Cortical and Subcortical Networks Underlying Syncopated and Synchronized Coordination Revealed Using fMRI

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Abstract: Inherent differences in difficulty between on the beat (synchronization) and off the beat (syncopation) coordination modes are well known. Synchronization is typically quite easy and, once begun, may be carried out with little apparent attention demand. Syncopation tends to be difficult, even though it has been described as a simple, phase-shifted version of a synchronized pattern. We hypothesize that syncopation, unlike synchronization, is organized on a cycle-by-cycle basis, thereby imposing much greater preparatory and attentional demands on the central nervous system. To test this hypothesis we used fMRI to measure the BOLD response during syncopation and synchronization to an auditory stimulus. We found that the distribution of cortical and subcortical areas involved in intentionally coordinating movement with an external metronome depends on the timing pattern employed. Both synchronized and syncopated patterns require activation of contralateral sensorimotor and caudal supplementary motor cortices as well as the (primarily ipsilateral) cerebellum. Moving off the beat, however, requires not only additional activation of the cerebellum but also the recruitment of another network comprised of the basal ganglia, dorsolateral premotor, rostral supplementary motor, prefrontal, and temporal association cortices. No areas were found to be more active during synchronization than syncopation. The functional role of the cortical and subcortical regions areas involved in syncopation supports the hypothesis that whereas synchronization requires little preparation and monitoring, syncopated movements are planned and executed individually on each perception–action cycle. *Hum. Brain Mapping 17:214–229, 2002.* © **2002 Wiley-Liss, Inc.**

Key words: psychomotor performance; BOLD; cerebellum; SMA; pre-motor cortex

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INTRODUCTION

A key aspect of successful interaction with the surrounding world is the ability to coordinate movement with predictable external events. We examined two modes of sensorimotor coordination: synchronization (movement in time with a pacing metronome) and syncopation (movement in between successive metronome beats). Very limited research has been conducted to identify the neural structures engaged in these tasks and their underlying dynamics. Synchronization is typically established very rapidly if the rate of the metronome is within a range that one would normally call rhythmic (~0.6–4.0 Hz). Syncopated patterns, however, are much more difficult and can typically be carried out successfully only at lower rhythmic rates [Fraisse, 1982; Kelso et al., 1990]. As a result, when asked to syncopate at rates higher than

approximately 2 Hz subjects show a spontaneous switch to synchronization to stay coordinated with the metronome [Kelso et al., 1990, 1992]. Furthermore, even when both patterns are carried out at the same rate, evidence suggests there is a higher attentional load (increased probe reaction time) associated with syncopation [Carson et al., 1999; Temprado et al., 1999]. The stability of sensorimotor coordination appears directly related to attention demand: the more stable, less variable the behavior, the less demanding it appears to be of central processing resources, and vice-versa [Jantzen et al., 2001; Monno et al., 2002].

The reason why syncopation is inherently more difficult than synchronization is still, however, unclear. In principle, the performance of both synchronized and syncopated behavioral patterns requires one to generate a rhythmic response sequence at the metronome rate and then shift the onset times appropriately so as to produce the correct phase relationship/temporal delay with the stimulus, usually an auditory or visual metronome. In practice, however, shifting a response sequence by 180 degrees to produce a syncopated pattern is difficult even at low movement rates. There is a strong tendency, for example, to react to the stimulus rather than to time the response correctly [Engström et al., 1996]. Constraints on the ability to syncopate may arise because one has to predict not only when the next metronome beat will occur, but also the point in time that separates successive beats. Furthermore, although timing accuracy during synchronization is easily defined with respect to a single metronome beat, evaluating one's performance during syncopation requires knowledge concerning the temporal relationship between each movement and both surrounding stimuli. This delay in performance feedback during syncopation may impose additional demands on working memory.

Research has shown that it is possible for subjects to improve syncopation performance through the use of cognitive strategies [Chen et al., 2001; Kelso et al., 1990] and practice [Jantzen et al., 2001] that may effectively eliminate the extra timing demands of syncopation and reduce the task to one of synchronization. For instance, some subjects report perceptually doubling the rate of the metronome [Chen et al., 2001]. Other subjects, rather than syncopating finger movement to the target-movement phase (e.g., flexion off the beat), focused on synchronizing the counterphase motion (extension on the beat) to accomplish syncopation [Kelso et al., 1990; Kelso et al., 1998]. In the absence of such strategies, however, syncopated behavior may be organized on a cycle-by-cycle basis, that is, independently for each metronome beat. This

is in contrast to synchronization that may be organized as a continuous rhythmic sequence. Treating each perception–action cycle individually requires the planning and execution of each movement separately whereas a continuous motor sequence may only involve the execution of a single plan of action that is adjusted by sensory feedback. An obvious key cortical region known to play a role in the planning and preparation of movement is Brodmann area 6, generally classified as premotor cortex and consisting of the supplementary motor area (SMA) within and above the interhemispheric fissure as well as the dorsolateral premotor areas located anterior to each primary sensorimotor cortex. Both electroencephalographic [Barrett et al., 1986; Deecke et al., 1969; Deecke and Kornhuber, 1978; Kornhuber and Deecke, 1965] and magnetoencephalographic [Erdler et al., 2000; Lang et al., 1991] recordings have revealed activation of the SMA before the onset of voluntary movement, strongly indicating that it participates in the planning of movement. In addition, the role of premotor regions in motor planning and execution is supported by observations that activity in these areas increases with complexity of movement [Lang et al., 1989, 1990; Orgogozo and Larsen, 1979; Rao et al., 1993; Shibasaki et al., 1993; Simonetta et al., 1991]. Subcortical areas including both the cerebellum and basal ganglia have also been implicated in timing processes at motor and perceptual levels [e.g., Harrington et al., 1998; Harrington and Haaland, 1999; Ivry et al., 1988; Ivry and Keele, 1989; Larsson et al., 1996; Lejeune et al., 1997; Malapani et al., 1998; Penhune et al., 1998; Rao et al., 1997; Schubotz et al., 2000]. Given our hypothesis that syncopated coordination patterns require the planning and execution of each motor response separately, one might predict an increase in activation of these motor planning and preparation areas during syncopation compared to synchronization.

Recent investigations from our laboratory using both electroencephalography (EEG) and magnetoencephalography (MEG) have addressed whether distinct patterns of neural activity are associated with the two timing patterns. Mayville et al. [1999] showed that event-related potentials recorded from sites approximately overlying contralateral sensorimotor cortex were significantly stronger during performance of syncopated versus synchronized auditory-motor coordination. Investigations of non time-locked brain oscillations have also showed differences in sensorimotor and premotor cortices related to the two timing modes. MEG signal power in the β (15–30 Hz) [Chen et al., in press; Mayville et al., 2001] as well as in the μ (8–12 Hz) frequency ranges [Jantzen et al., 2001] is

significantly reduced in sensorimotor regions when subjects syncopate compared to when they synchronize, indicating a relative suppression of brain rhythms during syncopated movement. Moreover, β suppression is eliminated when subjects switch modes of coordination [Mayville et al., 2001]. Interestingly, the same effect was observed when subjects only imagined syncopating and synchronizing with an auditory metronome [Mayville et al., 2000] suggesting that the underlying neural mechanisms are dependent upon timing strategy and planning rather than execution of movement, per se.

Although EEG and MEG provide excellent temporal resolution, they do not provide the precise spatial information available with other imaging techniques such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI). Furthermore, with the former techniques it is not possible to accurately measure activity in the many subcortical regions that are putatively involved in different kinds of sensorimotor coordination. We sought to follow up spatiotemporal analyses of neural activity in the frequency and time domain [e.g., Mayville et al., 2001] with blood oxygen level dependent (BOLD) contrast measures. Preliminary work using fMRI to investigate cerebellar function in syncopation and synchronization timing tasks suggested that the cerebellum is more active when subjects move off the beat [Fuchs et al., 1999]. The later study only examined four to eight coronal slices primarily covering the cerebellum, however, and did not extend far enough in the anterior direction to encompass the basal ganglia or frontal cortical areas (including premotor cortex). Using the BOLD effect, we studied the entire brain volume using 20 axial slices that covered the full superior-inferior and anterior–posterior range of the brain. Our aim was to identify the distribution of cortical and subcortical structures engaged in these two basic forms of coordination, and to determine if and how brain regions are affected by different sensorimotor task requirements.

SUBJECTS AND METHODS

Subjects

Nine subjects (5 male, 4 female) participated in this experiment. Subject ages ranged from 20 to 41 years. All subjects were right-handed according to self-report. Informed consent was obtained from each subject before any data collection. This experiment conformed to all ethical standards regarding research with human subjects.

Task conditions

Subjects carried out a rhythmic coordination task that involved squeezing a pillow between their right index finger and thumb in time with an auditory metronome presented at 1.25 Hz. Two different timing relations were examined: syncopation (press between successive beats) and synchronization (press on each beat). In addition, there were two control conditions; an auditory-only condition in which subjects only listened to the metronome without moving, and a motor-only condition in which they attempted to self-pace rhythmic movements at a rate of ~1.25 Hz. These controls provided a measure of activity associated with each component task event (motor response at 1.25 Hz, auditory stimulus at 1.25 Hz). Each control was then contrasted with the coordination conditions to investigate whether activity in primary auditory (auditory-only) or motor cortices (motor-only) changed as a result of integration of the two task components.

A standard block design was used for the collection of functional MR images with each condition consisting of four interleaved rest (OFF; 30 sec) and task (ON; 30 sec) blocks. In the coordination and auditory-only conditions, the onset of the metronome cued the start of the ON-period. Likewise, the OFF-period was signaled by the absence of the metronome. For the motor-only condition, the experimenter cued subjects from the control room with the words "move" and "rest" for the ON and OFF periods, respectively.

All subjects carried out the auditory-only condition first to familiarize themselves with the required pacing rate. They then carried out the motor-only followed by the two coordination conditions. The order of the coordination conditions was balanced across subjects such that half carried out the syncopation task first and the other half did synchronization first. Subjects were given breaks between each condition as needed.

Task instructions

For the coordination conditions, subjects were instructed to perform the timing relation prescribed by the task condition as best they could when the metronome was on, with explicit instruction to avoid strategies such as those mentioned in the introduction. They were further told to try and maintain the target timing relation at all times. If

they felt themselves losing the correct pattern they should try to regain it rather than adopt a different mode of timing.

Experimental procedure

Subjects carried out each task condition with their eyes closed. All subjects were given earplugs to minimize interference from the scanner noise. The metronome was delivered via plastic headphones designed for use with MRI (Avotec, Stuart, FL). The volume and tone frequency of the metronome was adjusted so as to be clearly distinguishable from the magnet. Response signals were measured by air pressure changes in a small pillow that were subsequently transduced into a voltage and recorded by computer located outside the scanner room. The metronome signal was simultaneously recorded so that subjects' success at performing the different timing relations could be quantified.

Image acquisition

Structural and functional MR images were acquired using a 1.5 T MR scanner (General Electric, Milwaukee, Wisconsin) equipped with real-time image processing capability. Full-head 3D anatomical scans were collected at the beginning of each session. These were 256 × 256 T1-weighted axial images collected with a 3D gradient echo SPGR pulse sequence (TE = 5.0 msec, TR = 34 msec, flip angle = 45 degrees, bandwidth = 15.63 Hz). The field of view and total number of slices (2.0-mm thick) were adjusted for each subject. These full-head volumes were used to identify structures necessary for standardization into Talaraich space [Talairach and Tournoux, 1988]. High-resolution (256 × 256) background images were then collected for 20 axial slices (5.0-mm thick, 2.5-mm gap) placed so as to cover the entire brain volume, including the cerebellum. These were collected using a 2D gradient echo SPGR pulse sequence (TE = in phase, TR = 325 msec, flip angle = 90 degrees, bandwidth = 15.63 Hz). Background images were used for real-time display of fMRI data during collection and to coregister functional images to each subject's full-head structural scan. During the experiment, functional images (64 × 64) were acquired at the same 20 slice locations (gradient echo EPI sequence: TE = 60 msec, TR = 3 sec, flip angle = 90 degrees, bandwidth = 62.5 Hz). The field of view for both background and functional images was 240 mm. Each functional series began with four baseline images (12 sec) to obtain signal equilibrium and an initial baseline state, followed by 80 images per slice location corresponding to 10 images for each OFF- and ON-period.

Image analysis

High-resolution background images were coregistered to the 3D full-head scan using SPM99 [Friston et al., 1995] and the resulting transformation matrix was applied when functional data were imported into the Analysis of Functional NeuroImages (AFNI) [Cox, 1996; Cox and Hyde, 1997] analysis package through which all subsequent analyses were carried out.

Before analysis of functional time series, the full-head scan was transformed into Talairach space and interpolated to 1-mm^3 voxels. The analysis of each functional data set proceeded as follows. Head motion detection and correction was carried out on each data set. In all data sets head motion never exceeded 2 mm. The task-related activity of each voxel was assessed by correlating the time series with a boxcar function representing the timing of the ON/OFF blocks. To minimize effects due to the rise and fall time of the hemodynamic response, only the final eight images within each OFF- or ON-period were included. All voxels for which the correlation coefficient was >0.5 were defined as task-dependent. Finally, the correlated data sets were transformed into Talairach space (again yielding 1-mm cubic voxels) before being blurred (FWHM = 4 mm) and clustered (minimum cluster volume = 1,000 μl).

A one-way (factor = task condition), within-subjects ANOVA was carried out on each voxel in the full 3D volume to determine significant differences between conditions. The dependent variable for each voxel was an intensity measure that was proportional to the amplitude difference between OFF- and ON-periods [Cox, 1996; Cox and Hyde, 1997]. For all voxels not defined as task-dependent this value was set to zero. Differences between pairs of conditions (normalized by the pooled error variance from the overall ANOVA) were then examined post-hoc. Such differences fall off with the Student's t-distribution. The threshold significance level was set to 0.01 for all difference maps. Post hoc condition differences could be the result of either 1) more intense activity in Condition X, less intense activity in Condition Y; or 2) presence of activity in Condition X, absence of activity in Condition Y. To help distinguish these two cases, we also examined task activation maps on an individual basis and recorded how many subjects showed activity in a given brain area for each condition.
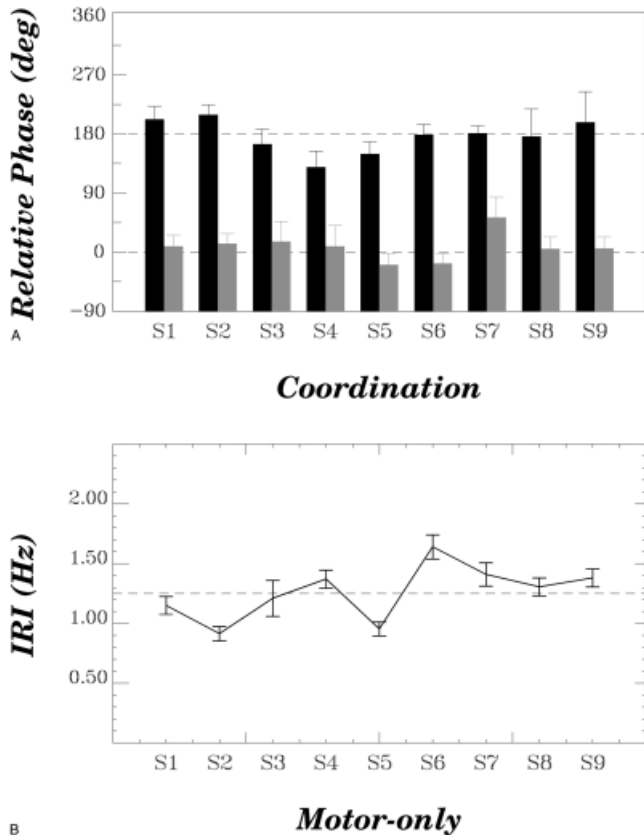
Figure 1.

Individual subject performance on the coordination (**A**) and motor-only (**B**) conditions. A: Mean relative phase between the peak of the response (maximal pressure) and onset of each metronome beat for the both the syncopate (black) and synchronize (gray) coordination conditions. B: Mean inter-response interval (IRI), expressed in Hz, carried out by each subject during the motor-only condition. Dashed line indicates required rate of 1.25 Hz. Error bars = 1 SD.

RESULTS

Task performance

Subjects' performance in the coordination conditions was assessed by calculating the relative phase between each response peak (defined as the point of maximal pressure on the pillow) and the onset of the preceding metronome beat. All subjects were successfully able to both syncopate (180-degree phase) and synchronize (0-degree phase) with the auditory metronome (Fig. 1, top). Grand average relative phase values were 176.3 degrees $\pm$ 35.2 degrees and 10.3 degrees $\pm$ 32.8 degrees for the Syncopate and Synchronize conditions, respectively. It is also apparent that subjects were able to self-pace move-

ment at the required rate during the motor-only condition (Fig. 1, bottom). Most subjects' movement rates (the inverse of the average inter-response-interval) were very close to 1.25 Hz and also showed very little variability over time (vertical bars).

Contrast 1: Syncopated vs. synchronized condition

Areas of primary interest

The main goal of the research was to investigate whether a different array of brain areas is involved when subjects perform off-the-beat syncopated, as opposed to on-the-beat synchronized coordinative timing patterns. Our initial focus was on cortical and subcortical areas that are known to be crucial for motor planning and control, especially for timing. In the neocortex these include sensorimotor cortex as well as premotor areas (dorsolateral premotor cortex and the SMA). Subcortically, previous evidence suggests the involvement of the basal ganglia, cerebellum, and thalamic nuclei to which they are interconnected. With the exception of sensorimotor cortex, all of these areas were found to have stronger activation ($P < 0.01$) during syncopated relative to synchronized coordination (Fig. 2, Table I) . No areas showed differences in the opposite direction (i.e., more activation during synchronization).

Starting at the superior surface, both left and right dorsolateral premotor cortices (middle frontal gyrus, Brodmann area 6) showed regions of significantly increased activation during syncopated coordination (Fig. 2A). A single region in the left SMA (superior frontal gyrus, Brodmann area 6) was also identified. Examination of individual maps of activation for both coordination conditions showed that only four of nine subjects showed task-related activity in dorsolateral premotor areas when synchronizing (Table II) as compared to eight of nine subjects during syncopation. Furthermore, though some SMA activity was observed for both coordination conditions, the spatial extent of this activity varied with timing mode. Synchronization resulted in posterior SMA activity whereas syncopation involved these regions as well as an additional anterior SMA region in the left hemisphere (difference in anterior–posterior direction = 21 mm). Within the basal ganglia, bilateral differences were observed in the striatum. Voxel clusters in both the caudate nucleus and putamen (Fig. 2B) showed increased activation during syncopation. In addition, we identified a region in the right ventral anterior nucleus of the thalamus (Fig. 2B), an area known to receive
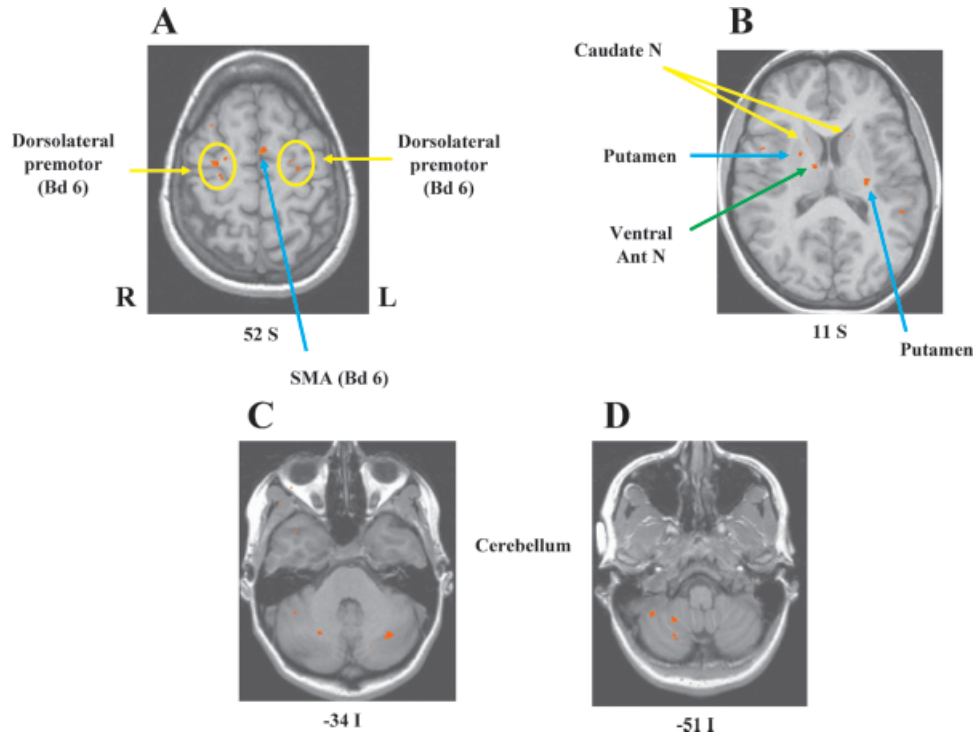
Figure 2.

Significant differences between the Syncopate and Synchronize conditions in the areas of primary interest; that is, those concerned with motor-control and or timing (see also Tables I and II). Colored voxels represent those for which the two conditions differed at a significance level of P < 0.01. All differences were positive (red/orange) corresponding to stronger task-related signals during the Syncopate condition. **A:** Premotor areas, including dorsolateral premotor cortex (Brodmann area 6) and SMA. Note the lack of differences in the primary sensorimotor areas. **B:** Basal ganglia (striatum) and thalamus (ventral anterior nucleus). **C,D:** Cerebellum. Bd, Brodmann area. Slices are shown using the radiological convention with the right hemisphere on the left side. Slice location along the superior–inferior axis is indicated below.
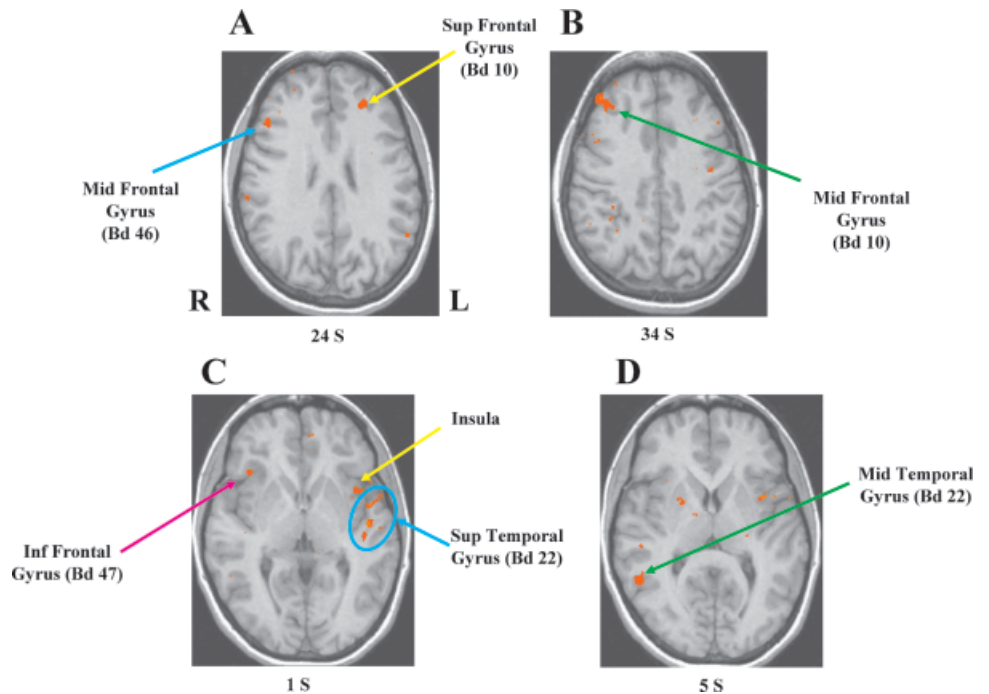
Figure 3.

Additional areas showing significant differences between the Syncopate and Synchronize conditions (see also Table III). **A,B:** Prefrontal areas. **C,D:** Other frontal and temporal areas, including the insula, inferior frontal gyrus (Brodmann area 47), superior temporal gyrus (Brodmann area 22), and the middle temporal gyrus. All areas showed increased activation during syncopation. Conventions for displaying the slices are the same as in the previous figure.

TABLE I. Areas of primary interest that show greater activation during syncopation as compared to synchronization

Area	Left	Right
Sensorimotor cortex (Bd 1–4)	None	None
Premotor cortex (Bd6)		
Middle frontal gyrus	−25L −1P 52S	26R −13P 52S
	−29L −7P 52S	30R −4P 52S
		23R 0 52S
Superior frontal gyrus (SMA)	−4L 6A 52S	None
Basal ganglia		
Caudate nucleus	−13L 18A 11S	16R 15A 10S
Putamen	−27L −14P 9S	21R 6A 5S
Thalamus		
Ventral anterior nucleus	None	11R −4P 8S
Cerebellum		
Anterior lobe-culmen	−22L −57P −20I	None
Posterior lobe-tonsil	−30L −62P −34I	39R −45P −34I
		20R −59P −34I
Deep	None	35R −43P −47I
		5R −68P −47I
		35R −43P −51I
		18R −49P −51I
		18R −60P −51I

major projections from the basal ganglia and project to motor and premotor areas of the neocortex [Alexander et al., 1986]. Individual maps confirmed that differences in these nuclei were the result of a relative lack of activation during the Synchronize condition (3 of 9 subjects) as compared to the Syncopate condition (8 of 9 subjects, see Table III).

The final area of primary interest was the cerebellum (Fig. 2C,D). Syncopation was associated with clusters of increased activation distributed throughout the entire inferior–superior extent of the cerebellum. These clusters were primarily localized to the right (ipsilateral) hemisphere (Fig. 2D) with additional contralateral clusters in more superior slices (Fig. 2C). Although cerebellar activity was generally present for both Syncopate and Synchronize conditions (Table II), during synchronization it was restricted to only a few clusters in the ipsilateral hemisphere.

Other areas of interest

In addition to the areas of primary interest discussed above, we observed rather large clusters of voxels in several other frontal and temporal areas that also displayed significantly stronger activation during the Syncopate as compared to the Synchronize condition (Fig. 3, Table III). Prefrontally, syncopation was

associated with activity in Brodmann area 10, both in the left superior and right middle gyri (Fig. 3A). In addition, an active cluster was found in Brodmann area 46 in the left middle frontal gyrus. Other frontal areas (Fig. 3C,D) that were involved in syncopated coordination include the left insula and the right inferior frontal cortex (Brodmann area 47). Within the temporal lobes several clusters were localized to the anterior part of Brodmann area 22 in the left superior temporal gyrus (Fig. 3C). A second region in the right posterior middle temporal gyrus was also identified as Brodmann area 22 (Fig. 3D). None of these frontal or temporal areas showed task-related activation in the Synchronize condition when individual maps were examined, again suggesting their recruitment only for the more difficult syncopated timing relationship. Talairach coordinates corresponding to the approximate center of each cluster are listed in Table III.

Contrast 2: Coordination vs. control conditions

A further question of interest was whether the coupling of auditory and motor events during the coordination tasks entailed a greater amount of activation in cortical areas engaged by auditory or motor component events alone. Results from the Auditory-only condition and its comparison to the coordination conditions are shown in Figure 4 (see

TABLE II. Individual subject data displaying significantly activated regions for both syncopate and synchronize conditions

	SM1		Premotor			Basal Ganglia		Cerebellum	
	Left	Right	Left	Right	SMA	Left	Right	Left	Right
Syncopate									
S1	*		*	*	*	*	*	*	*
S2	*		*	*	*	*	*	*	*
S3	*		*	*	*	*	*	*	*
S4	*		*	*	*	*	*	*	*
S5	*				*		*	*	*
S6	*		*	*	*	*	*	*	*
S7	*		*		*				
S8	*	*	*	*	*	*	*	*	*
S9	*	*	*	*	*	*	*	*	*
Synchronize									
S1	*		*	*	*				*
S2	*		*	*	*				*
S3	*		*		*				*
S4	*		*	*	*				*
S5	*					*	*	*	*
S6	*				*			*	*
S7	*							*	*
S8	*				*	*	*	*	*
S9	*				*	*	*		*

also Table IV). Simply listening to the metronome resulted in the activation of a small cluster within primary auditory cortex (Brodmann area 41; Fig. 4B), as well as a small number of clusters in the right middle temporal gyrus (Brodmann area 21; Fig. 4A). Neither of these temporal areas showed significant differences in activity when the Auditory-only condition was compared to either coordination condition. A subtraction of the Auditory-only from the Syncopate condition yielded several significant bilateral clusters in auditory association areas (Brodmann area 22; Fig. 4C). In contrast, there were no differences in auditory-related cortical areas when the Auditory-only and Synchronize conditions were compared (Fig. 4D). These results suggest that syncopating places a higher demand on brain resources involved in auditory processing than do synchronizing or listening to an auditory signal in the absence of any movement. Not surprisingly, self-paced movement resulted in large regions of activity in contralateral sensorimotor cortex, the SMA, and cerebellum (Fig. 5, top row; Table IV). There were no differences in sensorimotor cortex activity when the Motor-only condition was subtracted from either coordination condition. Like-

wise, SMA activity during self-paced and synchronized movement was statistically equivalent. Consistent with results discussed above, however, post-hoc comparisons between the Motor-only and Syncopate conditions showed that syncopation engaged an additional anterior SMA region not activated during self-paced movement. With respect to the cerebellum, both contralateral and ipsilateral regions showed stronger activation during syncopation as compared to self-paced movement (Fig. 5 middle row, right two panels; Table IV). In contrast, negative bilateral differences were found when the Motor-only condition was subtracted from the Synchronize condition, suggesting more cerebellar resources are used for self-paced than for synchronized movement (Fig. 5 bottom row, 3rd panel; Table IV).

As one might expect, no activation within motor-related cortical areas was observed during the Auditory-only condition. Similarly, there were no regions of activation within auditory-related regions during the Motor-only condition. For this reason, differences in activation between the control and coordination conditions in these areas, although present, add no additional information and as such are not reported.

TABLE III. Other areas of interest that show greater activation during syncopation as compared to synchronization

Area	Left	Right
Frontal cortex		
Superior frontal gyrus (Bd 10)	−25L 45A 24S	None
Middle frontal gyrus	None	
(Bd 10)		40R 43A 34S
(Bd 46)		46R 28A 24S
Insula	−40L 12A 1S	None
Inferior frontal cortex (Bd 47)	None	38R 25A 1S
Temporal cortex		
Superior temporal gyrus (Bd 22)	−50L 3A 1S	None
	−49L −11P 1S	
	−45L −19P 1S	
Middle temporal gyrus (Bd 22)	None	51R −49P 5S

DISCUSSION

The present research provides, for the first time, evidence that syncopated and synchronized timing patterns of auditory–motor integration involve distinct networks of cortical and subcortical brain areas. Specifically, syncopation appears to require the recruitment of additional neuronal populations above and beyond those engaged in synchronization, particularly within premotor cortex, the basal ganglia and cerebellum.

Premotor areas

Within premotor cortex, both lateral and mesial regions showed significantly stronger activation during

TABLE IV. Coordination vs. control comparisons

	Left	Right
Auditory only		
Primary auditory cortex (Bd 41)	−47L −26P 8S	None
Association cortex (Bd 21)	None	67R −13P −1I
		64R −25P −1I
Syncopate − Auditory only		
(Bd 22)	−47L −12P 5S	53R −24P 5S
	−43L −21P 5S	51R −49P 5S
Synchronize − Auditory only	None	None
Motor only		
Sensorimotor cortex (Bd 1–4)	−39L −28P 56S	None
Medial frontal gyrus (Bd 6-SMA)	0 −12P 56S	0 −12P 56S
Cerebellum	−15L −50P −44I	22R −52P −19I
		28R −63P −44I
Syncopate − Motor only		
Sensorimotor cortex (Bd 1–4)	None	None
Medial frontal gyrus (Bd 6-SMA)	−4L 6A 52S	None
Cerebellum	−22L −59P −18I	35R −43P −48I
	−5L −74P −18I	
Synchronize − Motor only		
Sensorimotor cortex (Bd 1–4)	None	None
Medial frontal gyrus (Bd6-SMA)	None	None
Cerebellum[a]	−30L −51P −46I	29R −68P −46I
		30R −74P −46I

[a] Stronger activation during Motor-only condition.

Figure 4.
A comparison of the Auditory only control (**A,B**) with the two coordination conditions (**C,D**; see also Table IV). Listening to the metronome was associated with activation of the left primary auditory cortex (Brodmann area 41) in the superior temporal gyrus and right temporal association cortex (Brodmann area 21) in the middle temporal gyrus. Within the temporal lobes, syncopation resulted in additional bilateral activation of Brodmann area 22 (C). No differences between the Synchronize and Auditory control conditions were found in either temporal lobe (D).
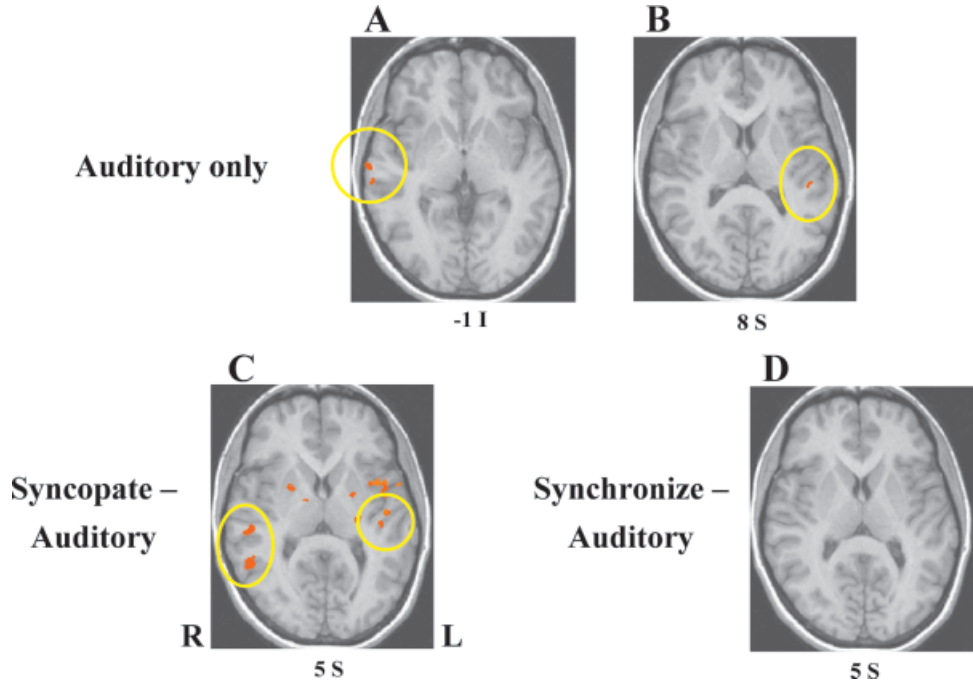
syncopated as compared to synchronized timing. The relationship between activity in premotor areas and motor planning/preparation processes has been well established [e.g., Barrett et al., 1986; Deecke et al., 1969; Deecke and Kornhuber, 1978; Erdler et al., 2000; Kornhuber and Deecke, 1965]. Additionally, it has been demonstrated that activation of premotor areas increases with increasing movement complexity [Lang et al., 1989, 1990; Orgogozo and Larsen, 1979; Rao et al., 1993; Shibasaki et al., 1993; Simonetta et al., 1991], and that transcranial magnetic stimulation of the SMA disrupts performance of complex sequential move-

Figure 5.
A comparison of the Motor-only control (top row) with the two coordination conditions (bottom two rows; see also Table IV). Large task-related clusters in the contralateral sensorimotor cortex, SMA and ipsilateral cerebellum were found for self-paced movement. Neither cortical region showed significant changes in activation levels during coordination (rows 2 and 3, left panel), however, during syncopation an activation in the anterior SMA is present. Relative to self-paced movement, cerebellar activation increased for syncopation (2nd row, right two panels) but decreased for synchronization (3rd row, right panel). Slice conventions are the same as in the previous figures.
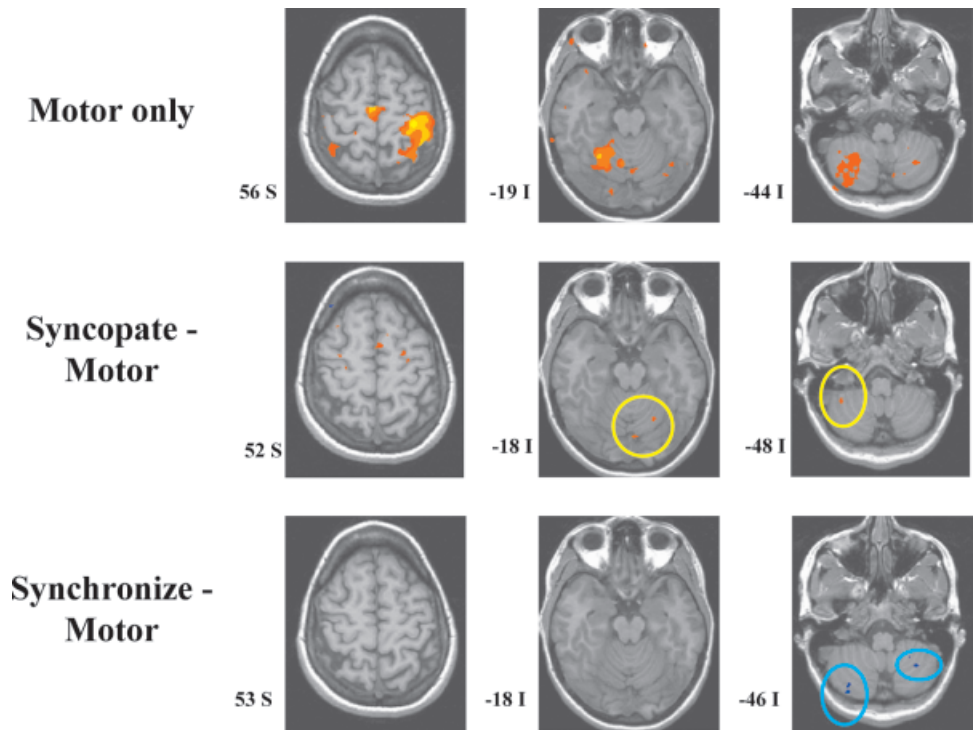
ments [Gerloff et al., 1997]. In previous studies related to motor complexity, increased activity resulted from manipulation of movement length and sequential pattern. We extend this to include complexity as defined by manipulation of a timing pattern.

Although both modes of coordination engaged posterior SMA regions, only syncopation resulted in activation of more anterior SMA areas. Previous neuroimaging [Boecker et al., 1998; Deiber, 1998, 1999; Jenkins et al., 2000] and single cell recording studies [Halsband et al., 1994; Mushiake et al., 1991] also indicate a functional distinction between anterior (rostral or pre-SMA) and posterior (caudal or SMA proper) portions of the SMA. In general, although SMA proper plays a role in executive motor processes, pre-SMA appears to be more involved in motor planning mechanisms, especially those concerning the initiation of movement [Larsson et al., 1996]. Using PET, Larsson et al. [1996] observed stronger activity in both lateral premotor cortex and SMA for internally generated vs. externally triggered movements, with the relative increases being stronger for SMA. In addition, the ability of patients to reproduce rhythms without external pacing is impaired with lesions of the dorsolateral premotor cortex and supplementary motor area [Halsband et al., 1993].

In light of this previous work, our results suggest that the performance of more difficult syncopated timing patterns, because of increased planning demands, necessitates the engagement of premotor resources not required for synchronization. The increased preparation needed to syncopate with a metronome is consistent with the notion that whereas synchronization can be carried out relatively automatically once the pattern has been established, syncopation involves the planning and execution of responses on a cycle-by-cycle basis. Such premotor planning structures may well be related to behavioral evidence showing that anti-phase coordination places greater demands on central processing [Temprado et al., 1999].

Basal ganglia

A role for the basal ganglia in timing has been largely motivated by studies of patients with Parkinson's disease in whom dopaminergic levels within these nuclei are known to be severely depleted. Parkinson's patients show deficits in the performance of a wide variety of rhythmic movements. Though Parkinson's patients are generally able to accurately reproduce a given temporal interval on average, their variability is significantly enhanced. This phenomenon has been observed for finger tapping [Harrington et

al., 1998; O'Boyle et al., 1996; Wing et al., 1984], wrist movements [Pastor et al., 1992a] and gait patterns constrained by an external metronome [Ebersbach et al., 1999]. Results of much of this work have been interpreted within the framework of a timing model that assumes that the basal ganglia acts as an internal clock whose variance is independent of that associated with motor implementation processes [Wing and Kristofferson, 1973; see Gura, 2001 for alternatives].

The role of the basal ganglia as an internal clock independent of motor activity is further supported by research showing that Parkinson's patients exhibit diminished time perception abilities [Artieda et al., 1992; Harrington et al., 1998; Pastor et al., 1992b; see Ivry and Keele, 1989 for exception]. Recent findings even demonstrate that the processing of intervals in the millisecond range is dependent upon the level of dopaminergic activity in the basal ganglia [Rammsayer, 1999]. Finally, evidence provided by several functional neuroimaging studies show increases in both PET and fMRI signals in response to perceptual or motor tasks that involve temporal processing [Harrington and Haaland, 1999].

Single cell recordings in animals during reactive movements have shown that the majority of basal ganglia neurons actually fire after movement onset in contrast to cells within the motor cortex that fire before [see Rothwell, 1994 for discussion], suggesting that the basal ganglia do not play a major role in the initiation of movements. In more complex tasks, however, changes in basal ganglia activity have been observed to occur during periods of motor preparation [e.g., Alexander and Crutcher, 1990; Jaeger et al., 1993]. Moreover, in tasks in which movement sequences are involved, firing bursts have been found to precede the onset of subsequent movements by ~100–200 msec when the subsequent movements are predictable in time [Brotchie et al., 1991]. A special role of the basal ganglia in sequential movement is also suggested by a PET study by Boecker et al. [1998] who observed regional cerebral blood flow increases in the SMA and associated pallido-thalamic loop as subjects carried out increasingly complex (and overlearned) sequences of finger movements. Together, these results support the hypothesis that the basal ganglia are involved in movements that have sufficient complexity or temporal structure so as to require detailed timing information.

The fact that the basal ganglia were predominantly active during syncopation relative to synchronization supports the hypothesis investigated here, namely that the former task involves a series of internally generated movements whereas the latter can be car-

ried out with little or no monitoring. Some recent findings are particularly relevant for this conclusion. Johnson et al. [1998] examined in-phase and anti-phase patterns of bimanual coordination, two motor tasks that have many parallels with the synchronized and syncopated modes of unimanual coordination investigated here [Kelso, 1984; Kelso et al., 1990]. They found that Parkinson patients were unable to perform anti-phase patterns of bimanual movement regardless of whether the movements were self or externally-paced, a finding consistent with the idea that the basal ganglia are preferentially involved in more complicated forms of sequential movement. A second finding in the Johnson et al. [1998] study was that patients' performance of in-phase bimanual movements was significantly worse in the absence of external cues. The latter finding highlights the likely role of the basal ganglia in movements that are internally determined [see also Georgiou, 1993, 1994; Jackson et al., 1995].

It is interesting to note that we observe basal ganglia activity during self-paced movement in only a few subjects. Although it is generally accepted that basal ganglia is involved in motor activity, the degree to which it has been reported in studies of motor control varies. Studies in which movements have been carried out at relatively high rates (~2.5–3.5 Hz) report basal ganglia activity [Jäncke et al., 2000]. Rao et al. [1997], however, reported basal ganglia activity at both 1.66 and 3.33 Hz only during the continuation phase of a paced finger tapping task (i.e., not during synchronization). Basal ganglia activity has also been reported in studies where movements were carried out very slowly (0.1–0.3 Hz), at rates considered to be non-rhythmic [Jenkins et al., 2000; Larsson et al., 1996]. Although basal ganglia activity has been reported during complex finger sequences carried out at 1 Hz [Boecker et al., 1998], no such activity was observed in similar studies carried out using a slightly lower movement rate (0.5 Hz) [Catalan et al., 1998]. These data indicate a possible sensitivity of basal ganglia to specific task parameters. The current results appear to be consistent with those of Rao et al. [1997] who reported a lack of basal ganglia activity during synchronization at rates similar to the one used here.

Cerebellum

Our results demonstrate that the cerebellum is required for the performance of both syncopated and synchronized coordination tasks. Although almost all subjects showed activity in ipsilateral cerebellum during both modes of coordination, several medially and laterally located ipsilateral regions had significantly higher signal intensities for the off-the-beat timing pattern, suggesting that the cerebellum's functional role may be different in the two cases. Further support for this hypothesis comes from the observation that eight of the nine subjects showed contralateral cerebellar activation during syncopation compared to four of nine for synchronization.

Several converging lines of evidence implicate a cerebellar role in timing processes. For instance, patients with lesions of the cerebellar lobes show impairment in rhythmic tapping tasks [Ivry and Keele, 1989; Ivry et al., 1988]. Lesions to either the lateral or medial cerebellum affect performance on a continuation task that requires patients to first synchronize with an auditory metronome and then continue to move at the same rate once the metronome is stopped [Ivry et al., 1988]. Increased variability during this task was observed when responding with a finger or the foot ipsilateral to the side of the lesion. Ivry et al. [1988] concluded that the poor performance of patients with lateral cerebellar lesions was due to deficits in a central timing process whereas patients with medially located cerebellar lesions knew when to respond but were unable to implement the motor act itself. Cerebellar activation during the performance of rhythmic movements has also been found using PET [Catalan et al., 1998] and fMRI [Rao et al., 1997]. In the case of fMRI ipsilateral activity increased both when the subjects synchronized with an external metronome and when they continued to move in its absence [Rao et al., 1997]. It has also been shown that activation of the cerebellum continues to increase with increases in task complexity [Catalan et al., 1998; Penhune et al., 1998].

Despite a long standing association between cerebellar involvement and motor behavior, it has become increasingly clear in the past few decades that the cerebellum is also involved in perceptual and cognitive tasks. For example, the ability to accurately and consistently judge temporal durations is impaired in patients with cerebellar damage [Ivry and Keele, 1989; Malapani et al., 1998]. In addition, Schubotz et al. [2000] identified bilateral regions of cerebellar activation when subjects monitored both visual and auditory rhythms for temporal deviations. Cerebellar activation during selective attention to visual shapes was also reported by Allen et al. [1997]. In a recent MEG study, Tesche and Karhu [2000] reported bursts of activation within the cerebellum that occur just before anticipated stimuli as well as when such stimuli are omitted. These results suggest that the cerebellum plays a role in the perception of timing patterns as well as in the generation of timed motor behaviors.

The finding of cerebellar activation in such a wide range of motor and non-motor tasks has led to the hypothesis that the primary function of the cerebellum may be the acquisition and processing of sensory information that then allows it to provide highly accurate temporal information [Ivry, 2000]. From this perspective, the deficits observed in many motor behaviors may be the result of a disruption of an internal temporal representation rather than a problem with the motor control systems per se [Bower, 1997; Gao et al., 1996; Ivry, 2000]. With respect to our current hypothesis, if syncopated movements are planned independently, the amount of timing information required is much greater than for synchronization. In the case of synchronization it is possible to set up a movement at a particular rate and then monitor it by determining whether the movements coincide with the metronome beat or not. In the case of syncopation, however, this is not possible. The interval between the metronome beat and the movement is sufficiently great so as to provide little information concerning accuracy or to allow for corrections. Therefore, each movement must be planned with respect to the previous metronome beat. The increased cerebellar activity observed here for syncopation likely reflects the additional timing requirements of estimating the point half-way between successive metronome beats.

Other frontal and temporal areas

Syncopation also resulted in significantly more activation of several regions distributed throughout the frontal and temporal lobes. A role of prefrontal cortex in the organization of motor behavior is generally thought to relate to attention or working memory rather than the direct temporal control of movement [see Harrington and Haaland, 1999 for discussion]. Activation of prefrontal areas is especially prominent during learning of new motor tasks, e.g., finger sequences, but is reduced or absent if such sequences are overlearned [Boecker, 1998; Jueptner et al., 1997]. Significant increases in rCBF to the middle frontal gyrus have also been observed during learning of a difficult inverted visuomotor coordination task [Lang et al., 1988], somewhat akin to syncopated, antiphase movements. Such increases were correlated with rCBF changes in the basal ganglia, supporting the idea that these cortical regions comprise part of a broad motor control network. With regard to working memory, experimental data obtained from monkeys implicate prefrontal neurons in sensory–motor coupling, especially when there are temporal delays [Fuster, 1989;

Goldman-Rakic, 1987; Quintana et al., 1988]. Increased prefrontal activation during syncopation as compared to synchronization may therefore reflect not only the fact that syncopated patterns appear to be associated with a higher attentional load [Carson et al., 1999; see also Temprado et al., 1999] but also that they require a delay between response and metronome, a task requiring the use of working memory. This hypothesis requires further study.

In temporal cortex, syncopation resulted in activation of several regions within Brodmann area 22 that were not associated with synchronization. A similar pattern of activation has been previously associated with music perception [Platel et al., 1997]. Specifically, Platel et al. [1997] identified brain regions (e.g., inferior frontal gyrus and superior temporal gyrus) involved when subjects were asked whether or not they recognized a given piece of music. Our results suggest that such areas may also be involved in the integration of rhythmic sensory information. The predominance of temporal activity in the left hemisphere may correspond to a specialization for the processing and production of sensory and motor events occurring in rapid procession as has been proposed in speech research [Tallal et al., 1993]. Because only right hand movements were investigated here, the possibility that such activation is localized to the temporal region contralateral to the side of movement cannot be ruled out.

Sensorimotor cortex

Sensorimotor cortex was the only area of primary interest whose activation showed no significant dependence on the timing pattern carried out. The absence of effects in sensorimotor cortex is in contrast to previous work demonstrating significant differences in the amplitude of neuroelectric [Mayville et al., 1999] and neuromagnetic [Jantzen et al., 2001; Mayville et al., 2001] signals recorded from sites overlying the contralateral sensorimotor area. It is likely that this discrepancy results from the fact that the BOLD effect is insensitive to fine timing differences in the activation of neuronal populations. Although differences in the temporal sequence of depolarization/hyperpolarization within a given cell population could significantly affect the summation of electrical currents thereby directly affecting the amplitude and frequency of electrical potentials or magnetic fields detectable at the scalp, it may not lead to a change in local deoxyhemoglobin and therefore would produce no change in blood oxygenation levels. Alternately, the sensorimotor amplitude differences detected in

these earlier studies may simply reflect differences in the sheer number of neurons that are simultaneously involved in performing the task (larger population for syncopation versus synchronization) but the population activity is not different enough to affect the local hemodynamic response.

CONCLUSIONS

The distribution of cortical and subcortical areas involved in intentionally coordinating movement with an external metronome depends on the timing pattern employed. Compared to rest, both synchronized and syncopated patterns require activation of contralateral sensorimotor and caudal supplementary motor cortices as well as the (primarily ipsilateral) cerebellum. Moving off the beat, however, requires not only additional activation of the cerebellar lobes, but also the recruitment of another network comprised of the basal ganglia, dorsolateral premotor, anterior supplementary motor, prefrontal, and temporal association cortices. These distributed neural activations support our hypothesis that different strategies are employed to perform synchronized and syncopated coordination patterns. Whereas synchronization can be carried out relatively automatically with little planning or monitoring, syncopation may involve the planning and execution of each movement individually. Moreover, syncopation may also be more attention demanding and involve learning-related mechanisms because the subject not only must predict the separation point of an empty interval but also is confronted with a delay in performance feedback. Direct tests of these hypotheses are currently underway.

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