping forces for the left (□) and right (▩) hand.

different task orders were used in different runs. Within runs all tasks were performed twice in the same order.

A similar block design was used in the control experiment. Here, an epoch length of 40 s was used. Task instruction and metronome beats were presented during the first 8 s of the epoch; data were analyzed from the subsequent 32 s of self-paced tapping. A rest condition and three bimanual tasks were used (see Fig. 5 and RESULTS): a polyrhythmic task (3:2), Isoseq, and in-phase (In-phase). For In-phase and 3:2 the metronome was set at 1.33 Hz (80 bpm). To match the number of tapping movements between the tasks, a metronome frequency of 1.78 Hz (107 bpm) was used for Isoseq (see Fig. 5A). Three different task-orders were used in different runs, and all tasks were performed twice in a run.

Data acquisition: fMRI

fMRI was conducted on a 1.5 T scanner (Signa Horizon Echospeed, General Electric Medical Systems). A plastic bite bar was used to restrict head movements. At the beginning of each experiment, a high-resolution, three-dimensional gradient echo T1-weighted anatomic image volume of the whole brain was collected. Functional imaging data were then collected as gradient-echo, echo-planar (EPI) T2*-weighted image volumes, built up from contiguous axial slices ($n = 24$) collected from the dorsal surface of the brain down to the caudal edge of cerebellum, using a blood-oxygenation-level-dependent (BOLD) contrast. The image volumes were collected continuously during separate runs, using different task orders in different runs (see preceding text). In the main experiment, the following parameter values were used for the fMRI scanning: echo time, 60 ms; field of view, 22 cm; matrix size, 64 × 64; pixel size, 3.4 × 3.4 mm; flip angle, 90°; number of slices: 24; slice thickness: 6.0 mm; repetition time (T_R), 6 s; epoch duration, 36 s; number of volumes per run: 84; number of runs: 7. The corresponding parameter values for the control experiment were: echo time, 60 ms; field of view, 22 cm; matrix size, 64 × 64; pixel size, 3.4 × 3.4 mm; flip angle, 90°; number of slices: 30; slice thickness: 5.0 mm; repetition time (T_R), 4 s; epoch duration, 40 s; number of volumes per run: 80; number of runs: 6.

Data analysis and image processing

Both the main experiment and the control experiment were analyzed in the same way, using the Statistical Parametric Mapping software package (SPM-99; http://www.fil.ion.ucl.ac.uk/spm/; Wellcome Department of Cognitive Neurology, London). The volumes were realigned, coregistered to each individual's T1-weighted image and normalized to the stereotactic coordinate system of Talaraich and Tournoux (Friston et al. 1995a; Talaraich and Tournoux 1988), using the template brain of the Montréal Neurological Institute Proportional scaling was applied to eliminate the effects of global changes in the signal. The time series were smoothed spatially with an isotropic Gaussian filter of 8 mm full width at half-maximum and temporally with a Gaussian kernel of width 4 s. The fMRI data were modeled with a standard linear regression model, as implemented in SPM-99, where we defined conditions of interest corresponding to the periods in each epoch when the subjects performed the tasks without hearing the metronome. The 6-s periods when the subjects heard the task instruction and metronome were modeled as conditions of no interest. The significance of the effects was assessed using *t* statistics for every voxel from the brain to create statistical parametric maps (SPMs), which were subsequently transformed into Z statistics. To increase the sensitivity of the analysis, we pooled the data from all subjects, performing a group analysis (fixed-effects model). In a complementary analysis, the consistency of the activations found in the group analysis was confirmed by examining the activation maps obtained in individual subjects (see Tables 1–3). Peaks of activity, i.e., local maxima, which after correction for the total number of comparisons for the whole brain volume corresponded to $P < 0.05$ on the basis on a test of peak height (Friston et al. 1995b), are reported. For the brain regions that showed differences in activity between tasks, we only report voxels that were active also versus Rest (uncorrected $P < 0.05$ at each voxel), using an inclusive mask procedure. By this means, we focused on brain areas that showed a stronger activity during hand movements than when the hand was relaxed and excluded the possibility that differences between the tasks merely reflected different degrees of deactivations. In the main experiment, differences in neural activity between the two inherent forms of bimanual coordination were examined by using the contrasts (Antiphase – In-phase) and (In-phase – Antiphase), with (Antiphase – Rest) and (In-phase – Rest), respectively, as inclusive masks. To reveal brain activity related to the generation of polyrhythmic tapping, the contrasts (3:2 − In-phase + 2:3 − In-phase) and (3:2 − Antiphase + 2:3 − Antiphase) were used to match the number of movements and avoid left/right asymmetries. Here, the contrasts (3:2 − Rest) and (2:3 − Rest) were used as inclusive masks. Anatomical localizations of the activated regions were determined from an average image made from normalized and intensity standardized T1-weighted images from all subjects.

RESULTS

Behavioral data

Typical examples of tap force recordings from the four bimanual tasks are shown in Fig. 1*A*: in-phase tapping (In-phase) where both hands tapped in synchrony; antiphase tapping (Antiphase) with an alternating coordination between the hands, and two symmetrical polyrhythmic tasks (3:2 and 2:3) where the fast hand continued at the metronome frequency, with three beats against two beats in the slow hand. Two polyrhythmic tasks were included so that left/right asymmetries could be avoided by analyzing these two conditions together (see following text). Subjects were highly accurate in their reproduction of all tasks. The relative timing of the hands, i.e., the mean phase of the beats of one hand in the cycle of the opposite hand is shown for all subjects in Fig. 1*B*. In all tasks, the deviation from the ideal value (In-phase: 0; Antiphase: 1/2; polyrhythmic tasks: 1/3 and 2/3 for the fast hand, 1/2 for the slow hand) was $<0.006 \pm 0.003$ (SE) cycles. The tapping frequency (mean values, all subjects) for the different tasks is shown in Fig. 1*C*. For in-phase and antiphase, the mean frequencies deviated <0.03 Hz from the period of the metronome (1.33 Hz). During 3:2 and 2:3, a slight drift in frequency was seen with mean frequencies for the fast hand of 1.45 and 1.44 Hz, respectively. Figure 1*D* shows the mean left- and right-hand tap forces. Mean forces varied between 1.32 and 1.70 N, and the difference in mean force of the same hand between tasks was always <0.33 N.

In summary, the motor output was thus closely matched for all tasks. To ensure that the total motor output of the hands during the polyrhythmic tasks was symmetrical and not higher than during In-phase and Antiphase, in spite of the slight frequency drift seen during polyrhythmic tapping, the activity during 3:2 and 2:3 was always averaged when analyzing the fMRI data (see following text). Only subjects that could perform all tasks while simultaneously conversing with the experimentor were included (see METHODS). To further test that the tasks were overlearned, i.e., that no significant improvement of performance took place during the scanning sessions, a comparison of performance variability at the beginning and end of the scanning was made. The SD of the first 18 temporal intervals produced in the first and last recorded epochs was calculated, separately for the two hands, for all conditions and subjects. Data from all subjects and both hands were pooled. No significant difference in SD was found between performance in the first and last epoch for either of the four conditions (In-phase, $P = 0.29$; Antiphase, $P = 0.1$; 3:2, $P = 0.27$; 2:3, $P = 0.40$; paired *t*-test). All conditions can thus be considered to be overlearned. In summary, the differences in brain activity discussed in the following text should essentially reflect the different temporal patterns of the tasks.

fMRI data

Contrasting Antiphase with In-phase (Table 1; Fig. 2) revealed large bilateral fronto-parieto-temporal activations that included the ventral premotor cortices (PMV) in the inferior part of the precentral sulcus, the SMA and preSMA, anterior parts of the superior temporal gyri, the supramarginal gyri and, on the right side, the anterior part of the intraparietal sulcus. Additional strong activity in Antiphase versus In-phase was seen bilaterally in the thalamus and in the right prefrontal cortex (Fig. 2; Table 1). When contrasting In-phase with Antiphase, fewer active regions were seen (Table 1). Notably, a strong activation was seen in lobules III and IV of the right anterior cerebellar lobe (Schmahmann et al. 2000), in the region of the motor representation of the right hand (Nitschke et al. 1996) (Fig. 3; see DISCUSSION). Additional activations were seen in the right caudal cingulate motor area (CMA), the left prefrontal cortex, the left precuneus, and the right cuneus (Table 1).

Contrasting the polyrhythmic tasks (2:3 and 3:2) with In-phase demonstrated strong activity in a number of cortical motor areas, including the left dorsal premotor cortex (PMD), the bilateral PMV, the right SMA, and the left cingulate sulcus. The latter cluster extended into the SMA, the CMA, and the preSMA (see Table 2 for further details). In addition, major

TABLE 1. *Activated brain regions in In-phase and Antiphase*

Anatomical Region	Side	*x*	*y*	*z*	*Z* Score[a]	*n*[b]
Antiphase vs. In-phase						
SMA/preSMA	Left	−16	0	60	4.56	6
Inferior part of precentral sulcus (PMV/area 44)	Left	−64	8	16	5.30	6
	Right	60	8	12	5.14	5[c]
Precentral gyrus (PMV/PMD)	Left	−52	−8	40	6.38	6
Inferior frontal gyrus, pars triangularis	Right	32	44	24	6.16	6
Lat fissure, superior temporal gyrus,	Left	−72	−24	20	6.70	6
Supramarginal gyrus		−64	−44	24	6.26	6
	Right	64	−36	20	Inf	6
Superior temporal gyrus	Left	−60	12	0	5.40	6
		−64	4	4	4.66	6
		−48	16	−8	4.93	6
	Right	52	12	−8	5.48	4[c]
		52	24	−8	5.40	4[c]
Insula	Left	−40	12	0	5.39	5[c]
Inferior parietal gyrus	Left	−60	−32	28	6.05	6
	Right	60	−20	28	5.01	6
Intraparietal sulcus (anterior part)	Right	40	−40	44	5.99	6
Thalamus	Right	20	−24	12	4.60	6
In-phase vs. Antiphase						
Cingulate sulcus (CMA)	Right	12	−32	48	4.89	5[c]
Superior frontal gyrus (PF)	Left	−8	60	32	6.37	5[d]
		−8	64	24	5.89	6
Precuneus	Left	−12	−56	12	5.40	6
Cuneus	Right	4	−84	24	5.45	6
		4	−72	24	4.85	6
Cerebellum, anterior lobe (lobule III–IV)[e]	Right	12	−40	−24	5.19	6

PMV and PMD, ventral and dorsal premotor cortices; PF, prefrontal cortex. [a] Only significant activations ($P < 0.05$), corrected for multiple comparisons, that were active also vs. rest are shown; *x*, *y*, and *z* give the Talaraich coordinates of the activity peak. [b] The number of subjects (of the total 6) that showed a statistical trend for the activity to increase ($P < 0.05$, uncorrected). [c] An additional subject showed a weaker activation in this region ($P < 0.2$). [d] The 6th subject showed a weaker activation in this region ($P < 0.1$). [e] The terminology for cerebellar lobules follows Schmahmann et al. (2000).

activations were found in the bilateral superior temporal gyri, including anterior parts of both gyri and the posterior part of the right superior temporal gyrus, the left inferior parietal and right postcentral cortices, the bilateral thalamus, and the cerebellum (Table 2). Cerebellar activity was observed both bilaterally in the hemispheres and in the posterior vermis (lobules VI and VIIA; Fig. 4; Table 2). When contrasting the polyrhythmic tasks with Antiphase, activity was seen only in the same region of the posterior cerebellar vermis and the left precuneus (Table 2).

Control experiment

The brain regions activated when contrasting the polyrhythmic tasks with In-phase could have various functional roles related to the control of learned, temporally complex bimanual sequences. To reveal which of these regions are specifically important for the control of the rhythmic pattern of the polyrhythm, on the one hand, and the serial order of finger movements, on the other hand, we performed a control experiment. Three bimanual tasks and a rest condition were used. Typical tap force recordings of the bimanual tasks are shown in Fig. 5*A*. Polyrhythmic tapping (3:2) and in-phase tapping (In-phase) were performed as in the main experiment. In the third task, Isoseq, subjects tapped an isochronous sequence that retained the same serial order of the finger movements as in 3:2. The only difference between this task and 3:2 was thus in the temporal structure of the movements.

Brain areas specifically involved in the rhythmic control of the movements were examined by a 3:2 versus Isoseq contrast. This revealed bilateral activity in the anterior parts of the superior temporal gyri, the SMA, the right intraparietal sulcus, and the thalamus (Fig. 5*B;* Table 3). Notably, in the main experiment, contrasting polyrhythm with In-phase gave superior temporal activations that similarly included anterior parts of both superior temporal gyri and in addition the posterior part of the right superior temporal gyrus (see Table 2). To further examine the reason for this difference, the corresponding 3:2 versus In-phase contrast (not shown) was also investigated in the control experiment, revealing an activation of the posterior right superior temporal gyrus (peak coordinates: $x = 60$; $y = -40$; $z = 8$) similar to that seen in the main experiment. Taken together, these findings thus suggest that the anterior regions of the superior temporal gyri could be particularly important for temporal control. No active areas were seen when contrasting the temporally less complex Isoseq with 3:2. Contrasting Isoseq with In-phase, to map brain regions involved in the control of the serial order of finger movements, revealed major activations in other regions that earlier were seen in the main experiment when contrasting the polyrhythmic tasks with In-phase: the bilateral PMD, the left PMV, the left CMA, the left inferior parietal gyrus and bilaterally in the lateral and the medial cerebellum (Table 3). In addition, a smaller cluster of activity was found in the left precuneus (Table 3).

DISCUSSION

We have mapped brain regions involved in different fundamental types of temporal coordination. All conditions were overlearned, had matched total motor output, and consisted of

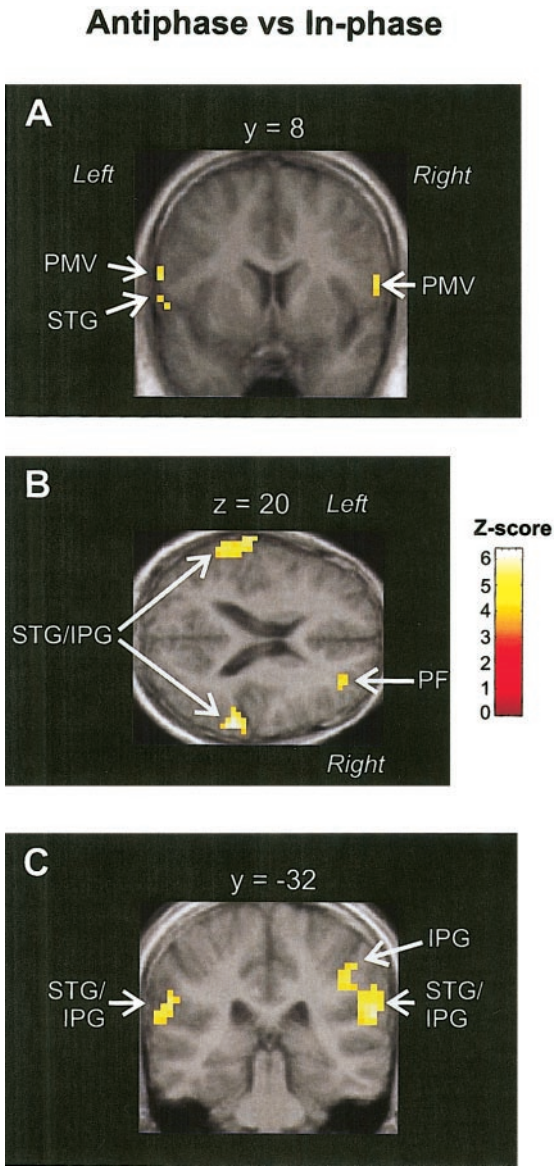

FIG. 2. Brain regions active in an Antiphase vs. In-phase contrast. *A–C*: activity maps of brain regions with significantly increased blood-oxygenation-level-dependent (BOLD) contrast signals during antiphase coordination as compared with in-phase coordination. Coronal (*A*: $y = 8$; *C*: $y = -32$) and axial (*B*: $z = 20$) slices show responses in the left and right ventral premotor cortex (PMV), superior temporal gyrus (STG), and inferior parietal gyrus (IPG),and in the right prefrontal cortex (PF).

brisk, rhythmic finger tapping movements, to minimize spatial coordination demands. The observed differences in brain activity can thus be ascribed essentially to the different temporal demands of the tasks. We will now for each coordination mode discuss the possible functional significance of these differences.

In-phase and antiphase coordination

In-phase and antiphase temporal coordination were associated with different patterns of brain activity, suggestive of different neural control circuits for these two coordination modes. As we hypothesized, In-phase was characterized by a conspicuous subcortical increase of activity relative to Antiphase, in the anterior cerebellar lobe, while extensive activations of nonprimary cortical areas in the frontal, temporal, and parietal lobes were seen when contrasting Antiphase with In-phase. These findings are in accord with callosotomy patient studies demonstrating the importance of subcortical mechanisms for synchronous temporal coordination (Ivry and Hazeltine 1999; Kennerley et al. 2002). In-phase tapping involves the coactivation of homologous muscles. The increased cerebellar activation was located in lobules III–IV of the right anterior lobe. A somatotopic organization of the human anterior cerebellum, with hand movement related activity in lobule IV has been demonstrated with fMRI (Nitschke et al. 1996). Cerebellar projections reach the hand areas of both the primary motor cortex and the SMA via the thalamus (Rouiller 1996). In

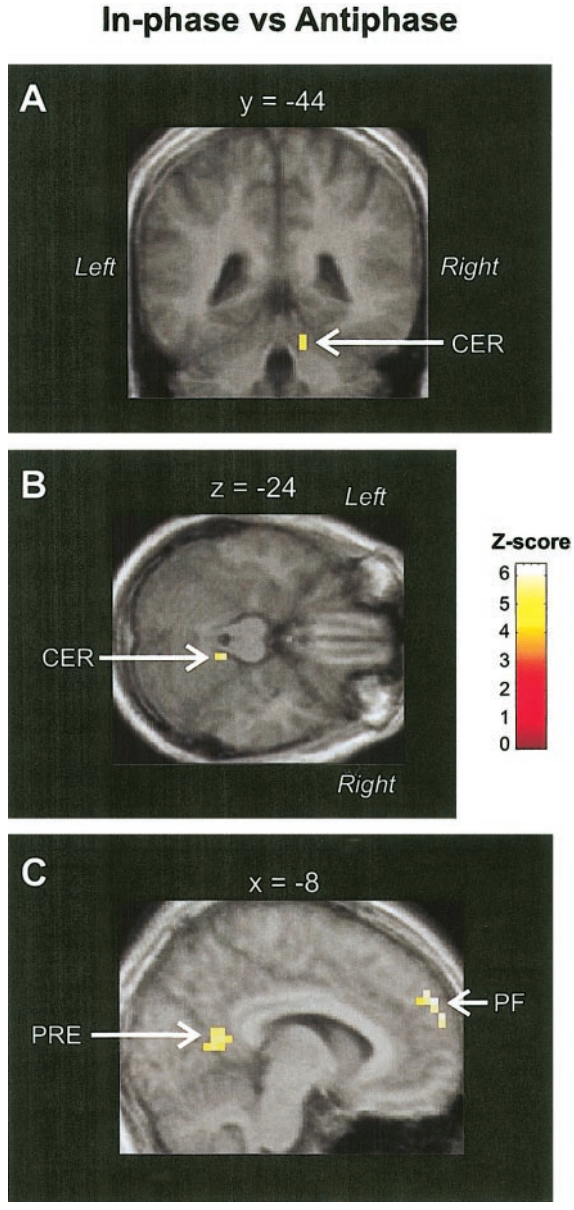

FIG. 3. Brain regions active in an In-phase vs. Antiphase contrast. *A–C*: activity maps of brain regions with significantly increased BOLD contrast signals during in-phase coordination as compared with antiphase coordination. The response in the lateral right anterior cerebellar lobe (CER) is shown in a coronal (*A*: $y = -44$) and an axial (*B*: $z = -24$) slice. Activations in the left PF and the left precuneus (PRE) are shown in a sagittal (*C*: $x = -8$) slice.

TABLE 2. *Activated brain regions in the polyrhythmic conditions*

Anatomical region	Side	*x*	*y*	*z*	*Z* Score[a]	*n*[b]
Polyrhythm (3:2 + 2:3) vs. In-phase						
Precentral gyrus (PMV/PMD)	Left	−60	0	36	5.82	6
		−52	−8	44	5.86	5[c]
Inferior precentral sulcus (PMV/area 44)	Right	56	8	24	5.59	6
Cingulate sulcus (SMA/CMA)[d]	Left	−8	−4	52	5.73	6
Superior frontal gyrus (SMA)	Right	16	−16	64	5.81	6
Middle frontal gyrus (PF)	Right	28	52	12	5.88	6
Postcentral sulcus	Right	40	−28	44	4.57	4[c]
Superior temporal gyrus	Left	−44	12	−4	4.63	6
	Right	52	16	−8	5.82	6
		64	−32	16	5.63	6
Inferior parietal gyrus	Left	−56	−24	32	4.63	6
Cerebellum, vermis (lobule VI–VIIA)[e]	Right	8	−64	−24	5.39	6
Cerebellum, hemisphere (lobule VI)[e]	Left	−32	−68	−32	6.53	6
		−24	−60	−28	4.77	6
	Right	28	−60	−32	5.70	6
Thalamus	Left	−24	−24	8	7.05	6
		−16	−4	12	4.83	4[f]
	Right	12	−16	8	5.99	5[c]
Polyrhythm (3:2 + 2:3) vs. Antiphase						
Precuneus	Left	−12	−56	32	5.51	6
		−8	−48	12	4.96	6
Cerebellum, vermis (lobule VI–VIIA)[e]	Med	0	−76	−32	4.75	6

SMA, supplementary motor area. [a] Only significant activations ($P < 0.05$), corrected for multiple comparisons, that were active also vs. rest are shown; *x*, *y*, and *z* give the Talaraich coordinates of the activity peak. [b] The number of subjects (of the total 6) that showed a statistical trend for the activity to increase ($P < 0.05$, uncorrected). [c] The other subject(s) showed a weaker activation in this region ($P < 0.2$). [d] The cluster extended into the pre-SMA. [e] The terminology for cerebellar lobules follows Schmahmann et al. (2000). [f] The remaining two subjects showed a weaker activation in this region ($P < 0.2$ and $P < 0.1$, respectively).

addition, our data indicate that the right CMA and precuneus could play a role for in-phase coordination. Impaired bimanual coordination has been reported in one patient with a focal lesion to the right CMA (Stephan et al. 1999a). Major projections from the precuneus to the SMA have been demonstrated in nonhuman primates (Luppino et al. 1993). It is thus possible that the precuneus could interact with the medial wall motor areas to contribute to some aspects of synchronous bimanual coordination.

The relatively small differences in brain activity between Antiphase and the polyrhythmic tasks (Tables 1 and 2; see following text and Fig. 6*A*) could reflect that these two coordination modes share neural mechanisms. Notably, both these patterns, in contrast to In-phase, require that a sequence of precisely timed, independent commands is transmitted to the muscles of the left and the right index fingers. Several of the brain regions seen in an Antiphase versus In-phase contrast—the inferior precentral sulcus, the supramarginal cortex, and the cortex lining the intraparietal sulcus—have earlier been shown to be high during tasks involving unilateral skilled finger movements (Binkofski et al. 1999; Ehrsson et al. 2000a) and may thus reflect the need for independent control of the hands during antiphase tapping. Activation of superior temporal cortex has been observed during self-paced finger tapping and has been interpreted as reflecting internal rehearsal of the metronome pulse (Rao et al. 1997). The larger activation in this area during Antiphase could be due to a higher demand on internal auditory processing: because each hand maintains the frequency given by the metronome, the total movement frequency will be twice that of the metronome. Activity in superior temporal cortex was also seen in the other contrasts where a task that required the generation of a temporal pattern was contrasted with a task that only required the replication of the metronome pulse: polyrhythm versus In-phase and 3:2 versus Isoseq.

Polyrhythmic coordination

A set of brain areas, including the medial wall motor areas, the PMD, the PMV, the left inferior parietal gyrus, the superior temporal gyri, and the cerebellum, was found to be activated when contrasting the polyrhythmic conditions with in-phase coordination. Important roles for the medial wall motor areas in spatial bimanual coordination have been firmly established with a variety of techniques, including electrophysiological recordings (Brinkman and Porter 1979; Donchin et al. 1998; Tanji et al. 1987), lesion studies in nonhuman primates (Brinkman 1981, 1984) and humans (Bleasel et al. 1996; Stephan et al. 1999a), and neuroimaging recordings (Ehrsson et al. 2000b; Goerres et al. 1998; Sadato et al. 1997; Stephan et al. 1999a,b; Toyokura et al. 1999). The SMA and preSMA have also been implicated in movement sequence control (see e.g., Sadato et al. 1996; Tanji and Shima 1994), and in explicit timing functions (Halsband et al. 1993; Ullén et al. 2001). The premotor areas, in particular the PMD, have similarly been shown to be involved in bimanual coordination (Sadato et al. 1997; Stephan et al. 1999a), motor sequence control (Sadato et al. 1996), and explicit timing (Halsband et al. 1993). A central role for cerebellum in the control of skilled motor acts, and temporal control in particular, has long been recognized (for a review, see e.g., Ivry 1996).

The polyrhythmic tasks require the execution of a bimanual sequence with a precise rhythmic structure and serial order of the finger movements (see Fig. 5) (Summers et al. 1993a). In

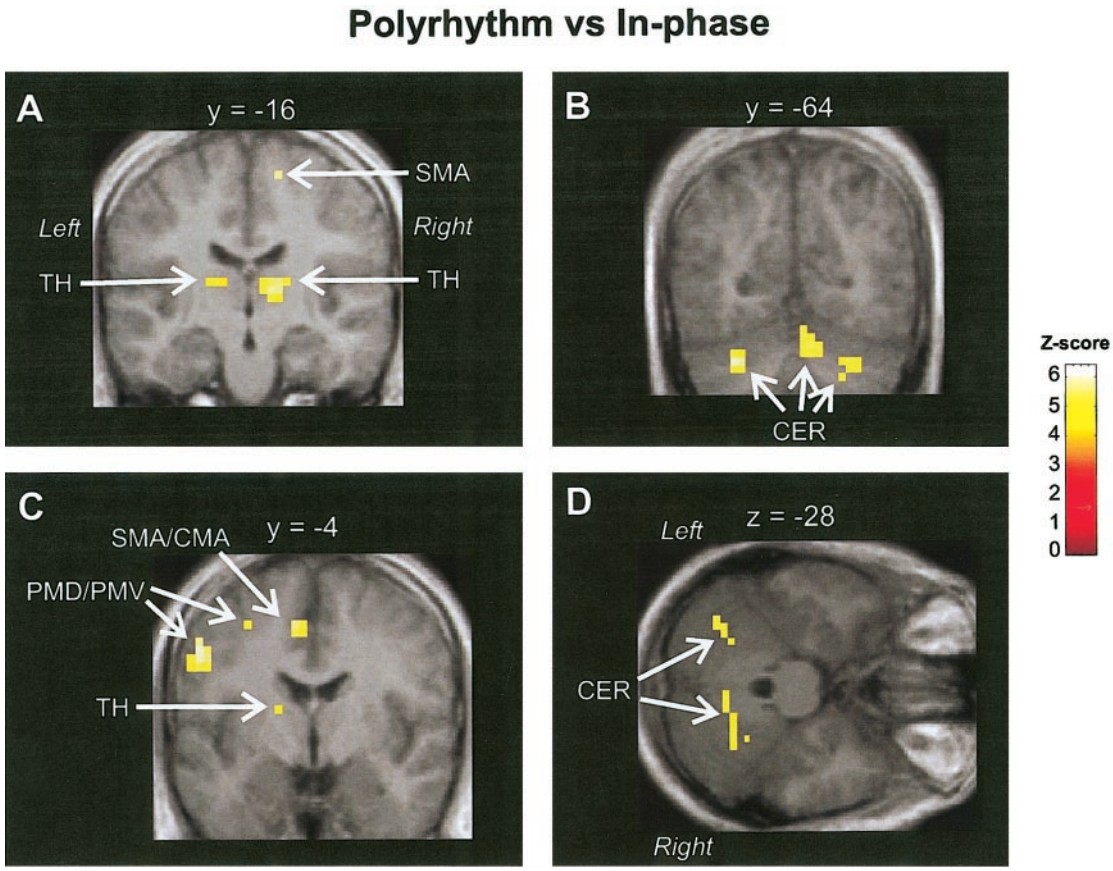

FIG. 4. Brain regions active when contrasting the polyrhythmic conditions with In-phase coordination. *A–D*: activation maps of brain regions with significantly increased BOLD contrast signals for a polyrhythms (3:2 and 2:3) vs. in-phase contrast. Coronal (*A*: $y = -16$; *B*: $y = -64$; *C*: $y = -4$) and axial (*D*: $z = -28$) slices show responses in the thalamus (TH), the supplementary motor area (SMA), the cerebellum (CER), the dorsal premotor cortex (PMD), and the ventral premotor cortex (PMV).

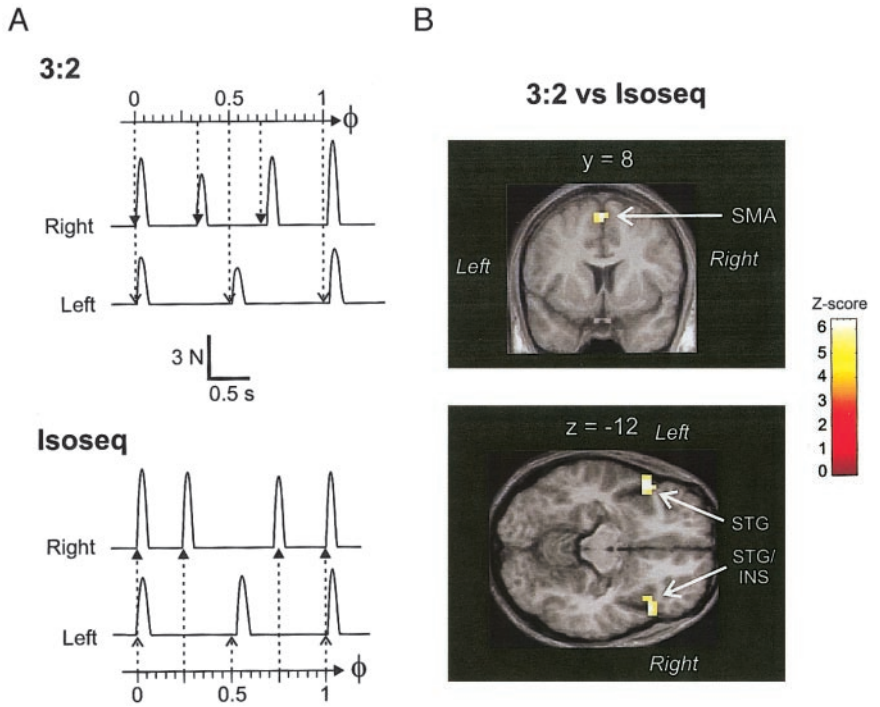

FIG. 5. Comparison of polyrhythmic performance with the performance of an isochronous sequence with the same structure. *A*: typical examples of tapping force recordings for the 3:2 and Isoseq tasks. Dashed arrows show the ideal timing of the target behavior. Isoseq retains the same serial order of movements as 3:2 but is isochronous. *B*: activation maps of brain regions with significantly increased BOLD contrast signals for a 3:2 vs. Isoseq contrast. Activations in the SMA and the superior temporal gyrus (STG), and insula (INS) are shown in a coronal ($y = 8$) and an axial ($z = -12$) section.

TABLE 3. *Activated brain regions in the control experiment*

Anatomical Region	Side	*x*	*y*	*z*	*Z* Score[a]	*n*[b]
3:2 vs. Isoseq						
Pre-SMA	Mid	0	8	60	6.06	3
Superior temporal gyrus	Left	−48	16	−12	6.23	3
Superior temporal gyrus[c]	Right	48	20	−16	6.32	3
Intraparietal sulcus	Right	52	−40	52	5.15	2[d]
Isoseq vs. In-phase						
Precentral gyrus (PMD)	Left	−28	−8	64	7.14	3
		−28	−8	48	7.13	3
	Right	24	−8	52	5.07	3
Precentral gyrus (PMV)	Left	−56	0	40	6.15	3
Cingulate gyrus (CMA)	Left	−8	0	48	5.15	3
Inferior parietal gyrus	Left	−44	−36	40	6.27	3
Precuneus	Left	−20	−64	−8	5.78	3
Cerebellum, vermis (lobule VI–VIIA)[e]	Left	−12	−56	−12	4.66	2[f]
	Right	4	−60	−12	5.57	2[f]
Cerebellum, hemisphere (lobule VI)[e]	Left	−28	−68	−28	4.95	2
	Right	20	−64	−24	5.45	3
		32	−56	−32	5.31	3

[a] Only significant activations ($P < 0.05$), corrected for multiple comparisons, that were active also vs. rest are shown; *x*, *y*, and *z* give the Talaraich coordinates of the activity peak. [b] The number of subjects (of the total 3) that showed a statistical trend for the activity to increase ($P < 0.05$, uncorrected). [c] The cluster extended into the right insula. [d] The third subject showed a weaker activation in this region ($P < 0.1$). [e] The terminology for cerebellar lobules follows Schmahmann et al. (2000). [f] The third subject showed a weaker activation in this region ($P < 0.2$).

the control experiment, 3:2 was compared with Isoseq, which had an even rhythmic structure but retained the same serial order of the movements as 3:2. To reveal areas specifically involved in the control of the rhythmic structure of the polyrhythm, 3:2 was contrasted with Isoseq; to reveal areas involved in ordinal control, Isoseq was contrasted with In-phase. The activations seen in these two contrasts were highly consistent with the activations seen in the polyrhythm versus In-phase contrast in the main experiment, thus corroborating those findings (Tables 2 and 3; Fig. 6, *A* and *B*). Furthermore, a dissociation of areas predominantly involved in rhythmic and ordinal control could be demonstrated. Our initial hypothesis, based on recent behavioral data (Bengtsson and Ullén 2002) that different brain regions active during polyrhythmic performance may be predominantly involved in the control of the rhythmic and ordinal structure of the movements, was therefore supported.

The 3:2 versus Isoseq contrast revealed activations in the preSMA and the anterior parts of the bilateral superior temporal cortices (Fig. 6*B;* Tables 2 and 3). These regions may thus be specifically involved in the control of the rhythmic structure of the polyrhythm. The superior temporal activity presumably reflects processing of the metronome rhythm (see preceding text). It appears possible, therefore, that the subjects used some form of acoustico-motor loop to time the movements. Evidence for preSMA involvement in the control of rhythmic structures has also come from studies where preSMA activity was demonstrated during rhythm learning (Ramnani and Passingham 2001) and during encoding of rhythmic information (Schubotz and von Cramon 2001). Notably, performance of both polyrhythms and rhythmic sequences with a single hand requires the handling of hierarchically organized rhythmic structures, where longer regular units (in this case, 1 cycle of the polyrhythm) are further subdivided into sequences of shorter rhythmic intervals (Wing 2002).

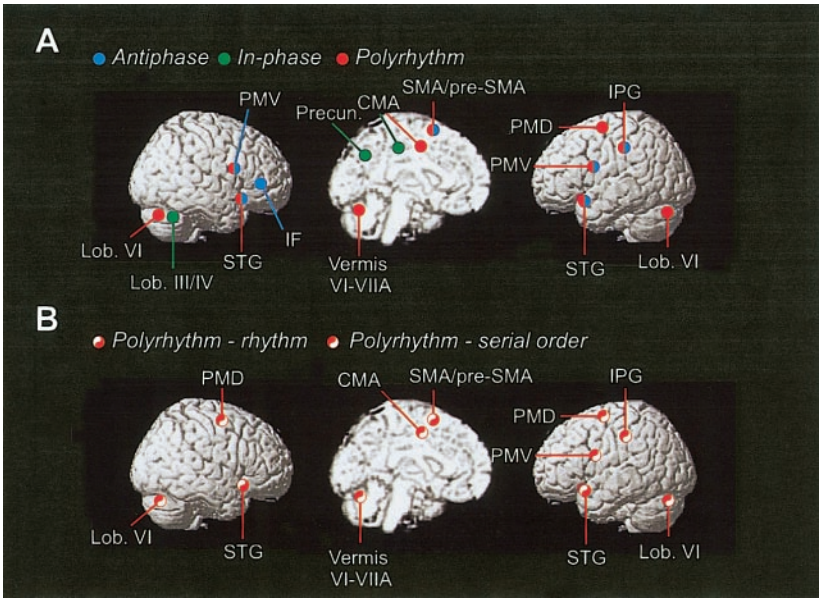

FIG. 6. Summary of brain regions specifically involved in the control of different modes of temporal coordination. Main activations are shown schematically as colored circles. For exact coordinates and a complete description of all activations, see Tables 1–3 and the text. *A*: major brain regions involved in In-phase (green), Antiphase (blue), and polyrhythmic (red) coordination as revealed in the main experiment. For antiphase and polyrhythmic coordination, in-phase coordination was used as a control task. In-phase coordination was contrasted with antiphase coordination (see text). Blue/red circles indicate regions that were involved in both antiphase and polyrhythmic coordination. Note the extensive overlap in brain activity during these 2 coordination modes. *B*: brain regions specifically involved in the control of the temporal (rhythmic; white/red circles) and serial (red/white circles) aspect of polyrhythmic coordination, as revealed in the control experiment. To dissociate between these two aspects of polyrhythmic execution, an isochronous control task with the same serial order of finger movements as in polyrhythmic tapping was used (see text).

One possibility is therefore that the preSMA is specifically involved in this type of hierarchical rhythmic control. Contrasting Isoseq with In-phase revealed activations in several of the remaining areas seen in the polyrhythm versus In-phase contrast in the main experiment, including the medial and the lateral cerebellum, the PMD, the PMV, and the CMA (Table 2 and 3; Fig. 6, *A* and *B*). These areas are thus presumably more involved in the sequential control of the serial order of finger movements, than in specific temporal control. However, activity in the posterior cerebellar vermis was seen when contrasting the polyrhythmic tasks both with In-phase and Antiphase in the main experiment and when contrasting Isoseq with In-phase in the control experiment. Activity in this region has also been demonstrated during temporal discrimination (Rao et al. 2001). The posterior vermis thus seems to play an important role for complex temporal coordination, although the lack of cerebellar activity in the 3:2 versus Isoseq contrast in the present study speaks against a specific cerebellar involvement in the temporal control of polyrhythms.

General conclusions

We conclude that different cortical and subcortical brain regions control different aspects of the timing of the hands during bimanual action (Fig. 6, *A* and *B*). Cerebellum was found to play a key role for both inherent and learned coordination modes. The anterior cerebellum was specifically involved in In-phase coordination (Fig. 6*A*), while the posterior cerebellum, both vermis and the hemispheres, appears more important for learned, complex coordination patterns (polyrhythms and Isoseq; Fig. 6, *A* and *B*). However, a specific role for cerebellum in the control of the rhythmic structure of polyrhythms could not be demonstrated. Somewhat surprisingly, the basal ganglia, which repeatedly have been reported to be involved in tasks requiring explicit timing (see e.g., Harrington and Haaland 1999), showed no activity specifically related to the pattern of temporal coordination. Basal ganglia activity in the presently investigated tasks may thus be more related to features common to all conditions, e.g., shaping of the motor response or the maintenance of a regular pulse. The PMD, the PMV, the superior temporal cortex, the inferior parietal cortex, and the preSMA/SMA were all activated both during polyrhythms, Isoseq, and Antiphase (Fig. 6*A*). This suggests that these areas could be key structures in a network for the control of more complex temporal coordination patterns. Among these regions, the preSMA and the superior temporal cortices are presumably specifically involved in rhythmic control, whereas the PMD, the PMV, the CMA, and the inferior parietal cortex appear more involved in the ordinal control of the sequence of finger movements (Fig. 6*B*).

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