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A parametric fMRI investigation of context effects in sensorimotor timing and coordination

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Abstract

Mounting evidence suggests that information derived from environmental and behavioral sources is represented and maintained in the brain in a context-dependent manner. Here we investigate whether activity patterns underlying movements paced according to an internal temporal representation depend on how that representation is acquired during a previous pacing phase. We further investigate the degree to which context dependence is modulated by different time delays between pacing and continuation. BOLD activity was recorded while subjects moved at a rate established during a pacing interval involving either synchronized or syncopated coordination. Either no-delay or a 3, 6 or 9 s delay was introduced prior to continuation. Context-dependent regions were identified when differences in neural activity generated during pacing continued to be observed during continuation despite the intervening delay. This pattern was observed in pre-SMA, bilateral lateral premotor cortex, bilateral declive and left inferior semi lunar lobule. These regions were more active when continuation followed from syncopation than from synchronization regardless of the delay length putatively revealing a context-dependent neural representation of the temporal interval. Alternatively, task related regions in which coordination-dependent differences did not persist following the delay, included bilateral putamen and supplementary-motor-area. This network may support the differential timing demands of coordination. A classic prefrontal–parietal–temporal working memory network was active only during continuation possibly providing mnemonic support for actively maintaining temporal information during the variable delay. This work provides support for the hypothesis that some timing information is represented in a task-dependent manner across broad cortical and subcortical networks.

Keywords: Continuation; Emergent timing; Context dependence

1. Introduction

A large amount of timing research at both behavioral and neural levels takes as its starting point one or more popular information processing approaches (Church, 2003; Gibbon, 1977, 1991). A common assumption of most psychologically based models is the notion of a series of hierarchically arranged discrete processing stages. Such models typically include a pacemaker component that operates in conjunction with perceptual, memory and decision making modules (Church, 2003). Although formal mathematical instantiations of these models have been used successfully to mimic and predict behavioral performance on a range of timing tasks in both animals and humans (Allan, 1998), it is still unclear whether such modeling accurately reflects the underlying brain processes that support timing (Gibbon, Malapani, Dale, & Gallistel, 1997; Matell & Meck, 2000).

The advent of brain imaging technology has inevitably led to questions concerning the nature of the mapping between discrete processing stages postulated by psychological timing models and activity within specific brain areas or networks identified during performance of temporal tasks (e.g. Harrington & Haaland, 1999; Lewis & Miall, 2003). A growing body of research indicates that the neural systems mediating timing behavior are modulated by how timing information is presented and consequently how temporal representations are formed. For instance, research using functional magnetic resonance imaging (fMRI) has revealed the engagement of modality-dependent

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brain networks for motor timing tasks paced using auditory or visual stimuli (Jancke, Loose, Lutz, Specht, & Shah, 2000; Jantzen, Steinberg & Kelso, 2005; Penhune, Zatorre, & Evans, 1998). This research is supported by behavioral work showing that performance on timing tasks depends on the sensory modality over which temporal information is presented (Goldstone & Goldfarb, 1964; Penney, Gibbon, & Meck, 2000; Repp & Penel, 2002; Wearden, Edwards, Fakhri, & Percival, 1998). Additional task parameters that suggest the existence of multiple neural timing networks include the duration of the interval to be timed, the involvement of motor processes in performing timing, and whether discrete or rhythmic intervals are presented (see Lewis & Miall, 2003). Taken together, the data offer experimental support for the idea that at least some timing processes postulated by psychological models are mediated by distributed neural systems themselves rooted in basic sensorimotor mechanisms (Matell, Meck, & Nicolelis, 2003).

Recent functional neuroimaging investigations using the continuation paradigm have demonstrated that neural activity patterns underlying the generation of internally paced movements reflect not only the timing demands imposed by the ongoing task, but also the method employed to establish the required movement rate (Jancke et al., 2000; Jantzen, Steinberg, & Kelso, 2004; Jantzen et al., 2005). Both the modality over which pacing information is presented (Jancke et al., 2000; Jantzen et al., 2005) as well as the coordination pattern adopted when moving in time with pacing stimuli (Jantzen et al., 2004, 2005) directly influence the network engaged during the subsequent continuation phase, when no external temporal information is available. BOLD patterns observed during continuation depend directly on whether subjects synchronize (move coincident with stimuli) or syncopate (move between stimuli) with the pacing metronome (Jantzen et al., 2004) during the pacing phase. Task related differences in BOLD activity distinguishing these coordination patterns (Jantzen, Steinberg, & Kelso, 2002; Mayville, Jantzen, Fuchs, Steinberg, & Kelso, 2002) persist during continuation despite similar sensorimotor and timing constraints. Such findings suggest that the neural representation of a temporal interval may be flexibly determined by the sensory and motor systems engaged during timing acquisition (pacing) and that subsequent temporal processing based on this interval (continuation) continues to rely on the same neural representation.

In order to further test this hypothesis, we studied the brain networks underlying sensorimotor coordination and continuation using a more traditional memory paradigm that involved encoding (pacing) and recall (continuation) phases separated by a short retention (delay) interval. By focusing on the pacing and recall stages in the context of an empty retention interval, this study aims to address more directly whether the imaging results reported previously reflect context dependence in the memory for the temporal interval or persistent activity related to other motor or timing processes not related to temporal memory. If the persistence in neural differences reflects context-dependent encoding of temporal information (i.e. related to the representation or memory of the temporal information), differences in neural activity patterns generated during pacing should continue to be observed as long as the same temporal information is referenced. Consequently, brain areas associated with the representation of temporal information during pacing should remain resident or be re-activated in the event of a physical delay between the establishment of an interval and its subsequent reproduction. Alternatively, persistent activity during continuation may reflect persistence in processes supported by the presence of the ongoing movement such as adoption of a specific sensorimotor strategy (e.g. stressing flexion or extension) or imagination of a stimulus-response relationship (Oullier, Jantzen, Steinberg, & Kelso, 2005). Such processes will likely be disrupted or reset by the cessation and reestablishment of motor activity at the offset of the encoding and onset of the recall phases respectively. As such, it is proposed that brain areas specific to these cognitive demands will not continue to be activated during recall. In addition, the inclusion of a delay interval in the current design will also allow us to explore the possibility that additional brain areas, not observed during pacing, may be recruited in order to support the ongoing representation of the temporal interval during continuation.

Moreover, these putative memory processes may be subject to a time-dependent decay such that parametrically increasing the delay between pacing offset and continuation onset may affect the representation of the temporal interval. Decay in the memory representation may be expressed as a decrease (reflecting a loss of memory) in context-dependent differences with increasing duration of the delay between pacing and continuation. Alternatively, the ability to maintain the temporal representation over increasingly longer temporal intervals may place greater demands on the underlying neural processes resulting in an increase in BOLD signal amplitude and subsequent increase in differences between coordination patterns. To address these additional hypotheses, we parametrically manipulated the delay to range from no delay (0 s) to a 3, 6 or 9 s interval between the offset of the pacing and the onset of the continuation (reproduction) phases.

2. Method

2.1. Subjects

Nine neurologically normal volunteers (seven males, two females; ranging from 24 to 56 years of age) gave informed, written consent to participate in the study. All subjects reported being strongly right handed. Procedures were carried out in accordance with the guidelines set out by the Internal Review Board at Florida Atlantic University and the human subject guidelines of NIH.

2.2. Experimental protocol

Each subject was placed in a supine position on the scanner bed with his/her head fixated by a vacuum pillow. A single trial consisted of the presentation of consecutive pacing and continuation blocks (Fig. 1). During pacing, subjects coordinated finger-thumb opposition movements with an auditory stimulus using two coordination patterns (Pacing Conditions). Finger movements were either synchronized with the stimulus such that the point of peak flexion coincided with the presentation of each tone, or syncopated with the stimulus such that each movement occurred directly in between consecutive tones (Kelso, DelColle, & Schöner, 1990). Movements were paced at 1.25 Hz to ensure stable performance of both patterns (Kelso et al., 1990) and to provide compatibility with previous studies (Mayville et al., 2002; Jantzen et al., 2004, 2005). Regardless of the coordination pattern employed during Pacing, subjects

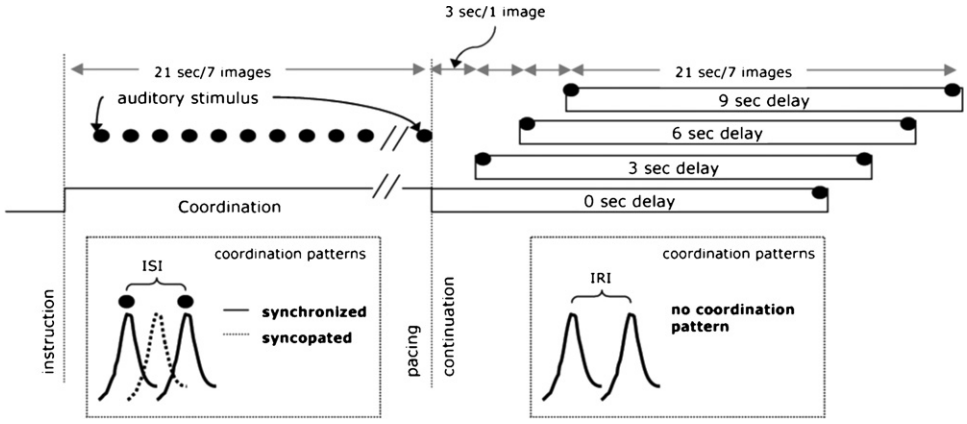

Fig. 1. Schematic diagram of the stimulus design. During pacing (left side of figure), the timing of movements was guided by auditory stimuli presented at 1.25 Hz. The inset on the bottom left provides a schematic of the two movement patterns required during pacing. The inverted u shaped curves represent finger flexion-extension as typically recorded by the pillow device employed. The solid curve represents the synchronization condition in which movements were made to coincide with the auditory stimuli (circles). During syncopation (dotted curve) movements were made directly in between consecutive stimuli. At the end of pacing the participants continued moving at the same rate in the absence of stimulus pacing after no delay, 3, 6 or 9 s. These delays corresponded to 1, 2 or 3 imaging time steps.

were instructed to maintain the movement rate as accurately as possible during Continuation. At the end of the pacing stage the metronome signal was discontinued and participants followed one of two instructions provided at the onset of the trial. In the delay conditions participants stopped moving and waited for a signal (auditory tone of 1 s duration) marking the beginning of the continuation period. In the no-delay condition participants continued moving without stopping. The duration of the delay interval between Pacing and Continuation was systematically varied with intervals of 3, 6 and 9 s. Delays were pseudorandomly introduced for each coordination pattern resulting in a total of eight different experimental conditions (two coordination patterns by four delays). For all conditions, the end of the Continuation stage was signaled by a 1 s tone informing participants to rest until the start of the next trial. Each trial was pre-empted by the presentation of a visual instruction indicating both the coordination pattern to be performed during pacing and whether to continue moving or wait for a tone to signal the start of the Continuation phase. During the trial subjects were asked to fixate vision on a central fixation cross.

Auditory stimuli were 440 Hz pure sine tones of 60 ms duration. Stimuli were presented to the subject through MR compatible headphones and instructions were given via VGA compatible, fiber optic goggles (Avotec Inc., Stuart, FL). Behavioral responses were recorded as a change 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.

2.3. 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 Sigma 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) = 60 ms, flip angle (FA) = 90°, field of view (FOV) = 24 cm, matrix = 64 × 64). Thirty-five 4 mm thick contiguous axial slices were selected so as to provide coverage of the entire brain every 3 s (TR = 3 s; voxel size = 3.75 mm × 3.75 mm × 4.0 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, 4 mm thickness) 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 = 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 trial was comprised of a rest period (9 images/location; 27 s) followed by Pacing (7 images/location; 21 s), delay (0, 1, 2, or 3 images/location) and Continuation (7 images/location; 21 s) conditions respectively (Fig. 1). A total of six trials (blocks) were presented for each of the eight experimental conditions resulting in a total of 48 trials completed in two blocks of 24.

2.4. 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 & Kelso, 1992).

2.5. Neuroimaging analysis

Unless otherwise stated, all analyses were performed using AFNI (Cox, 1996; Cox & Hyde, 1997) installed on a PC running Linux. All data were pre-processed in the same way. Data were corrected for motion by aligning all images in a session with the first image of the session. Images were then spatially smoothed with a Gaussian kernel with a full width at half maximum of 6 mm. High frequency noise was reduced by applying filtering in the time domain with a lowpass of 0.1 Hz. Model covariates representing each pacing and continuation condition were constructed by placing ones at time points in which the specific condition was being performed and zeros otherwise. To account for inherent low pass filter properties of the neurovascular system, each covariate was convolved with a canonical hemodynamic response model. Multiple regression analysis was used to determine the relative contribution of each covariate to the observed time series data from each voxel for each subject. As a final step prior to second level analysis, statistical data were co-registered with high-resolution anatomical images (SPM99) and transformed into the coordinate space of Talairach and Tournoux (1988). In order to allow generalization to the population, a random effects analysis of variance (ANOVA) was performed on the regression beta weights of each subject. As a final step images were corrected for multiple comparisons (voxels) using a combined threshold and cluster approach as implemented in the AFNI software package. Statistically significant clusters were defined as regions of active voxels that exceeded a minimum threshold of $P < 0.01$ and a spatial extent of 832 mm^3 (corrected to $P < 0.05$).

To assess the effect of increasing the delay on BOLD signal amplitude, a two-way ANOVA with factors of delay (0, 3, 6, and 9 s) and Pattern (syncopate and synchronize) was performed on the data from the continuation phase. Of particular interest was a determination of whether parametrically increasing the delay resulted in a systematic decrease (or increase) in BOLD amplitude in brain areas related to the representation of the temporal interval. In regions not

differentially activated by manipulation of coordination pattern, effects of the delay would be observed as a main effect of delay. In areas that were more active following syncopation than synchronization (Jantzen et al., 2004) such a decay would be identified as a Pattern by Delay interaction.

The remaining experimental effects were assessed by collapsing across delay using a two-way ANOVA with factors of Pattern (Synchronize, Syncopate) and Task (Pacing, Continuation). In this experiment, context dependence in neural activity is identified as a main effect of Pattern occurring in brain areas that demonstrate coordination related differences during both pacing and continuation. In contrast are areas that, while differentially activated for synchronize and syncopate coordination patterns, are not related to the maintenance of temporal information across the delay period. These areas are expected to be differentially activated during pacing and not during continuation resulting in a significant interaction term. Finally, areas that are more active during pacing than continuation (including regions related to processing of the auditory signal) as well as areas more active during continuation than pacing will be revealed by a main effect of Task.

3. Results

3.1. Behavior

During Pacing conditions participants accurately performed the requested coordination pattern with synchronized responses occurring close to the required 0°, and syncopated close to the required 180° (Fig. 2A, left). Responses tended to be slightly delayed with the peak compression of the pillow occurring slightly after the metronome for synchronization and slightly beyond the midpoint between metronome beats for syncopation. Stability of performance is represented by the standard deviation of relative phase as shown on the right of Fig. 2A. Both conditions were performed in a stable fashion with synchronization being slightly less variable (S.D. = 14.53°) than syncopation (S.D. = 22.35°). A between subject two tailed, paired *t*-test revealed this difference to be significant ($t_9 = 3.52$, $P = 0.0078$), a finding consistent with previous behavioral evidence (Kelso et al., 1990).

The mean (across subjects) inter-response interval (IRI) for all conditions and delays is shown in Fig. 2B. A three-way ANOVA was performed on the mean response interval with factors of Pattern (syncopate, synchronize), Task (pacing, continuation) and Delay (0, 3, 6, and 9). A significant ($F_{1,126} = 8.85$, $P = 0.0036$) Task × Pattern interaction was found. Inspection of part B of Fig. 2 shows clearly that the interaction results from a consistent increase in IRI (decrease in movement rate) of approximately 80 ms for the continuation following from syncopation condition (open circles). This increase occurred across all delays and was not observed for pacing conditions or for conditions in which continuation followed synchronization.

Stability of performance was assessed through inspection of the standard deviation of the IRI (Fig. 2C). For all conditions the standard deviation was relatively low, ranging between approximately 18 and 25 ms; values in the range of 3% of the total movement interval. Nevertheless, a three-way ANOVA revealed that the standard deviation during continuation conditions (open symbols) was significantly larger than that seen during pacing conditions ($F_{1,127} = 22.35$, $P < 0.001$). Although continuation was performed with greater variability than pacing, the two conditions were not significantly different from each other. Thus,

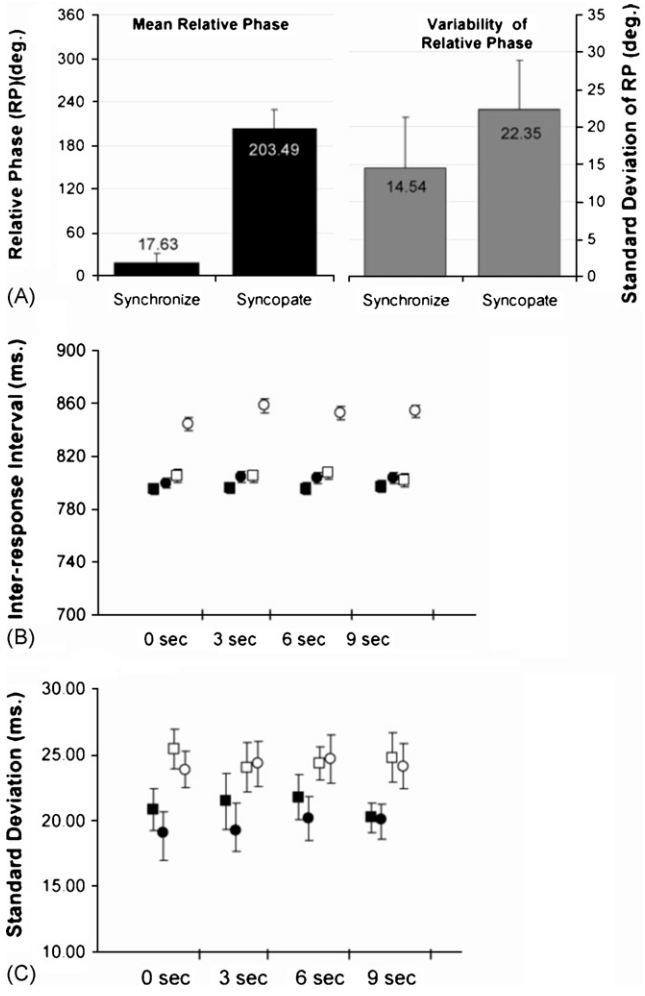

Fig. 2. Panel A depicts the between subject average (and standard error) of the mean relative phase (black bars) and standard deviation (grey bars) for both synchronization and syncopation during the pacing phase. The average of the mean (B) and standard deviation (C) of the inter-response interval is plotted as a function of delay for all conditions. Filled markers represent the pacing conditions and open markers represent continuation conditions. Synchronization conditions are shown as squares and syncopation as circles. Error bars are set at one standard error.

the small but consistent decrease in variability observed during pacing likely reflects the stabilizing effect of the metronome. In addition, the introduction of a variable delay appeared to have no impact on either the stability or the accuracy of the movements performed during continuation.

4. Neuroimaging

4.1. Delay effect

Focusing on data from continuation conditions allowed for an investigation of whether parametric increases in delay resulted in a gradual decrease or increase in BOLD amplitude in areas of the brain putatively related to the memory of temporal information. Such an effect could be observed as a main effect of delay, in which case activity following both synchronization and syncopation would respond similarly to increasing delays.

Alternatively, the occurrence of a Pattern × Delay interaction would indicate that a given brain area was specific to either synchronize or syncopate, and responds by increasing or decreasing its activity depending on delay. The results of the ANOVA, however, did not result in any significant main effects of Delay or Pattern × Delay interactions. To ensure that the lack of an interaction terms was not due to the application of an overly strict statistical threshold or cluster size requirement, we reduced the cluster size criteria from 832 to 200 mm^3 (uncorrected $P < 0.01$) with no change in results. The lack of any significant results related to the delay term allowed for the remainder of the statistical analysis to be performed by collapsing across delay.

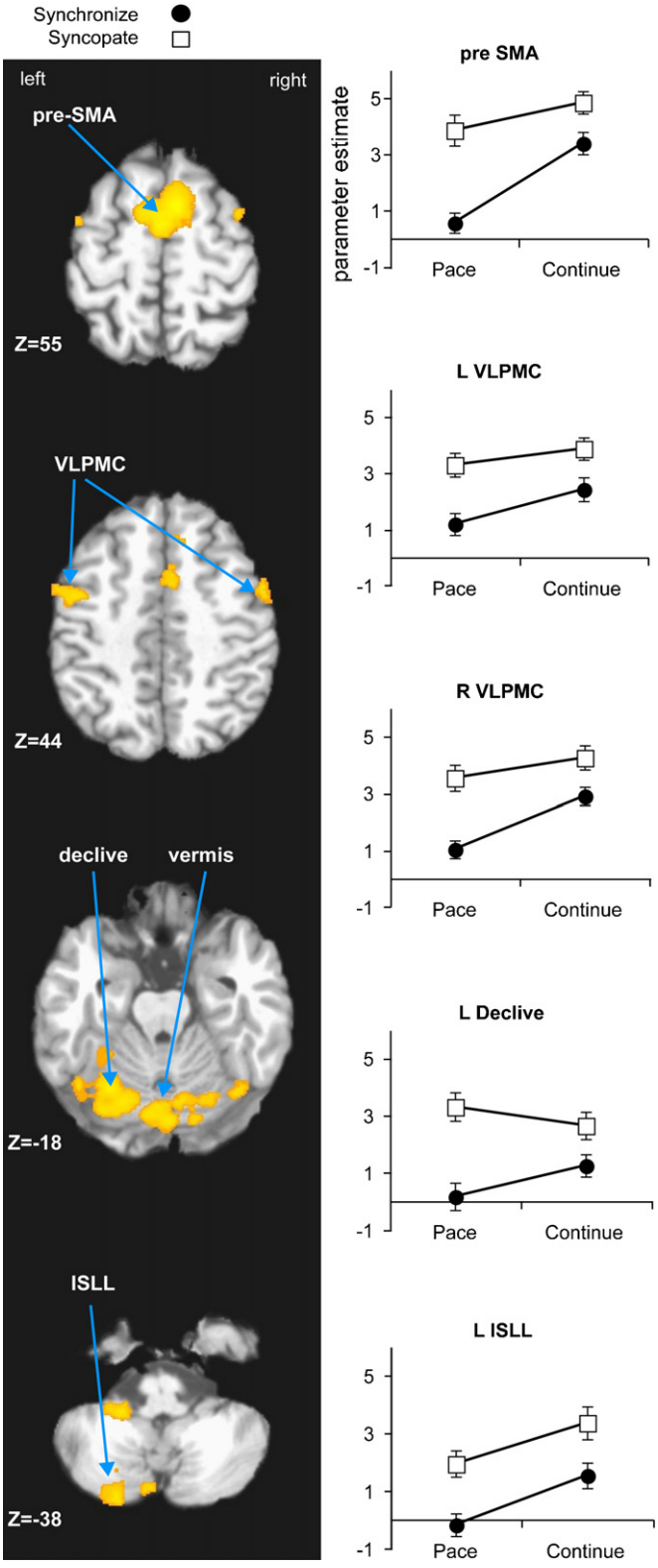

Fig. 3. Cortical and subcortical brain regions demonstrating a main effect of coordination pattern are shown in color overlaid on selected slices of a canonical brain in the coordinate space of Tailarach and Tournoux. Plots on the left show the mean (across subject) parameter estimates (Beta weight for peak voxel in the cluster) from the two pacing conditions (synchronize: black circle; syncopate: white square) during both encoding (pacing: left) and recall (continuation: right) phases. Error bars depict the standard error. From these plots it is evident that the main effect in all areas reflects the significantly greater activity during syncopation than synchronization across both phases of the trial. Areas demonstrating this effect are pre-supplementary motor area (pre-SMA), left and right ventro-lateral premotor cortex (VLPMC) bilateral (declive) and medial cerebellum and inferior cerebellum in the inferior semilinar lobule (ISSL).

5. Pattern × Task effects

Brain areas demonstrating a main effect of Coordination Pattern are shown in Fig. 3 as colored regions overlaid on a canonical brain. Table 1A provides details concerning the Talairach coordinates, anatomical location, Brodmann classification and peak *T*-value of each significant cluster of voxels. A significant main effect was observed in the pre supplementary motor area (pre-SMA), the region of the medial aspect of the middle frontal gyrus anterior to the VAC line (Rizzolatti, Luppino, & Matelli, 1996); bilateral ventro-lateral premotor cortex (VLPMC) and the left inferior semi lunar lobule of the cerebellum. In addition a large superior cerebellar cluster was identified as having a peak in the left declive and encompassed both bilateral vermis and portions of the right declive of the cerebellum. The parameter estimates (beta weight expressed in arbitrary units) from each condition are plotted alongside the statistical maps in Fig. 3. It is clear from these plots that BOLD signal amplitude was greater for syncopation than synchronization for all areas, and that this increase persisted during continuation despite the lack of the metronome and coordination constraints. Moreover, such differences persisted despite the imposition of a physical delay suggesting that neural activity in these areas either remained active during the delay or was re-established after the delay, i.e., during continuation. In addition, there was a trend for BOLD amplitude to increase from pacing to continuation in all but one cluster; however, this increase was not significant for any region but the SMA (see main effect of task results). No brain areas were more active for the synchronization condition.

When using the predefined volume corrected threshold of $P < 0.05$, a Pattern by Task interaction was observed only in the left putamen (Fig. 4 and Table 1B). Here again we investigated whether the general lack of an interaction term was due to the application of a strict statistical threshold by reducing the cluster size criteria from 832 to 200 mm^3 resulting in an uncorrected threshold of $P < 0.01$. Under this new criterion, additional interaction effects were identified in clusters in the right putamen and the right SMA-proper (caudal to the VAC line). The nature of

Table 1
Location of significant Pattern × Task effects in Talairach coordinates

Anatomy		BA	X	Y	Z	T
A. Main effect of Pattern: syncopate > synchronize						
MFG	R	6	39	2	56	3.56
SMA	B	6	8	6	55	5.467
MFG	L	6	−43	−1	49	4.37
MFG	R	6	54	1	42	4.8
Declive	L	–	−27	−61	−18	4.88
Culmen	L	–	−36	−36	−28	4.96
ISSL	L	–	−23	−77	−38	4.56

Anatomy		BA	X	Y	Z	F
B. Pattern × Task interaction						
SMA Proper	R	6	9	−1	53	9.62*
Putamen	L	BA-	−23	−3	4	9.68
Putamen	R	–	27	−4	−3	8.49*

Anatomy		BA	X	Y	Z	T
C. Main effect of Task: Pacing > Continue						
STG	L	41	−44	−19	11	8.96
STG	L	22	51	−18	10	10.52

Anatomy		BA	X	Y	Z	T
D. Main effect of Task: Continue > Pacing						
IFG	L	47	−36	24	−12	6.75
IFG	R	47	47	19	−9	7.15
DLPFC	L	46/10	−42	41	2	6.24
IFG	R	46	46	43	10	7.05
MTG	L	37	−59	−50	−5	7.24
MTG	R	21	61	−37	2	6.36
Ang. Gyrus	L	39	−50	−60	34	6.04
IPL	R	40	47	−58	46	5.33
SMA proper	B	6	4	−11	66	7.4

MFG: middle frontal gyrus; SMA: supplementary motor area; ISSL: inferior semilunar lobule; STG: superior temporal gyrus; IFG: inferior frontal gyrus; DLPFV: dorsolateral prefrontal cortex; MTG: middle temporal gyrus; IPL: inferior parietal lobe. Inf: inferior; B: bilateral; R: right; L: left; BA: Brodmann area. *Significant at uncorrected $P < 0.01$.

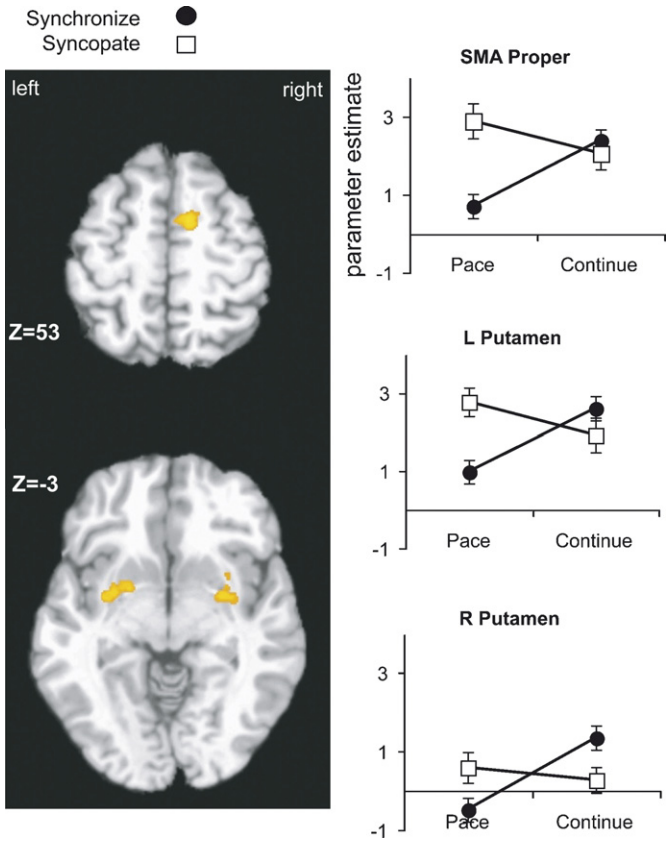

Fig. 4. Cortical and subcortical brain regions demonstrating a Pattern × Task interaction are shown in color overlaid on selected slices of a canonical brain in the coordinate space of Tailarach and Tournoux. Plots on the right show the mean (across subject) parameter estimates (Beta weight for peak voxel in the cluster) from the two pacing conditions (synchronize: black circle; syncopate: white square) during both pacing (left) and continuation (right) phases. Error bars depict the standard error. From these plots it is evident that the interaction arises because of the initial difference between syncopate and synchronize observed during pacing. During continuation, these differences are no longer observed as activity converges to an intermediate level. Areas identified are SMA proper, and bilateral putamen of the basal ganglia.

the interaction is revealed by investigation of the individual beta weights for each cluster (Fig. 4). During pacing significantly greater BOLD signal strength was observed during syncopation than during synchronization. During continuation, however, coordination dependent differences in BOLD amplitude were no longer observed; instead the signal amplitude tended to converge to a new intermediate value. This was particularly true for the SMA and left Putamen, locations where continuation appears to place similar hemodynamic demands regardless of the mode of temporal encoding. An exception occurred for the right Putamen in which there appears to be a reversal in activity from pacing to continuation. The importance of this result is debatable because, as can be seen from the amplitude of the BOLD signal, that activity in this region was not significantly above baseline for any of the four conditions portrayed.

Figs. 5 and 6 depict brain areas demonstrating a main effect of task (listed in Table 1C and D). Significantly greater BOLD amplitude during pacing compared to continuation was observed in bilateral superior temporal gyrus within the area of Heschel's gyrus (Fig. 5 and Table 1C). These auditory processing areas were activated similarly for both synchronized and syncopated pacing with no subsequent BOLD activity observed during continuation. The foregoing pattern of activity is consistent with previous results (Jantzen et al., 2004, 2005) and suggests that in the present context, the auditory cortex adopts a pattern independent role in the processing of the auditory pacing stimulus.

An increase in BOLD signal strength during Continuation compared to Pacing was observed across a broad frontoparietao-temporal network that included bilateral dorsal (BA 46) and ventral (BA 47) prefrontal cortex, anterior portions of bilateral middle temporal gyrus, right inferior parietal lobe, left angular gyrus and the SMA (Fig. 6 and Table 1D). Inspection of the associated plots of the parameter estimates confirms that, with the exception of the SMA, activity in these areas did not differ between syncopation and synchronization and that the brain areas were active only during continuation and not during pacing (beta weights near zero for the latter). The SMA cluster, on the other hand, was both more active during syncopation than synchronization and showed increased activity from pacing to

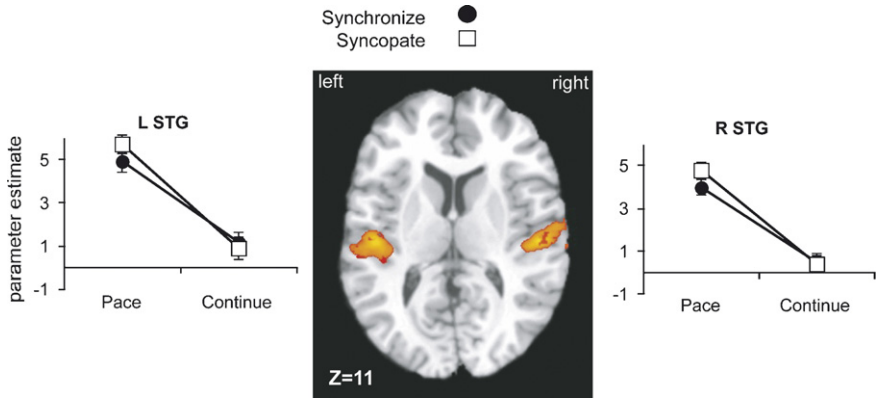

Fig. 5. The brain regions demonstrating greater activity for the pacing compared to continuation phases of the task (main effect of task) are shown in color overlaid on selected slices of a canonical brain in the coordinate space of Tailarach and Tournoux. Clusters are restricted to bilateral superior temporal gyrus (STG) in areas compatible with primary auditory processing cortex. The associated parameter estimate plots confirm that activity in these areas was observed only during pacing and not continuation, a pattern of activity consistent with a role in processing the auditory metronome.

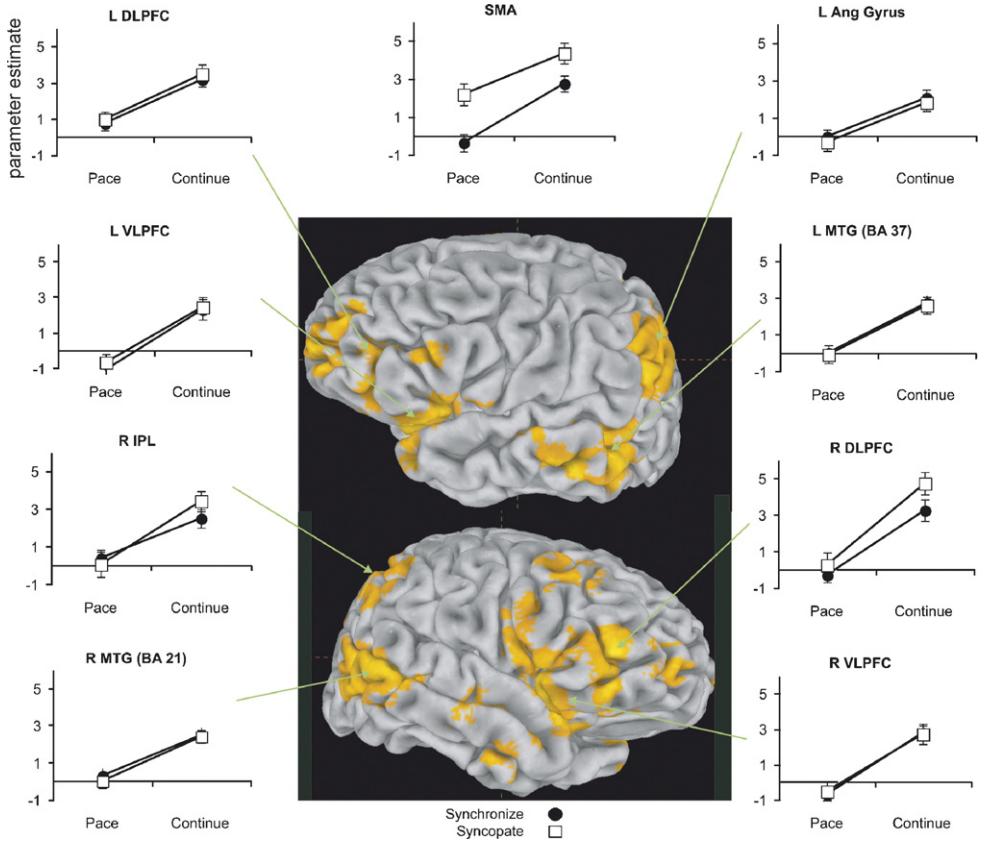

Fig. 6. The brain regions demonstrating greater activity for continuation compared to pacing phases (main effect of task) are shown in color on a three-dimensional representation of a canonical brain viewed from the left (top) and right (bottom). The associated plots of the parameter estimates confirms that, with the exception of the SMA, activity in all clusters was similar for both coordination modes. Moreover, these brain areas were not active during pacing, becoming active either during or following the delay period. SMA: supplementary motor area; VLPFC: ventrolateral prefrontal cortex; DLPFC: dorsolateral prefrontal cortex; MTG: middle temporal gyrus; Ang Gyrus: angular gyrus; IPL: inferior parietal lobe.

continuation (see also top panel in Fig. 3) indicating that this region was sensitive to both Task and Pattern.

6. Discussion

In previous reports we have demonstrated context dependence in a network of brain regions recruited to support simple self-paced timing tasks (Jantzen et al., 2004, 2005). Such findings suggest that timing related processes are flexible and may be rooted in other sensorimotor or cognitive processes. This conceptual approach is compatible with the idea of "emergent timing" as lately promoted by Zelaznik and colleagues (Zelaznik et al., 2005; see also Fowler, Rubin, Remez, & Turvey, 1980; Kelso & Holt, 1980; Kelso, Holt, Rubin, & Kugler, 1981; Kelso,

Southard, & Goodman, 1979; Kelso & Tuller, 1987; Ivry & Spencer, 2004; Turvey, 1977) where timing emerges from the dynamic processes underlying an ongoing movement without the need for an explicit representation of temporal information. This framework is also in line with modeling work demonstrating how timing information may be derived from short term plastic changes in generic cortical networks (Buonomano, 2000). Such work suggests that any network of cortical neurons may be capable of forming a representation of time (Buonomano, 2003). In the present framework timing information is mediated via a network of brain areas that is engaged to meet the specific sensory, motor and cognitive demands of the associated coordination behavior. Viewed in such a light, timing information is implicit within the functional action and interaction of these areas and arises from the basic sensorimotor processes of the coordination task (e.g. Lewis & Miall, 2003). As such, the engagement of coordination-specific patterns of neural activity, therefore, implies differential representation of temporal information.

This research specifically tested the hypothesis that the neural processes underlying timing are at least partially rooted in the sensorimotor networks engaged to extract timing information from the environment. Using a continuation paradigm we began with the hypothesis that aspects of temporal processing important to continuation are rooted in the coordination dependent pattern of activation generated during pacing (Jantzen et al., 2004). By imposing a delay between pacing and the subsequent continuation phase of this classic paradigm we hypothesized that coordination dependent differences in neural activity related to processes other than memory storage and retrieval should be reduced. Alternatively, differences in neural activity that represent context-dependent encoding and storage of temporal information were predicted to persist because this information is required for accurate performance during continuation. In support of these hypotheses, the results revealed a functional dissociation between task-dependent and context-dependent networks. In task dependent regions, namely basal ganglia and SMA, coordination related differences in neural activity were observed during pacing only; the pattern of BOLD changes was no longer present during the continuation period. In context-dependent regions that include pre-SMA, lateral premotor cortex and cerebellum, initial BOLD differences between synchronized and syncopated coordination patterns persisted during continuation even after a physical delay of up to 9 s. This result suggests a context-dependent representation of temporal information. An additional third set of brain regions became active only during the continuation phase of the task and may play a secondary role in supporting the memory of the temporal interval during and following the delay. The current data provide support for our hypothesis by showing that a context-dependent network for timing information is reengaged when the designated time interval is to be subsequently reproduced, despite the absence of the original behavioral or cognitive constraints. This implies that the short-term storage of temporal information arises through the interaction between multiple discrete brain areas that are selected in a context-dependent manner.

6.1. Task dependent brain regions

Coordination related differences in BOLD activity within bilateral putamen and SMA proper did not persist during continuation regardless of the presence or duration of the delay in motor activity. With respect to our original hypothesis, it would appear that activity in these areas is not related to the context-dependent representation of temporal information and instead may mediate motor or cognitive processes specific to performance of the individual coordination patterns. One possibility strongly supported by evidence from the literature is that activity in these areas is related to the explicit timing demands of the task. SMA and putamen form part of a closed basal ganglia-thalamacortical loop or "motor" circuit with the SMA providing the primary cortical input as well as acting a major output target (Alexander, Delong, & Strick, 1986; Graybiel, Aosaki, Flaherty, & Kimura, 1994; Nakano, 2000). Imaging studies in humans support the role of this dopamanergic network in both the perception of time and the generation of timed actions (Harrington & Haaland, 1999; Rao, Mayer, & Harrington, 2001; Schubotz, Friederici, and von Cramon, 2000). Indeed, patients suffering from Parkinson's Disease, characterized by dopamine depletion within the basal ganglia, demonstrate deficits in both time production and perception (Freeman, Cody, & Schady, 1993; Harrington, Haaland, & Hermanowicz, 1998; Nakamura, Nagasaki, & Narabayashi, 1978). Lesions of the caudate and putamen (Meck, Church, Wenk, & Olton, 1987) as well as pharmacological manipulation of basal ganglia function (Maricq, Roberts, & Church, 1981; Meck, 1996) have led to suggestions that this circuit acts as a central neural clock source by providing explicit time information to other neural systems involved in the storage, retrieval and comparison of temporal information (Meck, 1996). This suggestion has gained support from recent fMRI investigations demonstrating that basal ganglia activity is likely related to processes associated with encoding temporal information as opposed to storage or recall (e.g. Nenadic et al., 2003; Rao et al., 2001); however, the exclusive role of this circuit in the generation of an internal timing signal is still controversial and awaits definitive evidence. For instance, recent animal (Matell et al., 2003) and human (Malapani & Rakitin, 2003) studies have suggested that BG may play a role in both the encoding and storage of temporal information.

Activity in SMA and putamen was greater for syncopation than synchronization during pacing and converged to an intermediate level during Continuation. This pattern of activity highlights the differential timing demands of the various experimental conditions. The minimal demand on these brain areas during synchronization is compatible with the suggestion that the sensory-guided pattern of rhythmic movement is carried out relatively automatically (Monno, Temprado, Zanone, & Laurent, 2002; Temprado, Monno, Zanone, & Kelso, 2002) without a need for ongoing reference to an internal timing source (Mayville et al., 2002). The subsequent increase during continuation likely reflects the additional timing demands of switching from an external (metronome) to an internal timing source. The stronger activity in these areas during syncopation may reflect the relatively greater reliance on an internal timing source when

performing this pattern. Previous imaging work has suggested that, compared to synchronization, syncopation is organized on a more discrete movement-by-movement basis in which individual movements are planned and timed separately in response to each metronome beat (Mayville et al., 2002; see also Schaal, Sternad, Osu, & Kawato, 2004). Importantly, the convergence of activity within these areas to a common level during continuation confirms that the processes they support, be it the generation of temporal information or otherwise, are not context dependent, instead appearing to reflect underlying timing demands in a task dependent manner. As a final note it is worth remarking that although the data presented in Fig. 4 are consistent with the foregoing discussion, they should be regarded with slight caution in light of the relaxed statistical criterion adopted.

6.2. Context-dependent brain regions

Brain areas that continued to exhibit coordination dependent differences in neural activity during Continuation included bilateral ventral premotor cortex, pre-SMA and two regions of the cerebellum; the declive (lobule VI of Schmahmann et al., 1999) as well as left inferior semi-lunar lobe (Lobule VIIb, Schmahmann et al., 1999). The lack of a main effect of Delay or a Task by Delay interaction indicates that BOLD differences within these regions were preserved regardless of variable delays of up to 9 s. Brain areas exhibiting this activity pattern can be functionally and structurally subdivided into general premotor and cerebellar networks. In the following we will discuss the putative role of the brain areas in timing and memory within the context of the current experiment.

6.3. Premotor cortex, timing and memory

Lateral and medial premotor cortical regions have a well-established role in specific cognitive functions such as motor planning and preparation (e.g. Picard & Strick, 2001). Evidence from the literature also suggests a generalized role for these brain areas in implicit timing and memory and supports the notion that they can provide a central temporal representation (e.g. Lewis & Miall, 2003). The pre-SMA is defined in the AC-PC aligned brain as the portion of the medial middle temporal gyrus anterior to a line passing vertically through the anterior commissure (VAC) (Rizzolatti et al., 1996). Syncopation has consistently been shown to require greater activation in pre-SMA than synchronization (Jantzen et al., 2004; Mayville et al., 2002), a finding that has been attributed to a greater demand on cognitive processes such as motor planning, preparation and timing. Moreover, a growing number of imaging studies report timing related activation of the SMA (e.g. Lewis & Miall, 2003; Macar, Anton, Bonnet, & Vidal, 2004; Macar, Vidal, & Casini, 1999), although distinctions between SMA-proper and pre-SMA are seldom reported in timing studies. As such, the relative contribution of these structures remains less clear.

Although the specific timing related processes performed within pre-SMA are largely unknown, the present work suggests that this region may, together with lateral premotor areas, mediate processes critical for maintaining a cortical representation of the temporal interval in a context-dependent manner. The foregoing suggestion is compatible with both anatomical and functional evidence supporting the putative role of pre-SMA in working memory. In contrast to the SMA-proper which is highly interconnected with primary sensorimotor cortex, the pre-SMA shares dense reciprocal connections with prefrontal cortex (Rizzolatti et al., 1996), areas most recognized for their role in short term memory storage and retrieval (Jonides et al., 1996; Smith & Jonides, 1998). Moreover, the striatal-thalamic as well as cerebellar projections to pre-SMA and lateral premotor areas make them well situated to receive temporal information putatively generated by basal ganglia and cerebellar circuits.

Whereas lateral premotor cortex has traditionally been ascribed a role in the planning and preparation of externally guided movements (e.g. Wise, Boussaoud, Johnson, & Caminiti, 1997), several lines of evidence support the additional role of these areas in the memory of temporally specific information. In humans, lesions in lateral premotor cortex disrupt the ability to produce remembered temporal sequences (Halsband & Freund, 1990; Halsband, Matsuzaka, & Tanji, 1994). In primates, cells that are sequence specific as well as those that are active during the internal generation of a remembered motor sequence are found predominantly in dorsal premotor cortex (Mushiake, Inase, & Tanji, 1991). Recent neuroimaging studies have found premotor cortex to be active when performing motor sequences from memory (Grafton, Mazziotta, Woods, & Phelps, 1992; Shibasaki et al., 1993) and have shown that premotor cortical activity increases with the duration of the sequence to be performed (Catalan, Honda, Weeks, Cohen, & Hallett, 1998). The fact that premotor areas display persistent differences following relatively long delay periods of up to 9 s suggests that these brain areas, in addition to roles they may play in the planning, preparation and execution of movements, participate in the formation and maintenance of an implicit representation of temporal information. In support of this notion, a recent meta-analysis has shown that pre-SMA together with both dorsal and ventral portions of the lateral premotor cortex are commonly activated by classic working memory paradigms (Owen, McMillan, Laird, & Bullmore, 2005), a finding that attests to the general mnemonic role of the premotor cortex. Importantly, the present study demonstrates that the engagement of premotor areas for temporal memory occurs in a context-dependent manner, seeming to depend on whether these brain areas were recruited during an initial acquisition phase. This result suggests that these brain areas, while putatively recruited in response to the additional processing demands of syncopation, also provide a representation of temporal information during pacing and during continuation. The fact that coordination dependent differences within these areas persist after relatively long temporal delays bolsters this argument by making it less likely that this activity is related to the persistent adoption of a sensorimotor strategy.

6.4. Cerebellum and timing

Our results indicate that both bilateral superior and left inferior cerebellum exhibit a pattern of activity consistent

with the need to maintain a representation of temporal information during continuation. Whereas traditional views have emphasized the involvement of the cerebellum in the control of motor behavior and coordination, there is now substantial evidence that the lateral cerebellum also plays an important role in human timing (Ivry, 1996; Ivry & Keele, 1989; Ivry & Spencer, 2004; Lewis & Miall, 2003; Penhune et al., 1998). However, recent lesion (Harrington, Lee, Boyd, Rapcsak, & Knight, 2004) and imaging (Rao et al., 2001) studies that fail to confirm a cerebellar role in timing underscore the difficulty in consistently identifying the specific role this area plays. Recent evidence has led to the hypothesis that the cerebellum provides a signal specifying the timing of events within an event structure (Ivry & Spencer, 2004; Ivry, Spencer, Zelaznik, & Diedrichsen, 2002; Spencer, Zelaznik, Diedrechsen, & Ivry, 2003). That is, the cerebellum provides information concerning the temporal relationship between discrete or separable events. In contrast, timing of continuous movements lacking such a structure may arise as an emergent property of the underlying control processes (Ivry et al., 2002; Spencer et al., 2003). Within this framework, the present findings suggest that activity in lateral cerebellum may be engaged not only in the specification of an event structure, but also in the memory related representation of this structure and the temporal information it embodies. Consequently, although no temporal structure (or at least the same structure for synchronized and syncopated continuation) is explicitly specified during reproduction in this experiment, cerebellar activity (in conjunction with a broader cortical network) continues to reflect the temporal structure or pattern imposed during encoding. Therefore, while these results do not argue either for or against the role of cerebellum in providing an explicit representation of time, they do argue that in addition to the role of this structure in Pacing it also appears to play a critical context-dependent role in maintaining performance across delays.

Activity in the semilunar lobe of the cerebellum is not commonly reported in studies of coordination or timing. However, a series of studies has demonstrated the importance of the inferior lobule VIIB (a region compatible with the inferior semi-lunar lobule) in memory functions (reviewed by Desmond & Fiez, 1998). Chen and Desmond (2005) recently demonstrated a role for both superior lateral and inferior lobule in articulatory and phonological storage respectively. Results from the same group have also demonstrated a relationship between memory load and BOLD signal changes in inferior cerebellum (Kirschen, Chen, Schraedley-Desmond, & Desmond, 2005). Such findings, while interpreted exclusively within in the context of verbal working memory, highlight the putative role of inferior cerebellum in more general mnemonic processes. Since activity in the inferior portions of the cerebellum is not often observed during coordination, the activity in the present context may be related to specific sensorimotor memory demands imposed by the introduction of the delay. Given the novelty of finding activity in this region, however, it's specific role in temporal processing and coordination, particularly with reference to synchronized and syncopated movement patterns, remains to be clarified.

6.5. Continuation specific activity

A third set of brain regions was more active during continuation when compared to pacing regardless of the original coordination pattern performed. This network, composed of the bilateral dorsal and ventral prefrontal cortex, middle temporal gyrus (BA 37, 22) and bilateral parietal lobes, has been classically identified in tasks involving verbal, spatial and object working memory (Smith & Jonides, 1998, 1999). Such a network may reflect the cooperation between an implicit representation of the temporal interval (which we believe is rooted within the motor system, broadly conceived) and explicit working memory processes. This working memory network may have become active during the delay interval in order to provide mnemonic support in the absence of an active (motor based) representation of the movement interval. Such a conjecture fits well with previous work demonstrating a preferential role of prefrontal cortex in timing tasks that have a working memory component (Mangels, Ivry, & Shimizu, 1998). An anatomical basis for coupling this classic working memory system into the motor timing network identified in the present study is provided by strong reciprocal connections between prefrontal cortex and pre-SMA (Rizzolatti et al., 1996). However, the present interpretation remains tentative since this working memory network was found to be active even when there was no delay imposed (i.e. no Task × Delay interaction) and recent imaging work suggests that prefrontal portions of the network may play a more primary role in timing than previously suspected (Smith, Taylor, Lidzba, & Rubia, 2003).

Because the present work was primarily interested in recall of the temporal interval, a delay period of only 1–3 TRs was employed (3–9 s). Future studies would benefit from a lengthening of this interval to investigate how timing information is represented across the empty delay. If the same network is activated for even longer delays than imposed here, it may also be interesting to investigate network changes when new task conditions are introduced. Also, given the relatively short delay periods employed here it is possible that participants are adopting a mental rehearsal strategy to maintain the temporal interval across the delay. This explanation seems unlikely because such a strategy would not predict the differences in neural activity observed during continuation. That is, imagining the metronome should generate similar patterns of neural activity regardless of the preceding coordination pattern. Alternatively, recent evidence concerning the role of imagination in mediating neural patterns related to sensorimotor coordination (Oullier et al., 2005) leads to the suggestion that participants may be maintaining an explicit representation of the collective sensorimotor pattern as opposed to the motor or auditory components alone. The notion that subjects adopt different timing strategies during imagination of syncopated and synchronized patterns of coordination predicts that increased activity in basal ganglia and SMA should be observed for both performed and imagined syncopation. Therefore, while this suggestion cannot be completely discounted, the lack of such persistent activity in this striatal-cortical circuit provides preliminary evidence to the contrary.

7. Conclusions

There is growing support for the idea that at least some timing processes postulated by psychological models are rooted in basic sensory-motor processes. One emerging principle is that the topological organization of information in the cortex is influenced in part by an interaction with different perceptual and motor systems (Gabrieli, 1998), an observation supported by functional imaging research (Wheeler, Petersen, & Buckner, 2000). Similarly, timing tasks that involve different stimulus modalities will likely engage sensory specific brain areas for the representation and processing of temporal information (Jantzen et al., 2005). The present findings are in agreement with previous work (Jantzen et al., 2004) and appear to support the idea that the nature of the neural basis of interval timing changes depending on how temporal information is initially provided or encoded. Our observations provide additional support for the role of these brain areas in mediating a representation of the interval, since introducing a physical delay between pacing and continuation did not reduce differences in brain activity during continuation. Finally, in opposition to direct mapping approaches that promote the existence of generalized or centralized timing modules, the current data favor the hypothesis that at least some timing mechanisms are distributed throughout large scale cortical and subcortical networks and are recruited in a task dependent manner.

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