

Functional MRI reveals the existence of modality and coordination-dependent timing networks

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Growing evidence suggests that interval timing in humans is supported by distributed brain networks. Recently, we demonstrated that the specific network recruited for the performance of rhythmic timing is not static but is influenced by the coordination pattern employed during interval acquisition. Here we expand on this previous work to investigate the role of stimulus modality and coordination pattern in determining the brain areas recruited for performance of a self-paced rhythmic timing task. Subjects were paced with either a visual or an auditory metronome in either a synchronized (on the beat) or syncopated (off the beat) coordination pattern. The pacing stimulus was then removed and subjects continued to move based on the required interval. When compared with networks recruited for auditory pacing and continuation, the visual-specific activity was observed in the classic dorsal visual stream that included bilateral MT/V5, bilateral superior parietal lobe, and right ventral premotor cortex. Activity in these regions was present not only during pacing, when visual information is used to guide motor behavior, but also during continuation, when visual information specifying the temporal interval was no longer present. These results suggest a role for modality-specific areas in processing and representing temporal information. The cognitive demands imposed by syncopated coordination resulted in increased activity in a broad network that included supplementary motor area, lateral pre-motor cortex, bilateral insula, and cerebellum. This coordination-dependent activity persisted during the subsequent continuation period, when stimuli were removed and no coordination constraints were imposed. Taken together, the present results provide additional evidence that time and timing are served by a context-dependent distributed network rooted in basic sensorimotor processes.

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Introduction

Virtually all psychologically based models of human interval timing propose the existence of discrete hierarchically arranged processing stages that generally involve a timing signal, represented by a centralized internal clock source, that interacts or is operated on by some aspects of perception, memory, and decision making (e.g., Church, 2003; Creelman, 1962; Fraisse, 1963; Treisman, 1963). Over the last several decades there has been considerable experimental interest in uncovering the neuro-anatomical and neurophysiological underpinnings of such hypothesized clock and associated secondary processes. One major question that arises when attempting to map these putative temporal processes onto neural function is whether temporal processing is performed by a single centralized mechanism, or whether it is mediated by distributed brain areas (Buonomano and Karmarkar, 2002).

Contemporary viewpoints suggest that timing of subsecond intervals may be rooted in basic sensorimotor processes (Buonomano and Karmarkar, 2002; Lewis and Miall, 2003b; Penney, 2003; Todd et al., 2002) leading to the hypothesis that timing networks will change depending on perceptual and motor constraints. Neurophysiological support for the existence of task-dependent timing processes has come from recent functional imaging research demonstrating that the specific neural structures recruited for temporal processing may be at least partially determined by the way in which information about time is presented (Jantzen et al., 2004). This work employed a variant of the continuation task (Wing and Kristofferson, 1973) to demonstrate that overlapping but distinct neural networks may be recruited during performance of a simple internally paced rhythmic movement. In the first stage, movements were made in time with a rhythmic auditory stimulus. This provided pacing for the second, continuation stage, in which the stimulus was removed and participants were required to maintain movement at the same rate in the absence of pacing information. During pacing, movements were coordinated either in a synchronized (moving in time with pacing stimuli) or syncopated (moving in between pacing stimuli) coordination pattern. While both

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synchronization and syncopation are stable at low movement rates, and can therefore be used effectively to establish movement at the prescribed rate, synchronization is a more stable form of coordination (Kelso et al., 1990, 1992, 2001) that imposes fewer demands on neural resources than syncopation (Mayville et al., 2001, 2002; Monno et al., 2002). Even at low movement rates, syncopation compared to synchronization produces additional activity across a broad cortical and subcortical network (Jantzen et al., 2002; Mayville et al., 2002; for anti-phase limb movements, see also Debaere et al., 2001; Meyer-Lindenberg et al., 2002; Sadato et al., 1997). Such intrinsic neural differences provide a means for determining if the way in which a timing interval is established during pacing (neural differences between coordination pattern) influences the neural network recruited to perform the subsequent internally paced movement (continuation phase).

Three main results from the Jantzen et al. (2004) study are pertinent to the present research. First, in keeping with previous work (Jantzen et al., 2002; Mayville et al., 2002), syncopated pacing engaged a much broader network of cortical and subcortical areas than synchronized pacing including SMA, left premotor cortex, left posterior parietal cortex, basal ganglia, and bilateral cerebellum. Second, these differences persisted during continuation even though overt task demands and behavioral performance during both continuation conditions were the same. Third, the pattern of neural activity generated during each continuation condition was indistinguishable from that observed during the preceding pacing phase. These previous results demonstrated that cortical and subcortical areas recruited to support a simple motor timing task are influenced by context as defined by the pacing method employed to establish the movement rate during pacing. Activity during continuation reflected not only the sensorimotor and timing demands of the motor task, but also the timing pattern used to establish the behavior in the first place.

Here we use the same paradigm to specifically investigate how the stimulus modality employed during pacing affects the network of brain regions recruited for the production of internally timed movements during continuation. Behavioral evidence provides support for modality-specific timing mechanisms by demonstrating that stimulus modality can play a role in shaping our perception of time (Penney, 2003). For instance, auditory signals are consistently judged as longer than visual signals of the same duration (Goldstone and Goldfarb, 1964; Penney et al., 2000). In addition, temporal judgments based on auditory (Wearden et al., 1998) and movements made in time with auditory stimuli (Repp and Penel, 2002) are less variable and more accurate than movements to visual stimuli. The stimulus characteristics used to specify temporal intervals can also influence temporal estimation with decreased accuracy observed when bounding stimuli are not in the same perceptual modality (Grondin and Rousseau, 1991; Penney, 2003; Rousseau et al., 1983). Such data suggest that some or all components of the timing system may be supported by modality-specific neural mechanisms. However, despite the growing evidence for modality-dependent aspects of temporal processing, the neural underpinnings of these differences have not been widely investigated.

In the present research, pacing is carried out using both auditory and visual stimuli in combination with a synchronized or syncopated coordination pattern. Pacing stimuli are then removed and participants continue moving on the basis, presumably, of an

internal representation of the temporal interval. Comparisons of pacing conditions are expected to identify well-known visual and auditory-specific processing regions. Auditory-cued pacing at intervals within the range of hundreds of milliseconds is thought to involve brain areas similar to those engaged in speech perception and generation. Imaging studies support this view demonstrating activation in primary and secondary areas in superior temporal gyrus as well as bilateral frontal opercular areas comprising the insula (Cunnington et al., 2002; Jantzen et al., 2002; Rao et al., 2001; see also Ackermann and Riecker, 2004), and ventral premotor areas extending into Broca's area and its right hemisphere homologue (Jäncke et al., 2000; Jantzen et al., 2002; Lutz et al., 2000; as Rao et al., 2001). Visually guided coordination, on the other hand, is likely to engage the dorsal visual stream; a processing circuit that includes striate, extrastriate, parietal, and premotor areas (Rizzolatti and Matelli, 2003) that mediates sensory-motor interactions for visually guided movements (Goodale and Milner, 1992). We hypothesize that if these brain areas are important for modality-specific processing of temporal information beyond their primary role in registering sensory input, they should be active during both pacing and continuation phases, since the same temporal information is required for both phases. However, if sensory-specific brain areas are not active in processing or representing temporal information, activity should decline since the pacing stimuli are no longer present. To address this issue we identify brain networks that demonstrate modality-specific activity during synchronized and syncopated pacing. The degree to which these same brain networks remain active during continuation—when no explicit timing information is present—indicates their importance in maintaining an ongoing representation of the required interval.

The inclusion of both synchronized and syncopated coordination conditions serves two purposes. First, it allows us to establish whether coordination-dependent timing networks generalize across stimulus modality. Second, it also allows us to determine whether modality-specific effects interact with coordination pattern dependent timing networks. For instance, is the involvement of modality-specific brain areas during pacing and continuation modulated by the coordination pattern performed? Auditory pacing and continuation portions of these data have been described previously (Jantzen et al., 2004), but we do not know if context-dependent effects generalize to vision or not.

Method

Participants

Twelve neurologically normal volunteers (10 male, 2 female; mean age 28.5 years ranging from 23 to 37) gave informed, written consent to participate in the study. Self-report was used to determine the handedness of participants. Only participants who reported being strongly right handed were used in the study. Procedures were carried out in accordance with the guidelines set by the Internal Review Board at Florida Atlantic University and the human subject guidelines of NIH.

Experimental protocol

Each subject was placed in a supine position on the scanner bed with his/her head fixated by a vacuum pillow. During the

pacing stage subjects coordinated finger–thumb opposition movements with either a visual or an auditory stimulus presented at a constant rate of 1.25 Hz (pacing conditions). This rate was chosen because it is well below that at which transitions from syncopation to synchronization have been observed (Kelso et al., 1990). The stimulus was then discontinued and subjects were required to continue moving at the same constant rate in the absence of the pacing stimulus (continuation conditions). Pacing conditions were performed using two different coordination modes and two different stimulus modalities. For synchronization, participants were instructed to produce finger movements such that the point of peak flexion coincided with the presentation of each stimulus (visual or auditory). For syncopation, the instruction was to place peak flexion directly in between consecutive stimuli. Regardless of the coordination pattern during pacing, subjects were instructed to maintain the movement rate as accurately as possible during continuation. A single 1 s tone was presented at the end of the continuation phase signaling the subject to rest until the start of the next pacing interval.

The visual pacing stimulus was a red dot presented in the center of a computer screen against a black background (approximately 1–2° visual angle; 60 ms duration) through a set of VGA compatible, fiber optic goggles (Avotec Inc., Stuart, FL) mounted to the head-coil. Auditory stimuli were 1000 Hz sine tones of 60 ms duration and were presented binaurally to the subject through MR compatible headphones (Avotec Inc., Stuart, FL). Behavioral responses were recorded as changes in pressure in a small air-filled pillow placed between the index finger and thumb of the right hand. Behavioral data as well as a marker channel indicating the onset of each pacing stimulus were recorded digitally using an A/D converter sampling at 500 Hz.

Magnetic resonance imaging

Changes in neural activity were determined by measurement of changes in local blood oxygenation (BOLD effect) using echo planar imaging on a 1.5 T GE Signa Scanner equipped with real time fMRI capabilities (General Electric Medical Systems, Milwaukee, WI). Echo-planar images were acquired using a single shot, gradient-echo, echo-planar pulse sequence (echo time (TE) = 40 ms, flip angle (FA) = 90°, field of view (FOV) = 24 cm, matrix = 64 × 64). Twenty axial 5 mm thick slices spaced 2.5 mm apart were selected so as to provide coverage of the brain every three seconds (TR = 3 s; voxel size = 3.75 × 3.75 × 7.5 mm). Prior to functional imaging, high resolution anatomical spoiled gradient-recalled at steady state (SPGR) images (TE = in phase, TR = 325 ms, FA = 90°, FOV = 24 cm, 5 mm thickness, 2.5 mm spacing) were collected at the same slice locations as the functional images. These images served as the background onto which the functional information was displayed and were also used to co-register the functional scans onto anatomical 3D SPGR axial images (TE = 5 ms; TR = 34 ms; FA = 45°, FOV = 24 or 26 cm; resolution = 256 × 256; thickness = 2 mm) collected at the end of each experimental session.

A block design was employed in which a single block comprised a rest period (9 images/location; 27 s) followed by pacing (7 images/location; 21 s) and continuation (7 images/location; 21 s) conditions, respectively. A total of four blocks were completed for each coordination pattern and modality condition. The order of grouped blocks was randomized such

that half the subjects started with synchronization, and the other half syncopation. Visual and auditory conditions were blocked with auditory occurring first for each subject.

Behavioral analysis

The time of each behavioral response was defined as the point of maximum compression of the air pillow (i.e., peak flexion of the index finger and thumb). Two relative measures of performance were calculated. Inter-response interval was defined as the time between consecutive behavioral responses and relative timing (phase) was defined as the time between each behavioral response and the preceding stimulus onset, divided by the stimulus period (Zanone and Kelso, 1992).

Neuroimaging analysis

Unless otherwise stated, all analyses were performed using AFNI (Cox, 1996; Cox and Hyde, 1997) installed on a PC running Linux. Preprocessing included motion detection and correction followed by spatial smoothing by convolution with a Gaussian kernel (FWHM 4 mm) and temporal filtering below 0.1 Hz. Multiple regression was used to determine the relative contribution of auditory and visual pacing and continuation model functions to the observed time series data from each voxel. Model time series were created by convolving a hemodynamic response function (HRF) with a binary vector representing the relative timing of each condition. Additional covariates of no interest included a baseline offset and a linear drift term. The resulting fit coefficient for each covariate of interest was divided by the mean intensity of each voxel time series to give a measure of percent signal change. SPM99 was employed to co-register the functional images to the anatomical images prior to transformation into Talairach and Tournoux (1988) coordinates, and to further statistical evaluation.

Areas of significant activity for each of the eight conditions (simple means) as well as differences between individual experimental conditions were assessed by submitting individual beta weights to a three-way analysis of variance (ANOVA) performed with stimulus modality (visual, auditory), coordination pattern (synchronization, syncopation), and task (pacing and continuation) as factors. Subjects were treated as a random factor allowing inferences to be made beyond the sample population. Correction for multiple comparisons was performed using a combined threshold and clustering approach. A Monte Carlo simulation was used to determine the random distribution of cluster sizes for a given per voxel threshold (for similar approaches, see Ledberg et al., 1998). According to this empirically derived distribution, a volume level corrected alpha of $P < 0.05$ is achieved through the combination of a per voxel threshold of $P < 0.005$ and a cluster size of at least six contiguous voxels (632 mm³).

Differences in neural activity associated with synchronized or syncopated coordination were characterized in terms of areas demonstrating a main effect of coordination pattern ([syncopated pacing and continuation] versus [synchronized pacing and continuation]). Modality-specific pacing and continuation networks were identified by investigation of the main effect of stimulus modality ([visual conditions] versus [auditory conditions]). Brain areas active only during the presentation of pacing stimuli were identified by examining the statistical interaction between stimulus modality and task.

Results

Behavior

Participant's ability to perform the requested coordination pattern during pacing was assessed by the mean and standard deviation of the relative phase between the onset of each metronome and the subsequent motor response. Table 1 shows (A) the between-subject mean coordination error (\pm one standard deviation) expressed as the difference from perfect synchrony (relative phase of 0°) and perfect syncopation (relative phase of 180°) and (B) the mean standard deviation of the relative phase averaged across subjects (\pm one standard deviation). A two-way ANOVA performed on the coordination error, with factors of coordination pattern (synchronization, syncopation) and modality (visual, auditory), showed that the error was significantly greater for visual conditions compared to auditory conditions (main effect of modality, $F_{1,44} = 4.33$, $P = 0.043$). A similar ANOVA performed on the standard deviation of the relative phase (a common measure of stability) demonstrated that syncopation was significantly less stable than synchronization across stimulus modality (main effect of coordination pattern, $F_{1,44} = 5.33$, $P = 0.025$). Visual conditions, in addition to being less accurate, showed a tendency towards being less stable than auditory conditions. However, this difference did not reach significance ($F_{1,44} = 3.31$, $P = 0.075$).

Inter-response interval (IRI) was used to assess timing accuracy across pacing and continuation conditions (Fig. 1). A three-way ANOVA performed on IRI with factors of modality (visual, auditory), coordination mode (synchronization, syncopation), and task (pacing, continuation) revealed main effects for both pattern and task. Syncopation was found to be performed slower than synchronization ($F_{1,88} = 16.7$, $P < 0.001$). Subjects also tended to slow down once the metronome was removed with significantly longer IRI's during continuation than during pacing ($F_{1,88} = 17.0$, $P < 0.001$). No modality-dependent differences in IRI were found indicating that the interval produced was not affected by the modality through which pacing information was presented. No significant interactions were found indicating that the decrease in movement rate from pacing to continuation was a consistent feature of the experimental paradigm and not specific to the mode of pacing per se.

Overall, the variability of the IRI (Fig. 2b) was relatively low for all conditions, ranging from 5.9% to 8.85% of the average interval. A three-way ANOVA revealed that variability during

synchronization was significantly greater than during syncopation with a main effect of coordination mode ($F_{1,88} = 7.38$, $P = 0.008$). There were no other significant main effects or interactions. Despite small but statistical differences in movement variability, it is clear that movements performed in both coordination modes were successful in establishing a viable representation of the required movement rate.

Functional imaging

In Fig. 2, clusters containing voxels demonstrating a main effect for mode are depicted in red overlaid on a semitransparent cortical reconstruction of a normalized brain transformed to the stereotaxic space of Talairach and Tournoux (1988). A lateral view of the right hemisphere is shown together with a dorsal view of the whole brain (center) and selected single axial slices showing the midbrain and cerebellum. Bar graphs show the mean percent signal change (\pm standard error) in each experimental condition averaged across the voxels of each cluster and subject. The anatomical location and coordinates for each of these clusters is also provided in part A of Table 3. It is clear that all main effects result from greater activity during syncopation (PP and PC) than synchronization (NP and NC). Syncopation resulted in increased activity bilaterally in the medial wall of the middle frontal gyrus (MFG, BA6) and on the dorsal surface of the MFG. These areas may be defined functionally as supplementary motor area (SMA) and dorsal premotor cortex (DPMC), respectively (Picard and Strick, 2001). Increases were also observed in left middle frontal gyrus (MFG) in the prefrontal cortex, right insula (BA13), left superior parietal lobe (SPL), left thalamus extending into the caudate, and left cerebellar dentate (lobule VI).

The bar graphs in Fig. 2 provide additional insight into the relationship between the eight conditions and illustrate several important results. First, syncopation always resulted in greater signal intensity than synchronization, during both pacing and continuation conditions and across both stimulus modalities. Second, this coordination-dependent difference was expressed similarly across both stimulus modalities providing evidence that coordination-dependent increases in neural activity are not modulated by modality. Thus, it appears that the pattern and intensity of the BOLD response observed during continuation is strongly influenced by the coordination mode employed during pacing. These data are in agreement with those reported for the auditory case (Jantzen et al., 2004) and support the hypothesis that the brain network engaged during internally paced continuation is strongly influenced by the manner in which temporal information is acquired.

Areas demonstrating a significant main effect of stimulus modality are shown in Fig. 3 and listed in Table 3 (section B). As in Fig. 2, bar graphs show the mean percent signal change for each cluster averaged across voxel and subject. All of the effects result from a significant increase in activity during visual conditions compared to auditory conditions. Clusters were located in bilateral inferior temporal gyrus (BA37), an area consistent with area MT/V5. Additional clusters were observed in bilateral superior parietal lobe (BA7 and 40) and in the right middle frontal gyrus (BA9) in an area compatible with ventral premotor cortex (Picard and Strick, 2001). Activation of these regions during visually mediated coordination is compatible with their established role in the integration of visual and

Table 1
Coordination performance

	Synchronize	Syncopate
A. Relative phase error (degrees) ^a		
Visual	38.15 \pm 35.5	62.84 \pm 47.9
Auditory	24.25 \pm 14.75	33.93 \pm 36.32
B. Relative phase standard deviation (degrees)		
Visual	37.86 \pm 10.25	44.85 \pm 13.68
Auditory	29.82 \pm 4.86	39.64 \pm 17.89

^a For synchronization the error (\pm one standard deviation) is calculated with respect to 0° , for syncopation it is calculated with respect to 180° .

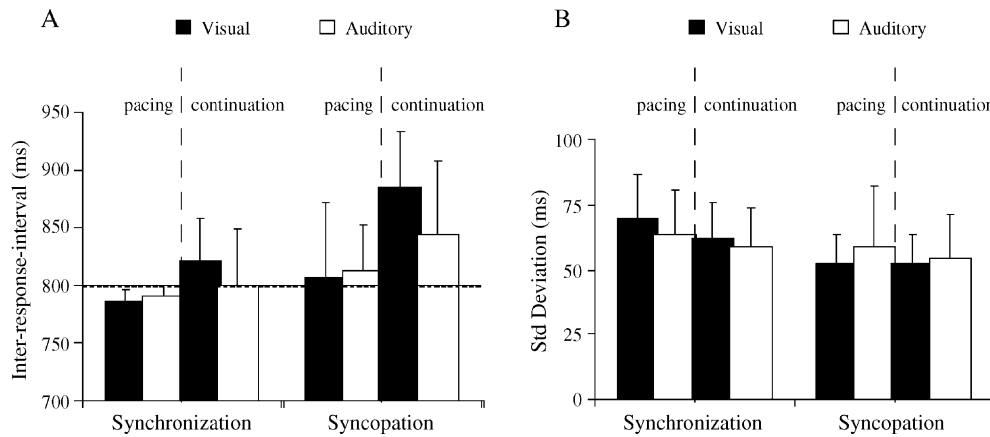


Fig. 1. Behavioral results. The (A) mean and (B) standard deviation of the inter-response interval during synchronization and syncopation are shown for both auditory (white bars) and visual (black bars) conditions. Error bars show the between subject standard deviation. The left two bars for each grouping show performance measures during pacing and the right two bars show the same information during continuation. The dashed horizontal line in A represents the required temporal interval prescribed by the metronome.

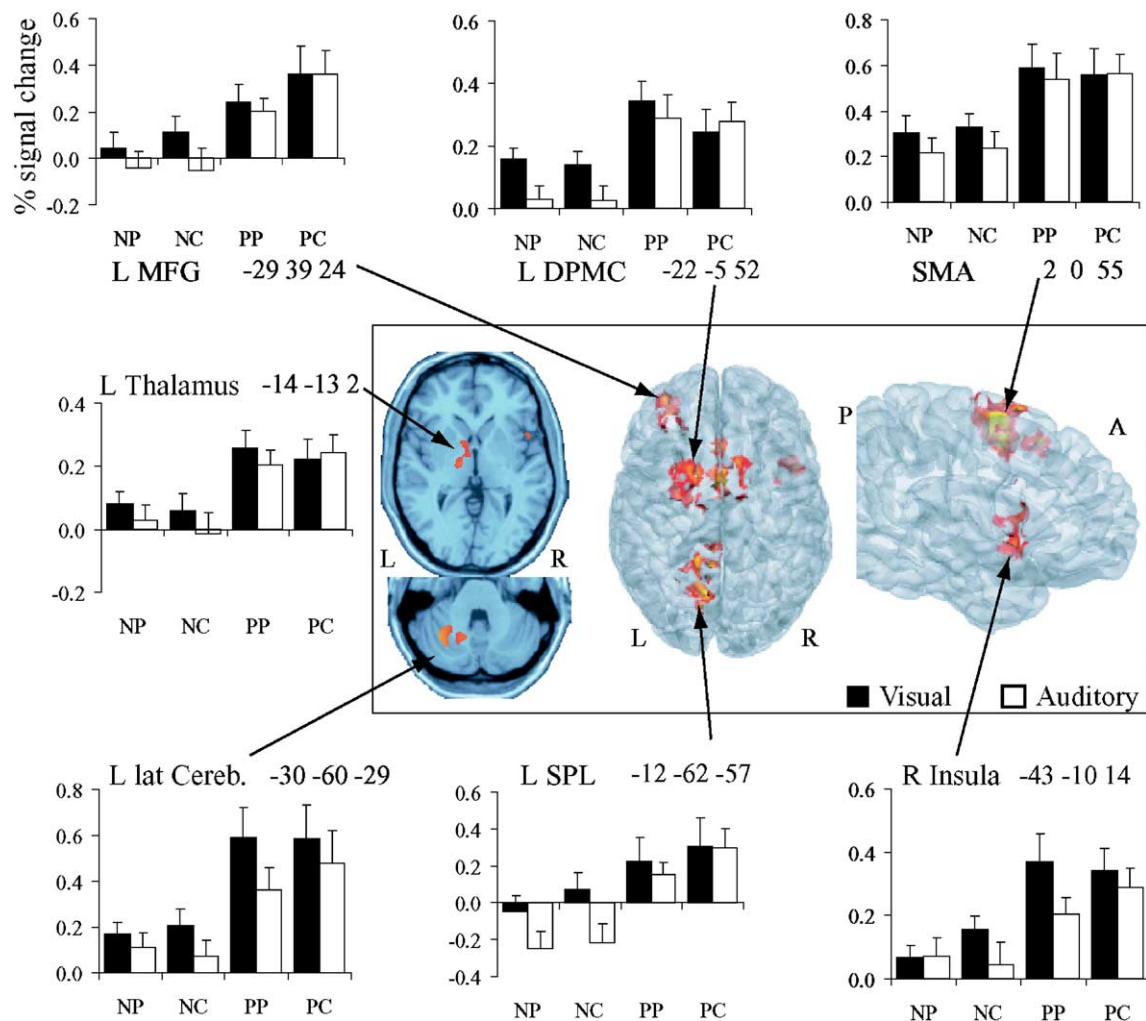


Fig. 2. Colored areas show brain regions demonstrating a main effect of coordination mode (syncopate > synchronize). The left part of the inset depicts two axial slices from the midbrain showing areas of significant difference in the thalamus (top) and cerebellum (bottom). The middle and right graphics show a semi-transparent 3D rendered brain viewed from the top (middle) and right with areas of significant difference overlaid in red. The bar graphs show the mean percent signal change (across subject \pm standard error) for the four conditions averaged across the cluster. Black bars show activation levels from visual conditions and white bars from auditory conditions. NP: synchronized pacing; NC: synchronized continuation; PP: syncopated pacing; PC: syncopated continuation; L: left; R: right; P: posterior; A: anterior; MFG: middle frontal gyrus; DPMC: dorsal premotor cortex; SMA: supplementary motor area; SPL: superior parietal lobe.

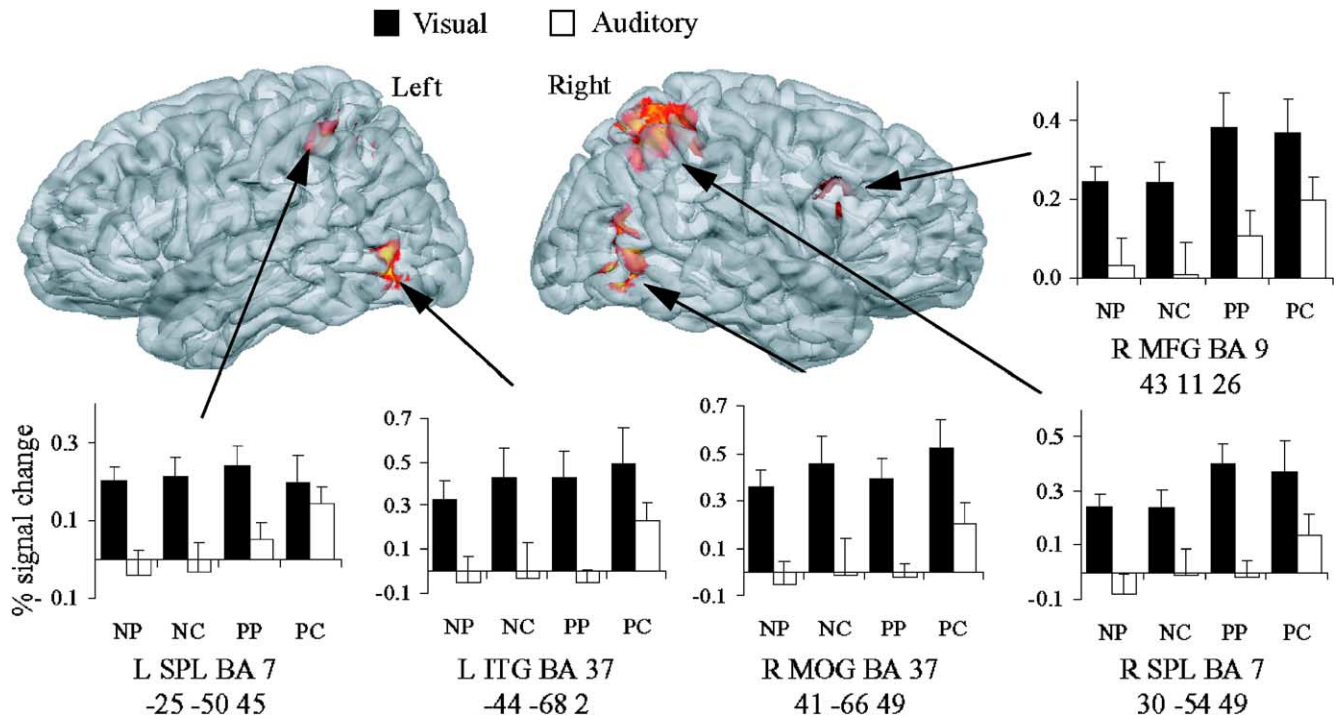


Fig. 3. Colored areas showing brain regions demonstrating a main effect of stimulus modality (visual > auditory) are plotted on semitransparent renderings of an average brain shown from the left and right in the coordinate space of Talairach and Tournoux (1988). The bar graphs show the mean percent signal change (across subject \pm standard error) for the four conditions averaged across the cluster. Black bars show activation levels from visual conditions and white bars from auditory conditions. NP: synchronized pacing; NC: synchronized continuation; PP: syncopated pacing; PC: syncopated continuation; SPL: superior parietal lobe; ITG: inferior temporal gyrus; MOG: middle occipital gyrus; MFG: middle frontal gyrus.

somatosensory information (Anderson, 1995) and the translation of visual input into motor output (Goodale and Milner, 1992). Importantly, however, these modality-specific regions remained active during continuation despite the fact that visual stimulation was no longer present. This is illustrated clearly in the bar graphs of Fig. 3 in which mean activity for each of the four visual conditions is shown to be elevated across both pacing and continuation conditions. In contrast, activity in these regions was virtually absent during auditory conditions (see also Table 2). However, one exception was noted: Table 2 and Fig. 3 show that activity in visual areas (left MTG and IPL and right IFG) is also observed during auditory continuation following syncopated pacing. It is possible that this activity reflects task difficulty since syncopated coordination is considered more difficult and attention demanding than synchronized coordination (Monno et al., 2002; Temprado et al., 2002). Moreover, during coordination, visual conditions were performed with greater variability and less accuracy than auditory ones leading to the possibility that observed increases in activity within temporal and parietal brain areas occurred in response to changes in task difficulty rather than processing of visual stimuli per se. This approach predicts that BOLD activity in bilateral V5 and inferior parietal cortex as well as right prefrontal cortex will increase with progressive decreases in task performance.

To examine the foregoing hypothesis more directly, we performed a regression between subjects' percent BOLD signal change and their corresponding mean phase error during pacing. This was performed separately for each brain region demonstrating greater activity in visual compared to auditory

conditions. If activity in these regions changed as a function of behavioral performance, we would predict a significant linear fit when regressing BOLD amplitude onto error. Moreover, since BOLD signal intensity and performance error both demonstrated increases for visual compared to auditory conditions, we would expect the slope of the linear regression to be positive. However, no such relationship was found for any of the experimental conditions. The r^2 values clustered very close to zero and reach a maximum of only 0.063 ($t_{18} = 1.16$, $P > 0.05$) for any single regression. In addition, no clear pattern in slope of the regressions was observed with most slopes hovering around zero. Together these data do not support the existence of a relationship between task difficulty and BOLD amplitude within these regions and support our original conclusion that these areas are related to processing and integration of visual information. It remains unclear why activity in these regions was present during a single auditory condition. One conjecture is that activation of these areas during continuation following from auditory syncopation may reflect the adoption of a (partially) visual strategy possibly brought on by the lack of formation of an adequate auditory representation during syncopated pacing. This interpretation seems plausible in light of recent data demonstrating common neural substrates for visual perception and imagination (Ganis et al., 2004) as well as executed and imagined coordination (Oullier et al., in press).

Investigation of the main effects did not reveal any auditory-specific regions. However, as seen in Fig. 4 and Table 3C, a significant stimulus modality \times task interaction was observed in bilateral superior temporal gyrus. Although some level of

Table 2

Anatomical location of significant clusters of activity for each experimental condition compared to rest

Region	Hem.	BA	Auditory												Visual											
			Synchronize						Syncopate						Synchronize						Syncopate					
			Pacing			Continuation			Pacing			Continuation			Pacing			Continuation			Pacing			Continuation		
			X	Y	Z	X	Y	Z	X	Y	Z	X	Y	Z	X	Y	Z	X	Y	Z	X	Y	Z	X	Y	Z
SMA	B	6	−3	−3	57	−2	−2	60	0	−1	56	0	−1	56	−1	2	57	−2	−4	58	0	2	56	−1	−7	59
SMC	L	3/4	−32	−28	58	−32	−17	61	−35	−16	56	−33	−19	58	−36	−17	54	−42	−21	52	−34	−20	53	−34	−19	54
MFG	L	6	−49	2	45	−49	3	43	−39	−6	58	−34	−8	56	−48	4	39	−50	2	37	−47	0	43	−48	0	45
	R	6	−	−	−	−	−	−	34	−2	49	42	−1	52	38	−1	50	−	−	−	47	1	44	50	−2	43
IFG	L	9	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−49	10	23	−50	5	32	−50	7	27
	R	9	−	−	−	−	−	−	−	−	−	53	7	27	50	4	31	52	3	31	52	12	28	49	9	24
IPL/SPL	L	7/40	−	−	−	−	−	−	−	−	−	−	−	−	−28	−48	47	−21	−57	41	33	−42	45	−33	−42	41
IPL/SPL	R	7/40	−	−	−	−	−	−	−	−	−	40	−43	47	33	−40	44	43	−36	49	−33	−41	42	40	−43	48
STG	L	41/42	−56	−19	14	−	−	−	−53	−22	13	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
	R	41/42	58	−17	12	−	−	−	58	−20	17	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
MTG	L	37	−	−	−	−	−	−	−	−	−	−51	−64	11	−49	−64	9	−50	−63	8	−38	−63	10	−51	−66	4
	R	37	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	52	−50	0	48	−58	9	52	−63	6
	R	22	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	60	−32	4	54	−38	10	57	−41	7
Putamen	L	−	−22	1	6	−	−	−	−24	1	8	−24	−11	10	−20	−1	10	−27	−7	10	−20	0	10	−23	−3	7
	R	−	−	−	−	−	−	−	22	−1	14	24	−3	14	23	0	11	−	−	−	24	2	10	26	−2	7
Caudate	L	−	−	−	−	−	−	−	−12	−8	19	−13	−6	20	−	−	−	−14	−1	17	−	−	−	−	−	−
	R	−	−	−	−	−	−	−	16	−5	21	16	−7	19	−	−	−	−	−	−	−	−	−	−	−	−
Insula	L	13	−	−	−	−	−	−	−49	10	2	−40	6	11	−	−	−	−47	10	4	−31	13	10	−36	14	−1
	R	13	−	−	−	−	−	−	48	9	8	47	13	6	−	−	−	51	6	11	49	11	13	41	18	3
Declive	L	−	−	−	−	−	−	−	−	−	−	−13	−66	−13	20	−55	−12	−21	−74	−12	−17	−66	−16	−17	−61	−13
	R	−	20	−56	−13	23	−58	−11	20	−57	−13	22	−59	−13	−	−	−	20	−56	−9	15	−58	−13	20	−56	−11

Coordinates are expressed in the coordinate system of Talairach and Tournoux.

SMA: supplementary motor area; SMC: sensorimotor cortex; MFG: middle frontal gyrus; IFG: inferior frontal gyrus; IPL/SPL: inferior/superior parietal lobe; STG: superior temporal gyrus; MTG: middle temporal gyrus; BA: Brodmann's area; Hem.: hemisphere.

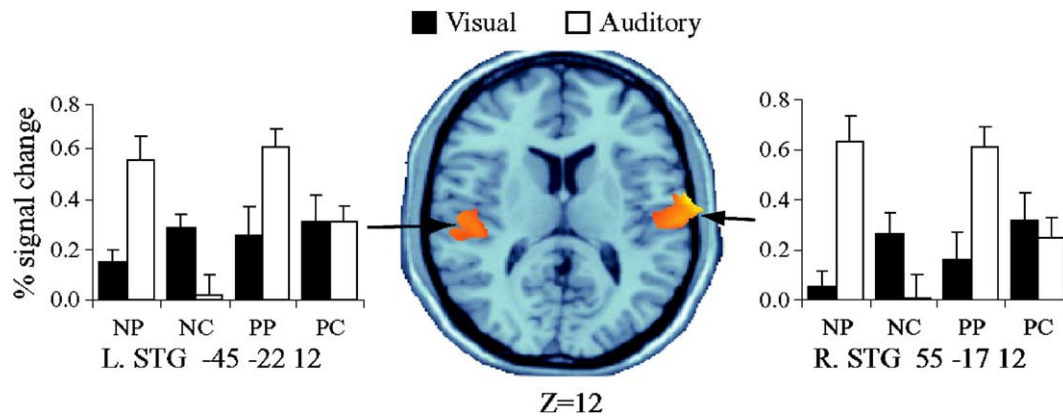


Fig. 4. Bilateral superior temporal gyrus (STG) areas demonstrating a significant stimulus modality (visual, auditory) \times task (pacing, continuation) interaction. The bar graphs show the mean percent signal change (across subject \pm standard error) for the four conditions averaged across the cluster. The bar graphs demonstrate that the interaction results from significantly greater activity in auditory processing areas only in conditions when the pacing tones were present. NP: synchronized pacing; NC: synchronized continuation; PP: syncopated pacing; PC: syncopated continuation.

activity was observed across virtually all conditions, there was a clear increase only during conditions in which an auditory stimulus was present (synchronized (NP) and syncopated (PP) pacing). Inspection of Table 2 reveals that BOLD increases observed in primary auditory cortex during the other six conditions were not significant when compared against rest. The observed interaction reflects the fact that the auditory-related activity did not continue in the absence of the auditory stimulus. No other brain areas were more active for auditory versus visual conditions.

Discussion

The present research confirms and extends previous work showing context dependence in the neural networks recruited to

support self-paced timing (Jantzen et al., 2004). Two important new findings were revealed: First, regardless of whether pacing was visual or auditory, the coordination pattern used to establish the time interval of movement directly influences the neural representation of the subsequent self-paced task. Second, for the visual case, modality-specific brain areas are involved not only in the processing of pacing stimuli, but also in making self-paced movements during continuation, when stimuli are no longer present.

Behavior

In general, participants demonstrated good performance on all coordination and continuation tasks. Nonetheless, differences in performance between conditions were observed, including an inverse relationship between measures of coordination stability and inter-response interval. Syncopation was found to be less stable than synchronization as indicated by a greater variability of relative phase, a finding compatible with existing literature (Kelso et al., 1990, 1992). At least part of this variability may be due to syncopation being performed at an interval slightly longer than the prescribed 800 ms. Conversely, synchronization was more stable with respect to the metronome and the response interval was closer to that prescribed by the task. However, the IRI variability was increased compared to syncopation. This would be expected if during synchronization a comparison between the metronome and movement was used to regularly update the response interval. Such updates, while having the goal of decreasing coordination error, would simultaneously increase IRI variability. During syncopation, however, updates may be more difficult by virtue of the temporal distance between the movement and metronome. As such movements may be made at a more constant interval with less frequent corrections. Such a strategy would reduce the IRI variability at the expense of coordination stability (see also Ding et al., 2002).

Visually guided coordination was less accurate and showed a tendency towards being less stable than auditory paced movements. This finding is in general agreement with previous studies employing paced finger tapping (Jäncke et al., 2000). It is also compatible with previous behavioral studies which showed that, in addition to being judged as shorter, judgments of intervals defined by visual stimuli are also more variable than those of equivalent duration defined by auditory signals (Wearden et al., 1998). In

Table 3

Anatomical location of regions demonstrating significant main effects or interactions

Region	BA	Hem.	X	Y	Z
A. Main effect of coordination pattern (syncopate > synchronize)					
MFG	10	L	-29	39	24
MFG	6	L	-22	-5	52
MFG	6	B	2	0	55
SPL	7	L	-12	-62	-57
Insula	13	R	-43	-10	14
Thal.	—	L	-14	-13	2
Declive	—	L	-30	-60	-29
B. Main effect of stimulus modality (visual > auditory)					
SPL	7/40	L	-25	-50	45
SPL	7/40	R	30	-54	49
ITG	37	L	-44	-68	2
MOG	37	R	41	-66	-49
MFG	9	R	43	11	26
C. Stimulus modality \times task interaction					
STG	41	L	-45	-22	12
STG	41	R	55	-17	12

Coordinates are expressed in the coordinate system of Talairach and Tournoux.

MFG: middle frontal gyrus; SPL: superior parietal lobe; Thal.: Thalamus; ITG: inferior temporal gyrus; MOG: middle occipital gyrus; MFG: middle frontal gyrus; STG: superior temporal gyrus.

sensorimotor coordination, variability is greater when sequences are presented visually than when presented auditorily (Chen et al., 2002; Repp and Penel, 2002; Kolers and Brewster, 1985). Modality-specific performance measures may reflect differences in the precision with which visual and auditory systems represent temporal information, an idea supported by recent behavioral work (Repp, 2003).

Coordination-dependent activity

In contrast to the quite restricted brain activity observed during synchronization, syncopating (regardless of stimulus modality) engaged a broader, more extended network of cortical and subcortical areas that included bilateral SMA, right insula, contralateral prefrontal cortex, dorsal premotor cortex, superior parietal lobe, thalamus, and cerebellum. This difference in the networks recruited for the performance of synchronized and syncopated coordination patterns bears a strong resemblance to those observed previously in studies using purely auditory pacing (Jantzen et al., 2002, 2004; Mayville et al., 2002).

It has been postulated that specific neural subsystems underlying syncopated pacing reflect the increased planning, preparation, and timing demands of the off-the-beat pattern (Mayville et al., 2002), a view supported by substantial evidence from the literature. For instance, the role of the lateral cerebellum in both the production and perception of temporal intervals is well documented (Casini and Ivry, 1998; Franz et al., 1996; Harrington et al., 1998; Ivry and Keele, 1989; Ivry et al., 1988; Mangels et al., 1998; Nichelli et al., 1996; Penhune et al., 1998). Similarly, the SMA has long been regarded as important for motor planning and preparation (Deecke et al., 1969; Larsson et al., 1996) and has also been repeatedly identified in functional imaging studies that require temporal processing (Jäncke et al., 2000; Macar et al., 1999, 2002; Rubia et al., 1998; Schubotz et al., 2000). Left frontal activation may be associated with the increased working memory demand during syncopation. Prefrontal cortex, an area often associated with working memory and decision-making (Smith and Jonides, 1998), has also been shown to be involved in timing tasks (Harrington et al., 1998; Lejeune et al., 1997; Macar et al., 2002; Rao et al., 2001). Finally, the role of insular cortex in auditory processing is steadily becoming established (Bamiou et al., 2003). Anatomically, insula shares reciprocal connections with a number of sensorimotor processing areas including precentral gyrus, secondary somatosensory cortex, the medial aspect of the middle frontal gyrus, and lateral premotor cortex (Augustine, 1996). Functionally, insula has been shown to respond to stimuli presented across multiple modalities (Downer et al., 2000) and has been implicated as playing an important role in multimodal integration (Calvert, 2001). The insula is a structure commonly identified by neuroimaging studies that typically investigate timing of longer, discrete intervals (for a review, see Lewis and Miall, 2003a,b). Taken together these data suggest that the insula may serve as a convergence zone for the integration of multisensory and motor information, though its specific role in timing remains unclear.

Visual conditions clearly recruited additional processing networks compared to auditory paced coordination. However, these networks were not modulated by the coordination mode performed during pacing. The lack of a coordination mode (synchronization, syncopation) \times stimulus modality (visual, auditory) interaction attests to the amodal nature of the neural differences distinguishing

networks underlying synchronized and syncopated coordination. There were no modality-specific brain areas that were more active during syncopated pacing and continuation compared to synchronized pacing and continuation. This result is important because it suggests that behavioral and neural differences between coordination patterns are substantiated at higher level processing stages beyond those engaged in processing sensory input and translating it into action (see below).

Modality-dependent activity

Modality-dependent differences between pacing conditions (Jäncke et al., 2000; Penhune et al., 1998) have been hypothesized to reflect requisite processing of the sensory information when performing timed movements with respect to an external signal (Jäncke et al., 2000). Compared to auditory conditions, performing coordination movements in time with a visual stimulus resulted in activity in bilateral V5/MT, superior parietal lobe (in the area of the intraparietal sulcus, BA7/40), and right middle frontal gyrus (MFG) in an area compatible with ventral lateral premotor cortex (VLPFC). Anatomically, this network is compatible with the well-described dorsal visual stream, a circuit through which visual-spatial information specifies movement (Goodale and Milner, 1992; Jeannerod, 1999).

A similar network has been reported previously to support visually guided coordinated movements (Debaere et al., 2003; Jäncke et al., 2000; Kawashima et al., 2000). Increased activity within these regions is compatible with visual-motor processing demands imposed during pacing (Anderson, 1995; Jackson and Husain, 1996; Maunsell and Ferrera, 1995). MT is a prominent visual motion sensitive area (Newsome and Paré, 1988; Suneart et al., 1999; Tootell et al., 1995) and is likely involved in extraction of visual information even though our stimulus does not move in space. (Newsome et al., 1995) Frontoparietal circuits are well known for their role in the translation of visual information into guided action (see Wise et al., 1997). In the current task, visual information enters this circuit through posterior parietal cortex via MT. The appropriate sensorimotor transformation may then be performed by the frontoparietal circuit to guide the temporal aspects of the task. (Rizzolatti et al., 1998)

One key finding is that the modality-specific visual processing network was active not only during visual pacing, but also during continuation when the visual pacing signal was no longer present (see also Jäncke et al., 2000). This suggests that the network is important for processes beyond those necessary for processing visual sensory input, including those necessary to continue making timed movements. A possible explanation is that timing-related processes such as the representation or memory of the interval to be performed are rooted in task-specific sensory and motor processes (Matell et al., 2003; Todd et al., 2002). This would imply that maintenance of specific sensorimotor and timing-related information developed during pacing and critical to performance during continuation activates sensory processing areas not typically considered to play a role in timing and memory. This notion is supported by recent imaging work demonstrating that activations associated with recall of visual images and auditory sounds largely overlapped with the areas involved in encoding those same stimuli (Wheeler et al., 2000). Among the areas identified by Wheeler and colleagues for visual recall were portions of bilateral middle temporal gyrus, bilateral parietal, and premotor cortex, similar to those reported in the

present study. Taken together current evidence suggests that areas engaged during processing of visually presented temporal information and important in visual–motor integration may also play a role in representing that information once the stimulus is no longer physically present.

It is interesting that visual conditions did not generate activation in primary visual areas. This may be because of the relatively small visual angle subtended by the stimulus and the low contrast generated by flashing a red stimulus against a black background. Imaging studies aimed at investigating properties of primary visual neurons typically employ rapidly flashing or rotating checkerboard patterns that last for durations ranging from hundreds of milliseconds to several seconds and subtend a large visual angle (in some cases the entire visual field). Such stimuli, when presented in the context of sensorimotor timing experiments, have been shown to evoke significant activity in visual areas (Jäncke et al., 2000). However, when low contrast, non-flicker visual stimuli of short duration are employed, as in the present research, a lack of statistical activity in primary visual regions is not unusual (e.g., Penhune et al., 1999). Such a finding is consistent with reported decreases in BOLD signal with decreasing image contrast (Olman et al., 2004; Zaletel et al., 2004).

Auditory coordination generated increased BOLD activity within bilateral superior temporal gyrus when compared to visual conditions. This increase was observed only during pacing, that is, when auditory stimuli were actually present. Such results indicate that primary auditory areas are not responsible for maintenance of temporal information during continuation. Previous studies have reported diverging results concerning the contribution of auditory cortex during pacing and continuation. Penhune et al. (1998), for example, found that reproduction of an isochronous tone sequence, when compared to perception of the same sequence, produced activation in right planum temporale. Subsequent patient studies provided support for the claim that right auditory areas are involved in temporal memory (Penhune et al., 1999). However, the Penhune et al. study differs from the present work in that the establishment of the interval to be reproduced did not involve motor coordination. As such the formation of a temporal memory may have relied more on purely perceptual systems. Rao et al. (1997) reported that right superior temporal gyrus was recruited during continuation, a result they suggest implicates subvocal rehearsal as a means of maintaining timing information. Our results, however, are more in line with those of Jäncke et al. (2000) who reported that primary auditory areas did not contribute to continuation. The lack of auditory-specific activation during continuation may indicate that auditory information is more easily extracted and directly integrated into the motor system than visual information, at least for rhythmic coordination. A more direct mapping between auditory and motor components might provide a physiological basis for the present behavioral results as well as others that demonstrate better coordination with auditory than visual stimuli (for a discussion, see Repp, 2003).

The current findings are compatible with recent views that temporal processing is mediated by distributed brain areas (Buonomano and Karmarkar, 2002) and may be rooted in basic sensorimotor processes (Lewis and Miall, 2003a,b; Matell et al., 2003; Todd et al., 2002). Within this framework, brain areas recruited to perceive and produce the required temporal interval during pacing form the basis for the temporal representation required during continuation. In the case of visually guided coordination, the present results suggest that areas traditionally

ascribed a role in visual–motor transformation and integration may not only be involved during pacing, but may also be involved in the ongoing representation of the temporal information during continuation when no visual stimuli are present.

Prevailing psychological models of interval timing posit the existence of discrete, hierarchically arranged processing modules that act sequentially upon a signal derived from a putative clock source. The popular scalar timing theory, for example, accounts for human timing behavior by invoking a separate pacemaker, switch, accumulator, memory storage and retrieval, comparator, and threshold detector (Allan, 1998; Church, 2003; Gibbon, 1991). When attempting to express such psychological processes in terms of brain function, it is tempting to apply a direct mapping between the components of a hypothesized mechanism and activity in localized neuronal areas. Such localization approaches have provided important insight into the functional specialization of discrete cortical and subcortical regions that have been shown to play an important role, for example, in basic sensory processing, memory, and language (Passingham et al., 2002). However, the present research suggests that for the networks supporting interval timing, such a straightforward mapping may be too simplistic and fail to capture the distributed nature of the neural structures involved, the connectivity between these structures and their context-dependent coordination dynamics.

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