The functional neuroanatomy of time estimation has not been well-documented. This research investigated the fMRI measured brain response to an explicit, prospective time interval production (TIP) task. The study tested for the presence of brain activity reflecting a primary time keeper function, distinct from the brain systems involved either in conscious strategies to monitor time or attentional resource and other cognitive processes to accomplish the task. In the TIP task participants were given a time interval and asked to indicate when it elapsed. Two control tasks (counting forwards, backwards) were administered, in addition to a dual task format of the TIP task. Whole brain images were collected at 1.5 Tesla. Analyses (n = 6) yielded a statistical parametric map (SPM) reflecting time keeping and not strategy (counting, number manipulation) or attention resource utilization. Additional SPMs involving activation associated with the accuracy and magnitude of time estimation response are presented. Results revealed lateral cerebellar and inferior temporal lobe activation were associated with primary time keeping. Behavioral data provided evidence that the procedures for the explicit time judgements did not occur automatically and utilized controlled processes. Activation sites associated with accuracy, magnitude, and the dual task provided indications of the other structures involved in time estimation that implemented task components related to controlled processing. The data are consistent with prior proposals that the cerebellum is a repository of codes for time processing, but also implicate temporal lobe structures for this type of time estimation task.

INTRODUCTION

Explicit time estimation is the conscious ability to estimate objective time without the cues of external clocks. A typical method for studying internal time estimation is time interval production, which involves giving a time interval (e.g., 12 s) and asking the participant to generate a response when the interval has elapsed. Such judgements are considered to be aided by possible internal biological clocks (to be called primary time keeper functions; Ivry, 1993), but such a procedure also induces explicit, conscious strategies for monitoring time and making estimations, and these strategies consume attentional resources (see Marma-ras et al., 1995; also Tracy et al., 1998). The functional neuroanatomy of explicit time estimation processes is unknown, and, in particular, there have not been tests for the presence of a primary time keeper function that might be operating concurrent with these other components of performance.

In a previous paper, Tracy and colleagues (1998) demonstrated that in both normal controls and schizophrenia patients time estimation accuracy was highly sensitive to whether a passing interval was filled with a concurrent activity. The authors concluded that explicit time judgments do not occur automatically, demand attentional resources, and utilize controlled processes such as working memory. Such research makes clear that identifying the substrates uniquely related to a time keeper function will require careful distinguishing of the neuroanatomical substrates that implement the conscious strategies for time keeping (e.g., counting), the call for attentional resources to maintain the activity (task load), and the particular cognitive components required by the task (i.e., working memory).

Models of internal timing processes can be divided into two types (see Block, 1990). Those that propose time keeping and monitoring are specific computations carried out in a specific brain region. Such “time-keeper” models suggest that a neural pacemaker exists which calibrates time. Treisman (1963) articulated a timer model arguing that a pacemaker generates a series of pulses with input from a specific arousal center influenced by external events. This pulse count is then connected to verbal labels and stored. Scalar timing theory also postulates a primary time keeper mechanism (Church, 1989; Weardon, 1991). Here, an internal clock gets switched on and off to allow pulses to
flow to an accumulator in a regular fashion. The accumulator holds a count of the pulses. The contents of the accumulator are then transferred to working memory and comparisons can then be made to longer-term memories of similar accumulator data before the time judgement is expressed. Such scalar theories suggest that the values created by the clock and stored bear an orderly, analogic relation to the passage of time.

Alternatively, “timing-without-a-timer” models propose that subjects construct their subjective sense of time through other ongoing cognitive processes such as working memory or attention. One approach emphasizes the role of attention allocation (Block and Zakay, 1997; Thomas and Cantor, 1975; Zakay and Block, 1995, 1997) and suggests that time judgements vary depending on whether the time estimation task is the focus of attention and demands attentional resources. In general, as attentional focus and resource demands increase from, for example, concurrent performance of a secondary nontemporal task, estimates of time worsen and typically lengthen. Results, however, will vary depending on the time estimation method used (Marmaras et al., 1995; see also Avant et al., 1975; Zakay and Block, 1997). In contrast, if attention is directed away from the time estimation process, underestimation is likely to occur from the failure to transfer or store the information generated by a neural pacemaker (Macar et al., 1994). Other cognitive functions, particularly working memory (Williams et al., 1989; Meyers and Levin, 1992; Block and Reed, 1978), have been implicated in the normal operation of explicit time estimation. The idea that time estimation processes are influenced by memory storage was first proposed by Ornstein (1969) who suggested that perception of time was a direct function of factors such as the amount and complexity of information stored during the interval duration. Research with “filled” versus empty intervals are consistent with this notion as “filled” interval estimates tend to be judged longer than those of empty intervals particularly for retrospective time judgement tasks (Coren et al., 1993; Rammsayer and Lima, 1991; Zakay and Block, 1996).

Two independent oscillators have been proposed for monitoring time sense and carrying out primary time-keeping functions in humans. One involves time perception of extremely brief durations (below 1000 ms). Basal ganglia structures mediated by dopamine have been implicated in this type of time processing (Church, 1984; Harrington et al., 1998; Meck, 1996; Rammsayer and Classen, 1997). The mechanism involved is considered to be the equivalent of a neural counter, which represents time in an analogic way through patterns of neural firing. For instance, Rammsayer (1993, 1997) showed dopamine antagonists can impair temporal discrimination for brief intervals in humans. Also, Parkinson’s disease patients where the primary neurological damage is presumed to be in the dopamine pathways of the basal ganglia (substantia nigra) are impaired at brief duration perception tasks (Harrington and Haaland, 1995; Harrington et al., 1998; Rammsayer and Classen, 1997) or the timing component of rapid motor tasks such as finger tapping (O’Boyle et al., 1996; Artieda et al., 1992). There are data implicating other subcortical structures such as the suprachiasmatic nucleus of the hypothalamus in the disruption of short duration time discrimination (Cohen et al., 1997). A lesion study has suggested cortical regions can influence time perception of short durations (300 to 600 ms). For example, Harrington et al. (1998) showed that right but not left hemisphere patients with lesions in Brodmann’s 6,8,9,46 (premotor and prefrontal) and parietal regions had deficits in tone pair discrimination. Important negative evidence from animal studies has also emerged showing that the hippocampus is not necessary in short interval time discrimination (Dietrich et al., 1997).

The second potential oscillator or primary time keeper governs internal time estimation processes in the range of seconds, minutes, or more, and is much more closely tied to the attentional or working memory processes noted above. These longer time estimation processes most commonly are considered to involve the cerebellum (Ivry, 1997; Ivry and Keele, 1989). Meck (1996), however, argued that time judgements for longer durations are closely aligned with acetylcholine functioning. The hypothesis that the cerebellum is an internal clock was first put forward by Braitenberg (1967, 1965) and more recently developed by Fahle and Braitenberg (1984). Many clinical and experimental results can be interpreted as supportive of the hypothesis (Dichgans and Diener, 1984; Eccles, 1977). Animal models have further linked the cerebellum to timing control as rhythmic activity during locomotion is abolished following cerebellar lesions in rats (Arshavsky et al., 1983). Work by Thompson and his colleagues (Thompson et al., 1984) in the area of motor learning found that lesions of the cerebellar hemispheres do not abolish the conditioned response during classical conditioning, but will seriously disrupt the timing of the response. Time discrimination studies have shown that cerebellar degeneration patients show time discrimination problems at long (8–32 s) but not short (100–325 ms) durations during bisection tasks (Nichelli et al., 1996). Ivry and Keele provided evidence for the general timing functions of the cerebellum (1989; see also Keele et al., 1987, 1985). They showed that lateral cerebellar lesion patients who displayed increased variability in performance during rhythmic tapping were also less accurate than the control group in making perceptual discriminations of temporal duration. In addition, these patients were deficient at judging the velocity of a moving stimulus even when fixation was maintained. Ivry and
Keele interpreted these deficits as specific to timing functions, because the patients were unaffected in a control task measuring the perception of loudness. Ivry (1996) linked brief duration temporal information processing to endogenous oscillatory processes in the basal ganglia and associated cerebellar activity with encoding and guiding longer duration temporal processes. In later work, Ivry (1997) suggested the cerebellum houses a near-infinite set of interval-type timers (multiple-timer hypothesis; see also Helmuth and Ivry, 1996).

Imaging studies where temporal processing is inferred or presumed to occur during task performance (velocity discrimination) have been conducted (e.g., Jueptner et al., 1996). Few imaging studies, however, have focused directly on time estimation. A PET study (Lejeune et al., 1997) involving a synchronization task (target duration 2700 ms) identified a complex set of structures in time processing (right prefrontal, inferior parietal, anterior cingulate cortex, left putamen, and left cerebellar hemisphere). Penhune et al. (1998) used PET to test for central control of temporal processing using a rhythm reproduction paradigm where the complexity of the rhythm pattern was varied and both auditory and visual input modalities were assessed. Their results suggested lateral and vermal cerebellar regions contributed to the timed motor response particularly when the pattern was complex or novel. They also observed that sensory regions and ventrolateral frontal cortex were involved in modality-specific temporal processing (e.g., planum temporale for auditory condition).

Other data directly testing temporal processing have implicated the prefrontal cortex (Schubotz et al., 1999; see also Schubotz and Friederici, 1997). Schubotz and Friederici found a frontolateral ERP focus from 500 to 2000 ms following stimulus onset during an auditory duration memory task. The Schubotz et al. (1999) study involved separate conditions of monitoring and reproducing the rhythm pattern of visual stimuli. They found basal ganglia and frontal opercular cortex activation most unique to the rhythm monitoring task which was absent movement. Rubia and colleagues also provided fMRI evidence of prefrontal cortex involvement in time processing during a sensorimotor synchronization task (Rubia et al., 1998). There is also data suggesting that the prefrontal cortex can code the interval between sensory cue and response, allowing for the prediction and timing of upcoming responses (Batuev et al., 1979).

Still other brain regions have been implicated in time estimation. A recent PET study that manipulated cued attention to the temporal interval between cue and target elicited parietal cortex activation bilaterally, stronger for the left hemisphere (Coull and Nobre, 1998; n.b., the study utilized relatively short temporal durations ranging from 300 to 1500 ms). Using PET, Maquet and colleagues had subjects compare the duration of two visual stimuli and found right prefrontal, right inferior parietal, anterior cingulate, cerebellar vermis, and left fusiform gyrus activation (Maquet et al., 1996). Finally, the temporal cortex can be seen as relevant to time estimation based upon evidence that lesions of the hippocampus disrupt trace conditioning of the rabbit’s classically conditioned nictitating membrane response (Solomon et al., 1986). Regarding the hippocampus, it is interesting to note that the clinical presentation of temporal lobe amnesia patients commonly includes disorientation to time (Reisberg et al., 1986). Also, Damaceno (1996) studied brain-damaged patients and found that the ability to reproduce durations (make a keypress to keep a light on for a specified interval) was impaired relative to controls in a frontal and temporal-limbic lesion group.

Purpose of the Study

In this research, we investigated the functional magnetic resonance imaging (fMRI) measured brain response to an explicit, prospective time interval production (TIP) task. The goal was to test for the presence of brain activity that could be considered to reflect a temporal oscillator, distinct from the brain systems involved either in conscious strategies to monitor time and the cognitive processes used to manage and accomplish the explicit task. Thus, primary time keeping is defined as those computational components of explicit time estimation that do not involve monitoring strategies, number/symbol manipulations, or controlled processes such as working memory. The degree to which primary time keeping requires attention allocation and the utilization of attention resources, as has been argued by some (Zakay and Block, 1995, 1997), is unclear and the data from this study will address that issue.

Toward this end, two control tasks that do not involve time keeping were administered in separate fMRI runs to identify the brain regions associated with strategies to accomplish time estimation without invoking any time keeping requirements. A relatively easy numeric monitoring task (counting forwards) and a more difficult number manipulation task (counting backwards) were utilized. To address the issue of attention resource allocation, we examined a dual-task version of the time interval production task. The goal here was to determine the brain structures whose activation was closely associated with this more demanding format of the TIP with the logic that this activity could not then represent the primary time keeper function. Brain activity associated with this format would be considered to reflect processing related to the dual-task, perhaps best characterized as implementing the increased demand for attentional resources. Such processes would include those invoked by the increased task load and difficulty,
increased effort, strategy and working memory demands, and the possible division of attention.

In the TIP task, participants were given a time interval and asked to indicate when it elapsed. The two control tasks involved counting forwards or backwards (by sevens) from a designated number. Counting backwards also served as the concurrent task imposed in the dual-task condition of the TIP task. Overall, the literature review suggested that cerebellar and basal ganglia structures implement different ranges of time in time monitoring and judgement tasks. Thus, in context of an explicit time interval estimation task in the range of seconds, we hypothesized that the time keeper function would be most closely tied to lateral cerebellar activation. Primary analyses yielded a statistical parametric map (SPM) considered to reflect: (1) primary time keeping functions and not strategy (counting or number manipulation) or attention resource utilization, (2) processes unique to dual task performance, i.e., increased demand for attentional resources. Additional SPMs |z| are presented related to the accuracy and magnitude of the estimation response during the TIP task.

METHODS

Participants

All participants (n = 6) were healthy, normal adults ranging in age from 21 to 43 years (mean = 26.5, SD = 8.4). There were two males and four females. All were right-handed as verified by the Edinburgh Handedness Inventory (mean laterality score = 83.1, SD = 14.6; Oldfield, 1971) and self-report. Participants were college educated (mean = 16.8 years schooling, SD = 2.2), and all were free of medical, neurologic, or psychiatric complications as established by an interview with a Ph.D. neuropsychologist. All participants provided written informed consent prior to the study and were paid for their participation.

fMRI Procedure

Brain functional magnetic resonance imaging was performed using the blood oxygen level-dependent contrast method as an indirect marker of neuronal activation. Whole-brain scans were conducted involving 19 parallel axial slices of 7 mm thickness (no gaps). A single-shot echoplanar gradient echo imaging sequence acquiring T2* signal was used with the following parameters: TE = 54 ms, TR = 3.8 s (interleaved collection, contiguous slices), FOV = 22 mm, 128 × 128 × 7 mm data matrix, flip angle = 90°, bandwidth = 1470 Hz/pixel. The in-plane resolution was 1.72 × 1.72 × 7 mm. These voxel sizes were chosen to provide good spatial resolution and allow full coverage of the brain. Also, there were constraints on the number of images that could be collected in a single fMRI run and a thinner z dimension would have caused a reduction in the total number of whole brain volumes collected and a consequent reduction in power.

Shimming was conducted at each location prior to acquisition to reduce system inhomogeneities and artifactual fluctuations in signal across images. A standard clinical Siemens Magnetom Vision Imager (1.5 tesla) was used. A shielded elliptical endcapped quadrature birdcage RF coil was used for both transmission and reception. Prior to collection of the T2* images, T1-weighted images (19 slices) were collected using a conventional spin echo pulse sequence (TR = 500 ms; TE = 14 ms) in positions identical to the functional scans to provide an anatomical reference to determine the slice location of the echoplanar images. The slices were axial in nature with the angle set by the anterior–posterior commissure line and the inferior slice set at the ventral base of the cerebellum.

Task Procedure and Data Acquisition

Participants were instructed on the tasks prior to scanning and provided with a brief practice period. The four tasks were administered in separate fMRI series. The main activation task, time interval production (TIP), required participants to estimate when they judged a specified interval had elapsed (trial values ranged from 12 to 24 s). Participants indicated their response by raising their dominant hand slightly and their interval estimate was then recorded by a research assistant with good view of the participant’s hand. An accuracy score was computed reflecting the absolute value of the deviation between the participant’s estimate and the time interval requested. In addition, a magnitude score was computed reflecting the size of the estimate relative the actual time interval, permitting discrimination of shorter from longer estimations. This magnitude score was based on the ratio of the actual to the estimated duration. There were nine TIP trials.

The Counting, Backwards, and Dual Task each involved four trials. For the Counting Task participants were instructed to mentally, silently count up by ones from the number given until told to stop. Trials used starting numbers randomly chosen from a range of 6 to 20, and all participants received the same numbers in the same order. For the Backwards Task participants were told to count backwards by sevens from the number given until told to stop. Participants were told that if they lost their place to just keep counting backwards from any close number. Trials included numbers from 67 to 100 and all participants received the same numbers in the same order.

For the Dual Task, the requirements of the TIP and Backwards Task were combined. That is, participants had to estimate a designated time interval and then during the passing interval count backwards by sevens.
As in the TIP task, participants were instructed to raise their hand when they judged the time had elapsed and to stop counting backwards. Participant responses were recorded, and accuracy and magnitude scores were again computed. For the Dual Task, the trials included time estimation intervals different from those used in the TIP task but within a similar range (11 to 22 versus 12 to 24 s for the TIP task alone). The mean of the time intervals used in the Dual Task and the TIP task were statistically equivalent though not identical (P < 0.71; Dual Task, m = 16.8, SD = 4.3; TIP m = 17.6, SD = 4.1). This was done to ensure that the intervals made very similar estimation demands on the subjects without inducing repetition or opportunities for practice. The numbers used for the counting backwards part of the Dual Task were also different from those in the Backwards Task but within the same range (62 to 96 versus 67 to 100 for the Backwards Task alone). Again, the mean values were statistically equivalent, though not identical (P < 0.61: Backwards alone, m = 83.0, SD = 15.9; Dual Task, m = 80.5, SD = 14.4).

All four tasks were composed of alternating rest and activation epochs with rest coming first. For the Counting and Backwards tasks all activation epochs were 30.4 s in duration and included collection of eight brain volumes. For these tasks the first rest epoch was 30.4 s (eight volumes collected) and subsequent rest epochs lasted 11.4 s with three brain volumes collected. There were four rest/activation cycles in the Counting and Backwards fMRI runs, involving acquisition of a total of 49 brain volumes (17 rest and 32 activation). The TIP and Dual Tasks also started with a 30.4 s rest epoch involving collection of eight volumes. However, for these tasks the length of subsequent activation and rest epochs depended upon the participant's estimation response. An activation epoch was considered to start with delivery of the time to estimate and end when the participant lifted their dominant hand slightly. Brain volumes were then "binned" accounting for a hemodynamic lag of one TR (3.8) s. Volumes up to the onset of the next time estimation trial, were "binned" as rest volumes. Thus, brain volumes acquired during the period when the participant was estimating or monitoring time were "binned" as activation volumes. The exception was that the brain volume acquired during or immediately after the actual response (i.e., if the hand was raised between acquisitions) were excluded from the analyses. For the TIP task there were nine time interval production trials and 104 brain volumes collected. For the Dual Task there were four time interval production trials and a total of 49 brain volumes collected.

During scanning the time interval to estimate, the numbers to count, and the command to "stop" (used in the Counting and Backwards tasks) were issued to the participant through headphones (Siemens standard). Lights inside the scanner were off. In order to minimize movement, the participant's head was secured with foam rubber pad, and all participants were instructed to lay still and relax throughout the scanning procedure. Background scanner noise was constant during all experimental conditions.

Post-Processing Image Analysis

The Unix-based software package, Medx 3.0 (1998) was utilized for all postprocessing image analyses. First, a cine mode evaluation was used to identify gross head motion. Next, a 3-D automated image registration program (6 parameter rigid body transformation) was utilized to coregister or computationally align the images within an fMRI run with the mean volume of the time series used as the reference or target (AIR 3.2; Woods et al., 1993). This procedure aligns images on a voxel-by-voxel basis using a 3-D automated algorithm and corrects for interscan movements. All functional data were normalized with a mean of 1000 and signal intensities less than 20% of maximum were thresholded out. Temporal filtering was applied. The variance in the functional data related to low frequency (e.g., physiologic) processes during the time course of the experiment unrelated to experimental condition was eliminated through a linear detrending procedure, which removed the best straight line fit through the data. All volumes were then transformed into standard anatomical space (Talairach and Tournoux, 1988) using the T2 EPI template and the Statistical Parametric Mapping normalization procedure (12 parameter affine transformation, trilinear interpolation, 4, 5, 4 basis functions for x, y, and z, respectively, with eight iterations; Friston et al., 1995). This procedure utilizes a linear 12-parameter affine transformation accounting for brain size and position, followed by a series of nonlinear basis functions to correct for morphological differences. Next, all volumes underwent smoothing by convolution with a Gaussian kernel of 3.44 × 3.44 × 14 mm FWHM (two times the voxel size) to increase signal-to-noise and account for residual intersubject differences.

The General Linear Model (GLM) procedure of the Statistical Parametric Mapping software (SPM 1996 version as implemented by Medx) was used to identify the voxels associated: (1) time estimation and not a time monitoring strategy or numeric manipulation procedure, (2) the Dual Task procedure (e.g., the utilization of attentional resources), but not the components of the dual task itself, i.e., activation associated with time estimation processes or the concurrent task of counting backwards. Both these SPM analyses utilized a multistudy, different conditions design with a single contrast used to create voxel-based t statistics and normalized (z score) transformations of these compiled into a single statistical parametric map (SPM2). Input
to the General Linear Model procedures were mean volumes, six for each participant, based on the volumes collected for the experimental conditions of the relevant tasks. For example, for the first SPM analysis (three studies, two conditions, six subjects) the mean of the volumes associated with each of the following tasks conditions were used: Time Perceived Interval (TIP) activation, TIP rest, Count activation, Count rest, Backwards activation, and Backwards rest. For the second or Dual-Task SPM analysis, the mean of the volumes associated with Dual Task activation, Dual rest, TIP activation, TIP rest, Backwards activation, and Backwards rest were used. Both analyses constitute a random effects models, allowing generalization to the population.

The first analysis used a contrast reflecting activation strongly associated with the TIP task by identifying voxels with significantly greater values in TIP task (coded 1) relative to the Count and Backwards tasks (coded −0.5) with all rest volumes coded zero (to be called the TIP SPM). This strategy utilizes standard subtractive methodology (Petersen et al., 1989) whereby experimental conditions are compared directly. This strategy was chosen because comparisons to rest are difficult to interpret and activation attributed to the TIP task needed to exceed the level present in these control conditions regardless of the presence of activation in these conditions compared to a resting baseline. As a precaution, however, we conducted the alternate approach of comparing the activation conditions to their rest (interaction term) and then utilized conjunction analysis to determine the overlapping activation in the two contrasts reflecting TIP activation. The interaction contrasts involved were ((TIP = 1 minus TIP rest = −1) minus (Count = 1 minus Count rest = −1)) and ((TIP = 1 minus TIP rest = −1) minus (Backwards = 1 minus Backwards rest = −1)).

The second SPM analysis used a contrast reflecting activation unique to the Dual Task but not its parts in isolation (to be called Dual Task SPM). This contrast identified voxels with significantly greater values in the Dual Task (coded +1) relative to the TIP and the Backwards Tasks (coded −0.5) with all rest volumes coded zero. This was considered to capture activation unique to the dual task, e.g., the increased demand for attentional resources.

The omnibus SPM |F| test for each of these models utilized an uncorrected threshold of P < 0.05. The SPM analysis corrected for multiple comparisons based upon the theory of Gaussian fields (Friston et al., 1994). Voxels significant in the TIP SPM |z| (corrected height, P < 0.001, and extent thresholds |k| = 29; error degrees of freedom = 15) that were not significant in the Dual Task SPM |z| (corrected thresholds: height, P < 0.01; extent, |k| = 11; error degrees of freedom = 15) were identified through an exclusionary masking procedure. The resulting image, to be referred to as the time estimation SPM, reflected voxels unique to time estimation processes per se not represented in the Dual Task SPM (e.g., attentional resource demands), and not involving time monitoring strategies (e.g., counting) or numeric manipulation procedures (e.g., counting backwards).

Additionally, we were interested in how imposition of the second, concurrent task modified activation in the voxels already significantly active during the TIP task. Thus, we report data comparing the mean z scores for the clusters common to the TIP Task and the Dual Task. The common areas were found through conjunction of the simple main effect contrasts (TIP minus rest; Dual Task minus rest).

Finally, separate SPM analyses were run to model two covariates of interest: the accuracy of time estimation and the magnitude (i.e., size) of the time estimation response relative the actual interval. Here, each GLM contained two orthogonal contrasts reflecting TIP activation relative to TIP rest (+1, −1) and the covariate effect during the TIP task (0, 0, +1). This second contrast, which modeled activation associated with either accuracy or magnitude, was the primary focus. For the accuracy and magnitude covariates, each participant’s mean score on this variable across the nine TIP trials was computed and then mean-centered (the grand mean, n = 6, was subtracted out). The resulting value was placed in the covariate vector in rows associated with the participant’s TIP volume. Rest volumes were assigned a zero. This vector summed to zero, maintained the relative rank of the participant’s covariate score, and allowed the covariate to be modeled uniquely by avoiding redundancy with the vector of values representing the experimental condition effect.

RESULTS

Figure 1 displays significant voxel clusters from the time estimation SPM. These are voxels significantly active during the TIP task (TIP SPM |z|) that also survived masking by the Dual Task SPM |z|. Data on these clusters is presented in Table 1. These regions reflect activation unique to time estimation processes per se and not time monitoring strategies or numeric manipulation procedures, nor activation associated solely with properties of the Dual Task such as attention resource utilization. A small cluster in the most right, most lateral area of the medial cerebellar gyrus was present (11 voxels; left panel of Fig. 1). Activation can also be seen in two clusters in the right inferior temporal gyrus (right panel of Fig. 1; medial cluster, 18 voxels; lateral, 26 voxels, both Brodmann’s Area, BA, 20). As noted, we also compared the activation conditions to their rest (interaction terms) and then utilized conjunction analysis to determine the overlapping activation in the contrasts reflecting TIP activation. This
procedure yielded identical results in that the same areas of significant activation were observed: inferior temporal (two clusters) and lateral, medial cerebellar.

For illustrative purposes, the maximum intensity projection from the Dual Task SPM analysis is shown in Fig. 2 (corrected height, $P < 0.01$, and extent thresholds, $k = 11$; error degrees of freedom = 15). This analysis was devoted to identifying voxels significantly active during the Dual Task relative to the components of the dual task itself, i.e., time estimation processes or counting backwards. This volume served as the exclusionary mask to produce the time estimation volume depicted in Fig. 1. Note, the less stringent height threshold made for a more stringent, more conservative mask. In order to isolate voxels related to primary time keeping and not dual task processing, a stricter criteria for this mask was warranted. As shown in Fig. 2, the activated regions include the occipital gyrus bilaterally (BA 18 and 19), left posterior parietal cortex (BA 7), medial posterior and right lateral cerebellar, superior (BA 6) and middle frontal gyrus (BA 8 and 9), and internal capsule. It should be noted that when a more stringent criteria was applied to this Dual Task volume (corrected height, $P < 0.001$; extent, $k = 11$) no clusters survived.

As the brain regions dedicated to time-keeping may interact with other cognitive/neural systems such as attention, particularly the call for attentional resources, we utilized conjunction analysis to determine activation common to the TIP and Dual Task (corrected height, $P < 0.25$, and extent thresholds $|k| = 3$; error degrees of freedom = 10), and then compared the mean $z$ scores for these common clusters under the separate tasks (main effect contrast for each task). The cluster in the medial, lateral cerebellar area (conjunction values:

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**TABLE 1**

Data on Areas of Activation in Brain Volume Reflecting Primary Time Estimation (Also See Fig. 1)

<table>
<thead>
<tr>
<th>Brain region (Brodmann's Area)</th>
<th>Z Score of region maxima</th>
<th>Talairach coordinates of maxima (x, y, z)</th>
<th>Extent of activation relative to AC–PC plane (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right lateral cerebellum</td>
<td>3.26</td>
<td>54, −38, −36</td>
<td>−38 to −35</td>
</tr>
<tr>
<td>Right inferior temporal gyrus, medial area (BA 20)</td>
<td>3.24</td>
<td>54, −28, −27</td>
<td>−30 to −24</td>
</tr>
<tr>
<td>Right inferior temporal gyrus, lateral area (BA 20)</td>
<td>3.63</td>
<td>69, −5, −27</td>
<td>−31 to −24</td>
</tr>
</tbody>
</table>

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**FIG. 1.** Significant areas of activation in brain volume reflecting primary time estimation. Left panel shows right lateral medial cerebellar activation. Right panel shows two clusters of right inferior temporal gyrus (GTI) activation (BA 20).
<table>
<thead>
<tr>
<th>set-level</th>
<th>cluster-level</th>
<th>voxel-level</th>
<th>uncorr $k$</th>
<th>uncorr $Z$</th>
<th>$x, y, z$ (mm)</th>
<th>Brain Region (Brodmann’s Area)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.000 (14)</td>
<td>0.985 (38.389)</td>
<td>0.959 (3.89)</td>
<td>0.06384</td>
<td>0.00005</td>
<td>-10.6, -96.24</td>
<td>Cuneus (BA 19)</td>
</tr>
<tr>
<td>0.998 (26.374)</td>
<td>0.994 (3.74)</td>
<td>0.11808</td>
<td>0.00009</td>
<td>-8.6, -96.24</td>
<td>Medial Posterior Cerebellum</td>
<td></td>
</tr>
<tr>
<td>1.000 (41.352)</td>
<td>1.000 (3.52)</td>
<td>0.05533</td>
<td>0.00021</td>
<td>-2.7, -70.4</td>
<td>Posterior Parietal (BA 7)</td>
<td></td>
</tr>
<tr>
<td>1.000 (31.348)</td>
<td>1.000 (3.48)</td>
<td>0.09052</td>
<td>0.00025</td>
<td>-26.5, 24.4</td>
<td>Middle Frontal Gyrus (BA 8)</td>
<td></td>
</tr>
<tr>
<td>1.000 (13.345)</td>
<td>1.000 (3.45)</td>
<td>0.26032</td>
<td>0.00028</td>
<td>42.0, -6.8</td>
<td>Superior Frontal Gyrus (BA 6)</td>
<td></td>
</tr>
<tr>
<td>1.000 (26.323)</td>
<td>1.000 (3.23)</td>
<td>0.11808</td>
<td>0.00061</td>
<td>36.4, 48.4</td>
<td>Middle Frontal Gyrus (BA 8)</td>
<td></td>
</tr>
<tr>
<td>1.000 (2.80)</td>
<td>0.00259</td>
<td>38.4, 48.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.000 (2.78)</td>
<td>0.00275</td>
<td>26.3, 64.0</td>
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<td>1.000 (21.317)</td>
<td>1.000 (3.17)</td>
<td>0.15678</td>
<td>0.00077</td>
<td>-2.2, 0</td>
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<td>1.000 (34.303)</td>
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<td>0.07771</td>
<td>0.00121</td>
<td>-28.6, 36.3</td>
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<td>1.000 (25.299)</td>
<td>1.000 (2.99)</td>
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<td>0.00138</td>
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<td>1.000 (2.80)</td>
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<td>0.00378</td>
<td>50.4, 2.36</td>
<td>Middle Frontal Gyrus (BA 9)</td>
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**Figure 2.** Dual Task SPM maximum intensity projection of brain volume used to mask the time estimation SPM $z$. Volume reflects activation unique to the Dual Task procedure relative to its two component tasks.

size = 10, max $z$ score = 3.82; $x$ = 44, $y$ = -46, $z$ = -36) did not significantly differ (dependent $t$ test) under the TIP and Dual Task procedures with mean $z$ scores of 2.53 and 2.61, respectively. Similarly, the mean $z$ score for the more medial cluster in the inferior temporal lobe (conjunction values; size = 8, max $z$ score = 2.9; $x$ = -56, $y$ = -26, $z$ = -32) did not significantly differ under the TIP and Dual Task (mean $z$ scores, 1.94, 1.86, respectively).

Figure 3 displays representative brain slices from the five significant clusters resulting from the SPM analysis capturing activation associated with the covariate effect, accuracy of time estimation (corrected height, $P < 0.001$, and extent thresholds, $k = 8$; error degrees of freedom = 4). Clusters of activation appeared in left posterior parietal cortex (panel 2), right lateral cerebellum (panel 4), right middle frontal gyrus (panel 5), right posterior white matter tracks at the level of the posterior corpus callosum (panel 3), and left superior longitudinal fasciculi (panel 1). Given the diminished resolution from spatial smoothing, gray matter averaging is a distinct possibility for these latter two clusters. The superior longitudinal fasciculus activation, for instance, may involve postcentral gyrus neurons. Thus,
interpretation of this volume will be limited to the above mentioned gray matter regions.

Figure 4 displays representative brain slices from the SPM analysis capturing activation associated with the covariate effect, magnitude, which represents the size of the time estimation response relative to the actual time interval (corrected height, \( P < 0.01 \), and extent thresholds, \( k = 8 \); error degrees of freedom = 4). Here, significant voxels reflect activation associated with shorter estimates relative to the actual interval. It should be noted that all (100%) of participant responses under the Dual Task condition were overestimates and a total of 83% of responses were overestimates during the TIP task. Figure 4 shows middle, superior, and inferior frontal gyrus activation in panels 1, 2, and 4, respectively. Note, the clusters of activation were mostly prefrontal in terms of location (BA 10 and 47) in regions inferior and anterior to those associated with the accuracy covariate. Additional areas of activation included inferior temporal cortex (panel 1) and a small white matter region anterior to the thalamus (panel 3). Again, interpretation of this volume will be limited to the gray matter regions.

Finally, we note that the accuracy of time estimation judgements during the Dual Task was substantially worse than for the TIP task (a drop of 57%; \( t_{20} = -4.2, P < 0.0001 \)). Also, as expected, the time judgements were significantly longer in the Dual Task (magnitude score; \( m = 0.62, SD = 0.14 \)) compared to the TIP task (\( m = 0.85, SD = 0.05; \) high score indicates shorter, more accurate estimations), and this difference was significant (dependent \( t \) test, \( t = -7.5, df = 14, P < 0.001 \)).

**CONCLUSIONS**

This study directly tested for structures associated with a primary time keeper function during explicit time estimation. The study accounted for subject strategies such as counting or number manipulation, in addition to cognitive processes associated with dual-task performance such as attention resource utilization. Activation most closely related to the time keeping component of the Time Interval Production task appeared to define a small medial, lateral cerebellar area and two regions within the inferior temporal cortex. There was no suggestion that the underlying hemodynamic signal from these regions changed substantially during the dual task format, indicating the change in task demands did little to modulate these neural structures dedicated to time keeping. The lateral cerebellar activation is consistent with prior reports that the cerebellum operates as a specialized module for timing (Ivry and Keele, 1989). Such work has been largely based on evidence showing that the cerebellum is involved in timing under multiple contexts such as rhythmic finger tapping tasks and duration perception (Ivry et al., 1988; Ivry and Keele, 1989; Jeuptner et al., 1995). The data of this study indicate the lateral cerebellum is also involved in contexts requiring explicit temporal judgements such as our time interval production task.

The exact nature of the inferior temporal cortex (BA 20) activation cannot be specified and was not tested by this study. One possibility is that participants compared the temporal information accrued during the time interval to stored temporal duration information residing in temporal cortex (Meeck et al., 1984; Williams et al., 1989). Lesions of the temporal lobe do seem to affect aspects of time processing (animal lesions disrupt trace conditioning see Solomon et al., 1986; global temporal orientation in humans see Reisberg et al., 1986). For instance, temporal lobe amnesia patients may be unable to judge temporal events related to a failure in accessing stored engrams of subjective “time experiences” such as information on duration intervals.

We did not find primary time estimation associated with activation in basal ganglia, frontal opercular, or parietal structures as has been reported by other groups (Coull et al., 1998; Coull and Nobre, 1998; Schubotz et al., 1999). The Schubotz et al. (1999) study found basal ganglia and frontal opercular activation for a task requiring the monitoring of external stimuli (visual rhythm patterns). Our study, in contrast, had no ongoing external temporal stimulus to judge. Instead, participants had to monitor an internal timing system (internal clock or procedures to track elapsing time) and use existing, stored knowledge about durations to judge whether a target interval had elapsed. The Coull and Nobre study, which found left parietal activation characteristic of temporal attention was not an estimation paradigm. Rather, attention was oriented to the time at which an upcoming external event that required a quick response would occur. Such a paradigm, in comparison to the present study, heightened the need for external vigilance and sensory monitoring, a factor which may explain the presence of parietal activation (Pardo et al., 1991; Posner et al., 1984). It is interesting to note these studies, which lacked temporal lobe foci, gave the participants external temporal stimuli (durations, rhythm patterns) to monitor and encode (Schubotz et al., 1999), or presented external stimuli from which to make a comparison (Maquet et al., 1996) or anticipate a future external stimulus (Coull and Nobre, 1998). The present project had no external temporal stimulus or standard, and this may explain why participants needed to access stored knowledge about durations in order to make their temporal estimates.

It is important to observe that working memory structures (e.g., BA 9, Petrides, 1994) were not represented in the primary time estimation image, most
FIG. 3. Significant areas of activation in brain volume reflecting accuracy during time interval production task (corrected thresholds: height, $P < 0.001$, extent = 8, error degrees of freedom = 4). Sagittal slice position relative to anterior/posterior commissure line: upper left panel, $+1$ mm; upper right panel, $-77$ mm; lower left panel, $-29$ mm; lower middle panel, $-45$ mm; lower right panel, $+9$ mm.
FIG. 4. Significant areas of activation in brain volume reflecting magnitude of time production during the time interval production task (corrected thresholds: height, \( P < 0.001 \), extent = 8, error degrees of freedom = 4). Sagittal slice positions relative to anterior/posterior commissure line are identical to those described in the legend of Fig. 3.
likely due to the working memory demands of the comparison tasks, particularly the Backwards task, which is considered to have such requirements (Baddeley, 1986; Lezak, 1995). Thus, our data do not argue against a role for these structures in time estimation as a place that either holds the accumulating information about a passing time interval (Block and Reed, 1978) or keeps accessible recently experienced time intervals so they can be compared and matched to stored temporal durations (Harrington et al., 1998). The data do, however, make clear that the prefrontal cortex is not associated with the primary time keeper function and is more likely involved in affiliated cognitive processes such as working memory. In this sense, our data stand in contrast with studies suggesting the prefrontal cortex is closely tied to time keeping functions. For instance, there are data suggesting that the prefrontal cortex can codify the interval between sensory cue and response, allowing for the prediction and timing of upcoming responses (Batuev et al., 1979). Halbig et al. (1998) report evidence of domain specificity (selective interference) for temporal duration processing in the context of a working memory task, which suggests prefrontal cortex localization for temporal processing. Our data are also at variance with an fMRI study emphasizing the role of prefrontal cortex in time processing during a sensorimotor synchronization task (Rubia et al., 1998). Rubia and colleagues report activation in left rostral prefrontal, medial frontal, supplementary motor, and supramarginal gyrus regions in association with short-event rapid rhythmic tapping (0.6-s interval), although the medial frontal activation appeared most related to output-rate-dependent attention processing.

Our data do not suggest that the prefrontal cortex plays no role in time keeping functions, only that it does not serve as primary time keeper and may be more closely aligned with other computational components such as working memory, particularly for tasks in the time range evaluated here (i.e., 12–24 s). In fact, the activation associated with both the accuracy (Fig. 3, panel 5, BA 9) and the magnitude (Fig. 4, panels 1, 2, and 4) of the time estimation responses clearly point to a role for the prefrontal cortex. These data indicate the prefrontal cortex helped implement the TIP task and show its involvement was crucial both to overall performance accuracy and the length of the time estimation response. Shorter and more accurate estimates invoked greater prefrontal activation than longer, less accurate estimation responses.

In understanding the nature of this prefrontal activation, it is helpful to turn to the behavioral data on accuracy. The accuracy of time estimation judgements during the Dual Task were substantially worse and longer than those for the TIP task, a finding consistent with prior data (Zakay and Block, 1997). Performance changes and, in particular, performance declines resulting from the introduction of a second, concurrent resource-demanding task are typically associated with the presence of resource-dependent or "controlled" information processing (Hirst and Kalmar, 1987; see also Schneider and Shiffrin, 1977). Thus, the performance decrements in time estimation we observed imposed by concurrent counting backwards suggest the procedures utilized for time estimation did not operate automatically and were, indeed, mediated by controlled processes. Our previous behavioral study with the TIP task (Tracy et al., 1998) demonstrated that one of the controlled processes involved was working memory. Prima facie, working memory processes such as keeping the target interval "in mind" or utilizing conscious time-keeping strategies would seem advantageous to performance on the TIP task. Our fMRI data on time estimation accuracy and magnitude certainly support the possibility that prefrontal-driven working memory processes mediated better performance on the TIP task, and such a finding is consistent with the large research based linking prefrontal cortex, particularly BA 9, with working memory (see Courtney et al., 1997; D'Esposito et al., 1998). Clearly, however, the role of prefrontal cortex in the TIP task is complex as the prefrontal activity was not limited to Brodmann's Area 9 (see Fig. 4, BA 10, 47) and prefrontal activation was also observed in the Dual Task SPM (see Fig. 2, BA 8 and 9) where activation had to exceed the counting backwards task and can be attributed to other aspects of task processing such as increased attention resource utilization.

The Accuracy and the Dual Task SPMs are concordant with regard to two other brain structures and these may give clues as to other controlled processes involved in this type of time estimation. Both SPMs showed activation in the right lateral cerebellar region and posterior parietal cortex (BA 7). The cerebellar regions differed from that observed in the primary time estimation image (n.b., the area for accuracy was posterior and inferior to the region observed for primary time estimation; cerebellar activation for the Dual Task was more posterior and medial to time estimation). This suggested that a different cerebellar function was at work. Neuroimaging work in the area of learning and the development of task efficiency suggest the cerebellum (along with prefrontal cortex) is important during the early, effortful stages of learning and performance (for discussion see, Raichle, 1997; Tracy et al., 1998). Certainly the controlled processing present during the TIP task would seem to involve such effortful, nonautomatic learning. The parietal regions observed for the Accuracy and Dual Task SPMs overlapped and were not present in the time estimation image. This indicated that the posterior parietal activation was not related to primary time keeping. Brain
lesion studies (Weintraub and Mesulam, 1989) and neuroimaging work (Pardo et al., 1991) has established a role for parietal cortex in tasks requiring alertness and sustained attention. In the TIP task, focus on the target time and preparation of one’s estimation response would seem likely to have induced such alertness and sustained attention. Note, the above interpretations are not tested by the current study and are provided only to highlight the fact that we distinguished a set of structures (prefrontal, posterior parietal, and lateral cerebellar) associated with important qualitative aspects of time estimation performance such as its accuracy, which were clearly distinct from those structures involved in primary time keeping. We cannot specify the exact role these other structures played in time-keeping during the TIP task except to say that they may have been involved in the implementation of controlled processes related to working memory, effortful/unmastered learning, sustained attention, or attention resource utilization.

As a caveat, we acknowledge that not all strategies involved in time estimation were controlled for by our design. In particular, there is the possibility that the periodic, regular noise of the radio frequency pulse provided a strategy, i.e., a kind of metronome effect. In counterpoint, we note that noise buffering headphones were used and that no subject mentioned the noise in describing their strategy. Also, it would appear that utilizing the noise of the radio frequency pulse, which had a reliable periodicity (i.e., a TR of 3.8), would itself have involved temporal estimation.

In summary, we identified brain structures that implemented explicit time estimation which could not be accounted for by subject strategies such as counting and number manipulation, or cognitive processes associated with dual-task performance such as attention resource utilization. The data are consistent with proposals that the cerebellum is a repository of codes for monitoring time, coding temporal distance, and judging target time and preparation of one’s estimation related to controlled processing. To argue that a cerebellar, temporal circuit implements primary time keeping functions involving explicit, nonautomatic processing is not to say that all time judgments rely on these structures or that these are the only structures involved. The empirical focus of this study was on the substrates of primary time keeping as separated from number monitoring and manipulation strategies and the influx of high-task demand, attentional resources and the cognitive processes that go with them.

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