The evolution of brain activation during temporal processing

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Timing is crucial to many aspects of human performance. To better understand its neural underpinnings, we used event-related fMRI to examine the time course of activation associated with different components of a time perception task. We distinguished systems associated with encoding time intervals from those related to comparing intervals and implementing a response. Activation in the basal ganglia occurred early, and was uniquely associated with encoding time intervals, whereas cerebellar activation unfolded late, suggesting an involvement in processes other than explicit timing. Early cortical activation associated with encoding of time intervals was observed in the right inferior parietal cortex and bilateral premotor cortex, implicating these systems in attention and temporary maintenance of intervals. Late activation in the right dorsolateral prefrontal cortex emerged during comparison of time intervals. Our results illustrate a dynamic network of cortical-subcortical activation associated with different components of temporal information processing.

Humans are remarkably proficient at perceiving the passage of time and producing precisely timed behaviors, many of which depend upon explicit prospective temporal judgments. For these events, multiple processes seem to determine our subjective perception of current time for intervals lasting several hundreds of milliseconds to several seconds. Most theories of prospective timing embody similar components[1], including an internal timekeeper, attention and memory[2,3]. A clock metaphor is used to describe the timekeeper mechanism, which represents subjective time through the accumulation or readout of pulses, possibly generated by oscillators. Our perception of time, however, is intimately related to the level of attention given to the passage of time. When attention is diverted, a systematic shortening of subjective duration occurs, implying that pulses from the timekeeper may be lost[4]. Attention may also mediate the flexible starting and stopping of pulses from the timekeeper, which enables anticipation of predictable events[5]. Hence, a representation of subjective time emerges from the interplay between timekeeping and attention mechanisms. This representation is then passed on to working memory, a short-term repository where interval representations are maintained and manipulated in accord with current goals (for example, comparing two intervals of time)[6]. Working memory functions can therefore alter stored representations of time as well. The combination of these different component processes gives rise to the subjective perception of time, although the relative contribution of each might differ depending on the interval duration or the cognitive demands of timing events[7].

The neural systems that support different component processes of time perception are a matter of debate. The basal ganglia and lateral cerebellum have been logical candidates for hypothetical timekeeping operations, as damage to these brain regions commonly disrupts behaviors that depend upon precise timing, such as rhythmic movements in Parkinson's disease[8] and regulation of agonist–antagonist muscle activity (for example, dysmetria) in cerebellar damage[9]. Although these movement abnormalities could be attributed to disruption of more generalized motor execution functions, the basal ganglia and cerebellum do seem to mediate time perception. Studies of Parkinson's disease patients[10,11] and pharmacological investigations in animals[12,13] have argued that timekeeping operations are regulated through dopamine neurotransmission in the striatum. Human lesion studies indicate that the lateral cerebellar hemisphere and its primary output, the dentate nucleus[14–18], are also involved in timekeeping mechanisms. Nonetheless, it has been difficult to isolate timekeeping and attention operations from working-memory and response implementation processes[1]. Timing deficits after basal ganglia or cerebellar damage could also be due to abnormalities in interconnecting cortical systems commonly associated with some or all of these processes[19,20]. Fewer studies have examined the involvement of the cerebral cortex in time perception. Focal lesion investigations in animals and humans have shown that the frontal and parietal lobes are also essential for accurate time perception, perhaps due to their purported attention and working memory functions[14,21,22]. Others have posited a role for the supplementary motor area[23], but this has been difficult to assess because focal lesions are uncommon in this region.

Functional imaging techniques can be used to dissect the contribution of each component of multiple neural systems, although studies of timing using these methods have produced conflicting or ambiguous results to date[7]. Most research[24–27] has focused on motor timing, making it difficult to separate activa-

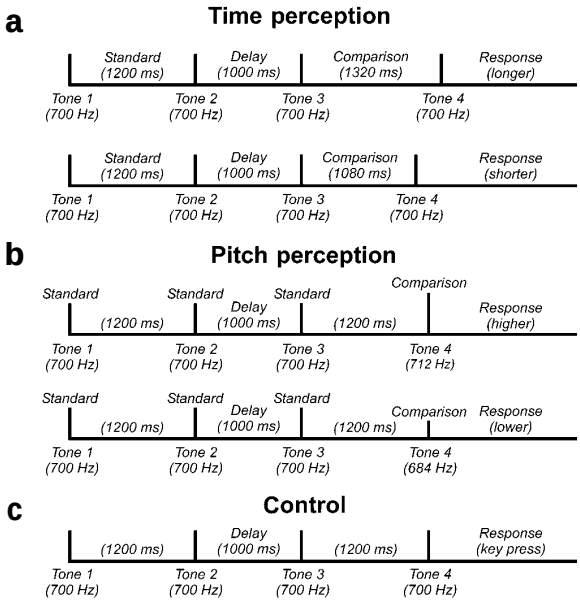

Fig. 1. Trial events in the time perception (**a**), pitch perception (**b**), and control (**c**) conditions. In the time perception condition, subjects indicated whether the comparison interval (defined by tones 3 and 4) was longer or shorter than the standard interval (defined by tones 1 and 2). In the pitch perception condition, subjects indicated whether the comparison tone (tone 4) was higher or lower in pitch than the standard tones (tones 1, 2 and 3). In the control condition, subjects pressed a key after the presentation of the four tones.

tion in systems traditionally associated with motor control, such as the basal ganglia and cerebellum, from those supporting timekeeping or other cognitive processes. Two PET studies[28,29] have specifically examined time perception. Unfortunately, the time scale of PET scanning is limited to blocked-trial designs that cannot disentangle processing associated with encoding an interval from processing associated with decision making and implementing a response. We reasoned that fundamental insights into this issue could be gained by studying the time course of brain activation patterns associated with different components of a time perception task. The present study exploited the finer temporal resolution of event-related functional magnetic resonance imaging (fMRI) to isolate patterns of brain activation that correlated with encoding time intervals from those associated with comparing two time intervals and implementing a response. Timing theory suggests that activation in systems integrally involved in encoding or formulating a representation of time (pacemaker and attention operations) should develop at the onset of a to-be-timed event[2,3], followed by activation in systems concerned with manipulating information in working memory (comparing intervals) and implementing a response.

We obtained fMRI scans of seventeen subjects as they performed three different tasks, the order of which was counterbalanced across subjects. In the time (T) discrimination condition, two tones (50 ms) separated by 1200 ms (standard tone-pair) were presented, followed by a 1-s delay and then a comparison tone-pair (Fig. 1a). Subjects indicated whether the comparison tone-pair was longer or shorter than the standard. To better separate neural systems specific to timing, subjects also performed a pitch (P) discrimination condition in which the auditory events were similar except that subjects indicated whether the fourth tone was higher or lower in pitch than the first three tones (Fig. 1b). Neural systems involved with processing time and pitch information were identified by contrasting imaging runs in each discrimination condition with a sensorimotor control (C) condition in which subjects responded after the presentation of two isochronous tone pairs of identical pitch (Fig. 1c). The T and P conditions were then contrasted to specify systems unique to time discriminations. These subtractions were conducted at each of four scanning intervals after trial onset (2.5, 5.0, 7.5 and 10.0 s). In all conditions, the typical motor response occurred approximately 4.5 s after trial onset (Fig. 2). Allowing 5 s for the hemodynamic response to peak, we proposed that the 2.5- and 5.0-s intervals after trial onset should reveal brain activation patterns specific to encoding time intervals. In contrast, the 10.0-s scanning interval should include activations associated with contrasting the standard and comparison intervals and implementing the response. Overlap between these processes should be particularly evident during the 7.5-s scan, due to encoding of the comparison interval. The results reported here show early sustained activation of the basal ganglia and right inferior parietal cortex, implicating these systems in formulating representations of time. Though activation in the cerebellum was more robust during time than pitch discriminations, activation was located in the vermis and unfolded late, suggesting a more general involvement in cognitive or sensorimotor functions. The evolution of activation in the bilateral premotor and right DLPF cortex differed from each other, consistent with previous work implicating these systems in different aspects of working memory.

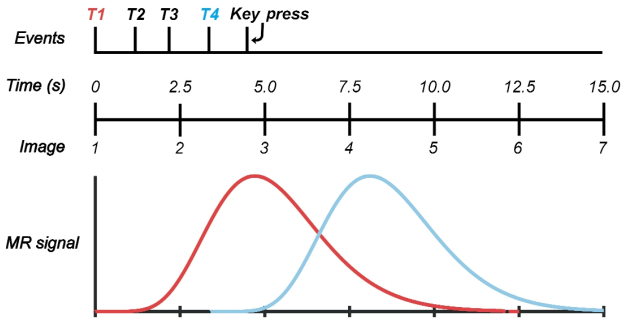

Fig. 2. Temporal relationship among the trial events, acquisition of images and hypothetical hemodynamic response functions to different task components. Seven scans were acquired during each 17.5-s trial (a 2.5-s interval between the seventh image and the first image of the next trial is not illustrated on the timeline). The first scan was acquired at the onset of the first tone (T1). The fourth tone (T4) was presented an average of 3.4 s after trial onset. The typical key press response occurred 4.5 s after trial onset. The two hypothetical time course functions illustrate early versus late MR signal responses to different trial events. An early response corresponding with the encoding of temporal information (red plot) would have a maximal signal change at 2.5 and 5.0 s after trial onset. In contrast, a late response due to decision making and response preparation processes (blue plot) would be observed primarily at 7.5 and 10.0 s after trial onset.

RESULTS

Behavioral data collected during scanning showed that response times and accuracy correlated with the difficulty of time and pitch discriminations. Reaction time was typically longer (Fig. 3a, $F_{5,76} = 4.2$, $p < 0.01$; Fig. 3c, $F_{6,87} = 4.0$, $p < 0.01$) and accuracy poorer (Fig. 3b, $F_{4,57} = 8.1$, $p < 0.001$; Fig. 3d, $F_{7,112} = 2.7$, $p < 0.025$) when the comparison stimuli were closer in time or in pitch to the standard stimulus. There were no significant differences between the two discrimination conditions in overall accuracy (T, 83 ± 3%; P, 78 ± 3%) or reaction time (T, 1111 ± 76 ms; P, 1076 ± 54 ms). Reaction times for the C condition (707 ± 39 ms) were significantly faster ($F_{1,16} = 48.9$, $p < 0.0001$) than those for the time and pitch conditions.

During the early imaging epochs (2.5 and 5.0 s), which emphasize encoding of temporal information, subcortical activations specific to the T condition (Table 1) were observed within the right putamen, head of the caudate nucleus bilaterally, and right centromedian and ventroanterior thalamic nuclei (Fig. 4a). Early activation specific to the T condition was also observed in various cortical regions (Fig. 5): right intraparietal sulcus (BA 40), bilateral dorsal and left ventral premotor areas (BA 6), and bilateral lateral temporal cortex (BA 21/22). Activation specific to the T condition was sustained during the 7.5- and/or 10.0-s imaging epochs in most of these regions. In the P condition, areas of activation during the early imaging epochs overlapped with those in the T condition. In both the T and P conditions (Table 2), activity unfolded early within the medial wall (preSMA and SMA proper, BA 6, and anterior cingulate, BA 32; Fig. 4c) and the anterior insula/frontal operculum (Fig. 4a), but was sustained during later epochs as well.

During the later imaging epochs (7.5 and 10.0 s), which included decision and response selection components of the tasks, activation specific to the T condition (Table 1) was observed in the posterior vermis (tuber) of lobule VIIB of the cerebellum (Fig. 4b) and the right dorsolateral prefrontal (DLPF) cortex (BA 46/10/9; Fig. 5). All other activation foci were observed in the left hemisphere in both the

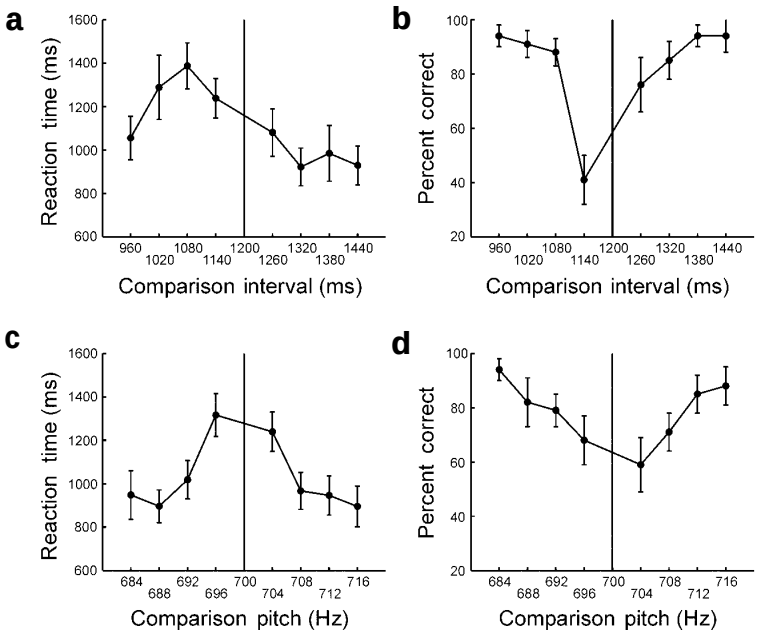

Fig. 3. Mean (± standard error of mean) reaction time and percent correct for the time perception (**a**, **b**) and the pitch perception (**c**, **d**) conditions. Data are depicted as a function of the comparison interval or comparison pitch.

Table 1. Stereotaxic brain atlas coordinates[49] for Time > Control subtraction.

Location (Brodmann Area)	Hemisphere	2.5	5.0	7.5	10.0
Basal Ganglia					
Medial caudate (head)	R		12, 7, 3	12, 6, 4	
	L		–12, 7, 5	–9, 7, 2	–8, 4, 8
Lateral caudate (body)	R				15, 6, 19
Putamen	R	22, 8, –1			23, 6, 8
					26, 6, –2
	L				–20, –1, 5
Cerebellum					
Vermis (tuber, lobule VIIB)	B			–3, –70, –30	2, –70, –29
Thalamus					
Centromedian nucleus	R		4, –21, 0	4, –21, 0	
Ventroanterior nucleus	R		4, –11, 0	5, –10, 0	
Frontal					
Dorsal premotor (6)	R		23, –7, 48	23, –3, 52	46, 1, 49
	L		–45, –7, 47		
Ventral premotor (6)	R		46, 8, 24		
	L	–54, –13, 26	–51, –15, 27		
Dorsolateral (46/10/9)	R			34, 23, 25	31, 46, 22
					41, 29, 22
Parietal					
Intraparietal sulcus, Angular gyrus (40)	R	38, –40, 41	36, –43, 40	37, –47, 38	30, –56, 35
Superior parietal lobule, Precuneus (7)	R				10, –68, 44
Temporal					
Superior temporal (22)	R		51, –39, 6		
Middle temporal (21)	L		–46, –56, 4		

R, right; L, left; B, bilateral. The activations reported in this table were not observed in the Pitch > Control subtraction.

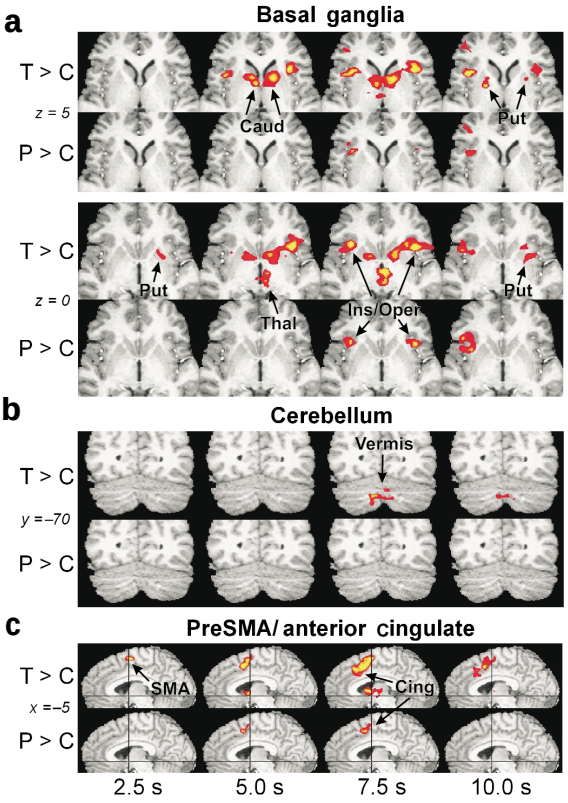

Fig. 4. Activation foci in the basal ganglia (**a**), cerebellum (**b**), and pre-supplementary motor area/anterior cingulate (**c**) resulting from subtraction of the control (C) condition from the time (T) and the pitch (P) perception conditions at 2.5, 5.0, 7.5 and 10.0 s after trial onset. Significant foci ($p < 0.001$) are displayed with a red-yellow intensity scale denoting greater activation for the T or P conditions. Slices are displayed in neurological view (left is on the viewer's left). Location of slices defined by the distance (mm) from anterior commissure: *x*, right (+)/left (–); *y*, anterior (+)/posterior (–); *z*, superior (+)/inferior (–). Caud, caudate nucleus; Cing, anterior cingulate area; Ins, insula; Oper, frontal operculum; Put, putamen; Thal, thalamus; SMA, supplementary motor area.

T and P conditions (Table 2), and included the inferior frontal gyrus (Broca's area, BA 44/45), intraparietal sulcus (BA 40), superior parietal lobule/precuneus (BA 7) and DLPF cortex.

The results from the T minus P subtraction were similar to the results for the T minus C subtraction (Fig. 6). During the earlier imaging epochs (2.5 and 5.0 s), subcortical activations unique to the T condition were in the right hemisphere and included the putamen (*x*, *y*, *z* = 24, 7, –2), caudate (15, 6, 13) and insula/frontal operculum (29, 16, 2). The later region, however, was also activated during the 7.5-s epoch in the pitch condition (Table 2, Fig. 4a). During the later imaging epochs (7.5 s), the right DLPF cortex (21, 21, 30) was also unique to the T condition (Fig. 6).

Discussion

The present findings provide compelling evidence for the involvement of the basal ganglia in formulating representations of time. Activation in the right putamen and caudate were uniquely associated with encoding time intervals. These results corroborate studies in Parkinson's disease showing that dopaminergic treatment improves motor timing[30,31] and time perception[32]. Pharmacological challenges in animals also suggest that dopaminergic antagonists and agonists respectively slow down and speed up timing operations[12,13]. Contrary to one proposal[33], these and other studies[10,11,27] show that the basal ganglia are involved in timing a wide range of intervals, from hundreds of milliseconds (300 ms) to tens of seconds (20 s). Collectively, these results implicate striatal dopaminergic neurotransmission in hypothetical internal timekeeping mechanisms.

Table 2. Stereotaxic brain atlas coordinates[49] for regions commonly activated in subtractions of Time and Pitch perception conditions relative to Control condition.

		Time > Control				Pitch > Control			
Location (Brodmann Area)	**Hemisphere**	**2.5**	**5.0**	**7.5**	**10.0**	**2.5**	**5.0**	**7.5**	**10.0**
Frontal									
Insula/operculum (47)	R		31, 17, 3	35, 16, 3	34, 17, 4			34, 17, 0	
	L		–35, 11, 5	–34, 15, 2	–36, 12, 4			–34, 18, 1	–36, 17, 0
PreSMA (6),									
Anterior cingulate (32)	L	–4, –1, 56	–4, 6, 49	–7, 10, 45	–5, 12, 43		–6, 7, 48	–4, 8, 49	
Inferior frontal gyrus (44/45)	R			37, 1, 32				37, 4, 28	
	L			–46, 4, 21	–47, 5, 18			–45, 4, 22	–44, 7, 26
Dorsolateral (46/10/9)	L			–39, 42, 12	–36, 46, 13				–36, 40, 8
				–42, 26, 28	–40, 14, 29				
Parietal									
Intraparietal sulcus,									
Angular gyrus (40)	L			–31, –49, 37	–29, –52, 33				
				–36, –53, 44			–32, –47, 38	–30, –55, 36	
Superior parietal lobule,									
Precuneus (7)	L			–21, –66, 49	–28, –49, 43			–13, –72, 50	–43, –57, 50
					–21, –63, 51				–25, –65, 50

R, right; L, left; B, bilateral

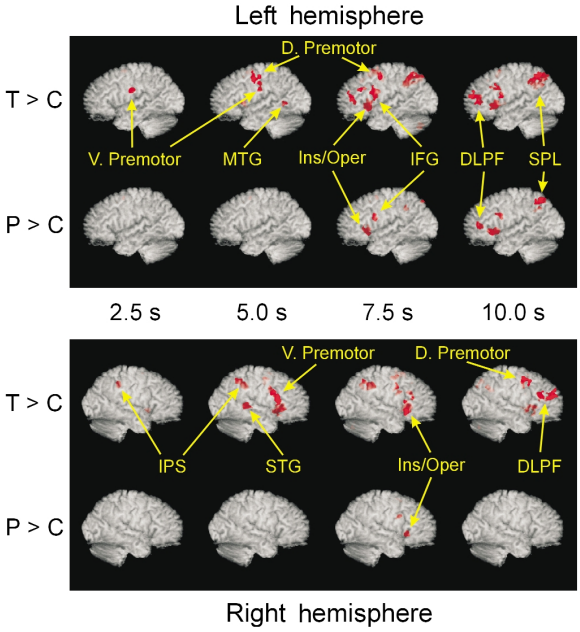

Fig. 5. Activation foci in the lateral surface of the left and right hemispheres denote greater activation for the time (T) and the pitch (P) perception conditions relative to the control (C) condition at 2.5, 5.0, 7.5 and 10.0 s after trial onset. Significant foci ($p < 0.001$) are displayed in red. DLPF, dorsal lateral prefrontal cortex; D. Premotor, dorsal premotor; IFG, inferior frontal gyrus; Ins, insula; IPS, inferior parietal sulcus; MTG, middle temporal gyrus; Oper, frontal operculum; STG, superior temporal gyrus; V. Premotor, ventral premotor.

Our findings did not support a unique role for the cerebellum in encoding time intervals. Nonetheless, cerebellar activation was observed during the time perception task (T minus C), consistent with several studies showing diminished time perception in patients with cerebellar damage[16,18,34]. However, in our study, activation was in the vermis rather than the lateral cerebellar hemispheres, contrary to reports that damage to the lateral cerebellum, but not the vermis, correlated with time perception deficits[15,18]. Cerebellar activation evolved later in the course of the trial, just before and during movement execution, suggesting an involvement in processes other than explicit timing. This is consistent with our previous fMRI study[27] showing that cerebellar activation was not specific to timing self-paced finger movements. Apart from its well-documented role in sensorimotor processing, neuroimaging research indicates that the cerebellum participates in many cognitive functions, including tactile perception[35] and working memory[36]. One lesion study has also shown that cerebellar damage produces pitch perception deficits[14]. Its broad role in sensorimotor and cognitive processing[37] has suggested that the cerebellum monitors and adjusts input from the cerebral cortex, but is not involved in computing a specific operation *per se*[38]. By this account, later activation in vermal lobule VIIB, which receives auditory and visual input[39], could be due to its involvement in optimizing sensory input from auditory systems, which facilitates the comparison of intervals in working memory. Although other explanations are possible, this account is appealing because it predicts that damage to the cerebellum will slow sensory acquisition, which should disrupt a broad range of behaviors, especially those involving timing. This view may explain why patients with cerebellar damage show deficits in timing[16,17], but not always in the perception of pitch or loudness[16,18].

Representations of time depend on the interplay of internal timekeepers with attention and working memory, functions more commonly identified with cortical systems. Neural systems associated with these functions should support a variety of computations, which may explain why they were not always unique to timing intervals (T minus P). However, in the comparisons involving the control condition (T minus C, P minus C), right hemisphere activations were observed during time but not pitch perception. These later results are consistent with findings from converging neuroscience approaches. Specifically, a neuroanatomical bridge for basal ganglia–cortical interactions is the thalamus[40], which was activated early during the encoding of intervals, along with two cortical regions, suggesting they work together in formulating representations of time. Coupled activation in the right inferior parietal cortex may suggest an interdependent role of this region in attention, which theoretically regulates the timekeeping mechanism. Neurological patients with right but not left inferior parietal damage show time, but not pitch, perception deficits that correlate with impairments in switching attention[21]. Electrophysiological recordings in humans have also shown a right hemisphere bias for temporal processing[41], especially in the parietal cortex[42]. The close relationship between timekeeping and attention is presumed by one influential theory[2], and has received empirical support in behavioral studies conducted on humans[4,5]. According to this view, representations of time are reflected in the pulse count accumulated over

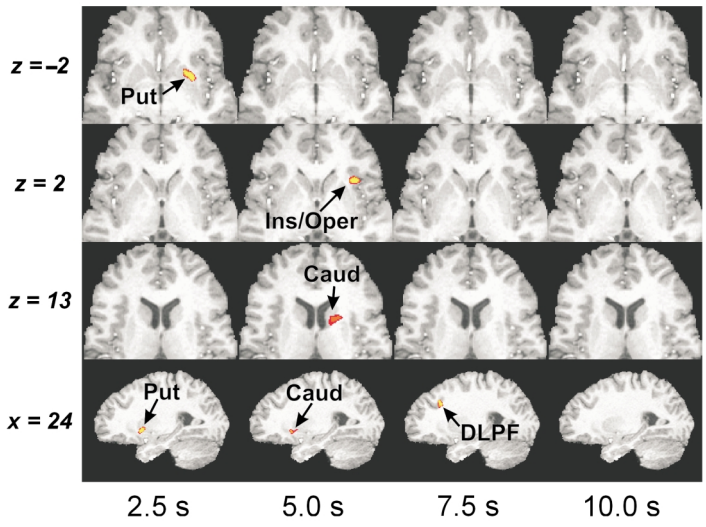

Fig. 6. Activation foci in the basal ganglia, insula/frontal operculum and dorsal lateral prefrontal cortex resulting from greater activation for the time (T) relative to the pitch (P) perception conditions at 2.5, 5.0, 7.5 and 10.0 s after trial onset. Significant foci ($p < 0.001$) are displayed with a red-yellow intensity scale. Slices are displayed in neurological view (left is on the viewer's left). Location of slices defined by the distance (mm) from anterior commissure. Caud, caudate nucleus; DLPF, dorsal lateral prefrontal cortex; Ins, insula; Oper, frontal operculum; Put, putamen.

a particular physical time, which critically depends on the degree of attentional engagement. Our results point to the right inferior parietal cortex in regulating the accumulation of pulses, because of its well-documented involvement in attention[43]. Bilateral projections from the inferior parietal cortex to the putamen and caudate nucleus in monkeys[44] provide a neuroanatomic basis for the interaction of attention and timekeeping operations.

The perception of time also relies on stored representations of intervals in working memory[2]. During time perception, activation was observed in regions commonly associated with temporary storage functions, including the bilateral premotor (BA 6) and right DLPF cortex (BA 9, 10, 46)[19,20,45]. Right DLPF activation was also unique to performing time discriminations. This corroborates our previous finding that damage to these same regions in the right, but not left, hemisphere produces time perception deficits[21]. Controversy exists over whether these areas support different working memory functions[45–47]. However, a recent meta-analysis of neuroimaging studies[20] implicated the premotor cortex in a 'rehearsal circuit' in tasks involving mainly the temporary maintenance of information, such as item recognition. In contrast, the DLPF cortex was associated with an 'executive circuit' in tasks requiring manipulation of stored information, such as the two- and three-back working-memory tasks. Our findings are compatible with this process distinction, as premotor cortex activation began early, consistent with the need for maintaining the standard interval during the trial, whereas DLPF cortex activation unfolded later in association with comparing the two intervals and selecting a response. Independent evidence for the DLPF cortex in executive functions of working memory was observed in the pitch condition as well, in which activation unfolded later during the comparison phase, but was confined to the left hemisphere. Though premotor cortex was not activated in the pitch condition, repeated presentation of the standard pitch across the trial may have minimized the need for rehearsal.

In summary, the present results are compatible with prevailing cognitive theory, and provide new insights into the evolution of activation in cortical and subcortical systems that are specific to different cognitive components of a time perception task. The reciprocal interactions among these specialized systems give rise to our perception of current time. The results are in agreement with converging avenues of research implicating a perceptual system in which the basal ganglia act as a timekeeper that is tightly coupled with an attention system in the right inferior parietal cortex. This right hemisphere bias for the encoding of temporal information is in agreement with converging focal lesion and electrophysiological research in humans. The distinct evolution of activation in the bilateral premotor and right DLPF systems, together with previous neuroimaging studies, provides evidence for different working memory functions underlying time perception. Our results also showed that time and pitch discriminations are mediated by shared parietal and prefrontal systems mostly in the left hemisphere, which were activated during decision and response selection components of both tasks. Presently, we are investigating the dynamics of brain activation patterns during longer delay periods to more directly distinguish systems involved in encoding and short-term maintenance of time intervals.

METHODS

Subjects. Right-handed subjects (2 male/15 female; mean age, 23.9 years) gave written informed consent and were compensated for participation. The experimental protocol was approved by the institutional review board of the Medical College of Wisconsin.

Experimental design. Tone stimuli were presented binaurally using a computer playback system. Sounds were amplified near the scanner and delivered to the subject via air conduction through 180-cm paired plastic tubes, which were threaded through tightly occlusive ear inserts that attenuated background scanner noise to approximately 75 dB sound pressure level (SPL). Background scanner noise consisted of pulses occurring every 205 ms throughout the imaging run; the intensity of the tone stimuli averaged 100 dB SPL. For all three conditions, the standard tones were 700 Hz in pitch separated by a 1200 ms interval (Fig. 1). In the T condition, the eight comparison intervals were ±60-ms increments of the standard interval, and were presented twice in a randomized order (16 trials); pitch did not vary across the four tones. In the P condition, the eight comparison tone pitches were ±4 Hz increments of the standard 700 Hz tones and were presented twice in a randomized order (16 trials); duration did not vary during this condition. In the C task, 16 trials of identical standard tones were presented. The C task was a baseline condition used for removing the effects of low-level sensory and motor processing from the functional maps in the two discrimination conditions. Subjects pressed one of two keys with their right index or middle finger to indicate longer/higher or shorter/lower in the discrimination conditions; subjects pressed a key using their index in the control task. Accuracy and reaction time were measured with a nonferrous key-press pad. Subjects briefly practiced the three conditions before scanning.

Image acquisition. Event-related fMRI was done on a 1.5T GE Signa (Waukesha, Wisconsin) scanner equipped with a three-axis local gradient head coil and an elliptical endcapped quadrature radiofrequency coil. Foam padding limited head motion within the coil. Echo-planar images were collected using a single-shot, blipped gradient-echo echo-planar pulse sequence (TE, 40 ms; TR, 2.5 s; 90° flip angle; FOV, 240 mm; resolution, 64 × 64 matrix). Seventeen contiguous sagittal 7-mm-thick slices were acquired to provide coverage of the entire brain. Scanning was synchronized with the onset of the first tone so that 7 images were acquired during each 17.5-s trial (Fig. 2) with a total of 112 images per run (16 trials per run). An additional 4 images (10.0 s) were added to the beginning of the run to allow the MR signal to reach equilibrium, and were discarded from further analysis; 4 images were added to the end of the run to accommodate the delayed rise of the hemodynamic response. Before functional imaging, high-resolution three-dimensional spoiled gradient-recalled at steady-state anatomic images were collected (TE, 5 ms; TR, 24 ms; 40° flip angle; NEX, 1; slice thickness, 1.2 mm; FOV, 24 cm; resolution, 256 × 128) for anatomic localization and co-registration.

fMRI data analysis. Functional images were generated using Analysis of Functional NeuroImages[48] software. Time series images were spatially registered in three-dimensional space to minimize effects of head motion. A deconvolution analysis was used to generate impulse response functions (IRFs) of the fMRI signal on a voxel-wise basis. This analysis produced an estimate of the hemodynamic response for each condition (T, P and C) relative to a baseline state (rest) without making *a priori* assumptions regarding the shape, delay or magnitude of the IRF. Anatomical and functional images were then interpolated to volumes with 1 mm^3 voxels, co-registered, converted to Talairach stereotaxic coordinate space[49], and blurred using a 4 mm Gaussian full-width half-maximum filter. Voxel-wise analyses of variance (T versus C, P versus C, and T versus P conditions) were done separately for images obtained at 2.5, 5.0, 7.5 and 10.0 s after trial onset. Pooled-variance *t*-tests were applied on a voxel-wise basis to the IRF estimates for each epoch to identify regions showing greater activation in the T and P discrimination conditions relative to the C condition and greater activation in the T than the P condition. An activated region was defined by an individual voxel probability less than 0.001 ($t > 3.61$; df, 16), and a minimum cluster size threshold of 300 microliters[50]. These two thresholds were established based on 10,000 Monte Carlo simulations demonstrating that the chance probability of obtaining a significant activation cluster for an entire volume (type I error) was less than 10^{-6}.

ACKNOWLEDGEMENTS

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