Title
Neural representation of interval encoding and decision making

Journal
Brain Research, 21(2)

ISSN
1385-299X

Authors
Harrington, Deborah L
Boyd, Lara A
Mayer, Andrew R
et al.

Publication Date
2004-10-01

DOI
10.1016/j.cogbrainres.2004.01.010

Peer reviewed

Available online at www.sciencedirect.com

SCIENCE DIRECT

Cognitive Brain Research 21 (2004) 193–205

COGNITIVE BRAIN RESEARCH

www.elsevier.com/locate/cogbrainres

Research report

Neural representation of interval encoding and decision making

Deborah L. Harrington[a,b,*], Lara A. Boyd[b], Andrew R. Mayer[b,c], Daniel M. Sheltraw[d], Roland R. Lee[a,d], Mingxiong Huang[d], Stephen M. Rao[e]

[a] *Psychology (116B), New Mexico Veteran's Affairs Health Care System, 1501 San Pedro SE, Albuquerque, NM 87108, USA*
[b] *Department of Neurology, University of New Mexico Health Sciences Center, Albuquerque, NM, USA*
[c] *MIND Institute, University of New Mexico Health Sciences Center, Albuquerque, NM, USA*
[d] *Department of Radiology, University of New Mexico Health Sciences Center, Albuquerque, NM, USA*
[e] *Department of Neurology, Medical College of Wisconsin, Milwaukee, WI, USA*

Accepted 13 January 2004
Available online 28 March 2004

Abstract

Our perception of time depends on multiple psychological processes that allow us to anticipate events. In this study, we used event-related functional magnetic resonance imaging (fMRI) to differentiate neural systems involved in formulating representations of time from processes associated with making decisions about their duration. A time perception task consisting of two randomly presented standard intervals was used to ensure that intervals were encoded on each trial and to enhance memory requirements. During the encoding phase of a trial, activation was observed in the right caudate nucleus, right inferior parietal cortex and left cerebellum. Activation in these regions correlated with timing sensitivity (coefficient of variation). In contrast, encoding-related activity in the right parahippocampus and hippocampus correlated with the bisection point and right precuneus activation was associated with a measure of memory distortion. Decision processes were studied by examining brain activation during the decision phase of a trial that was associated with the difficulty of interval discriminations. Activation in the right parahippocampus was greater for easier than harder discriminations. In contrast, activation was greater for harder than easier discriminations in systems involved in working memory (left middle-frontal and parietal cortex) and auditory rehearsal (left inferior-frontal and superior-temporal cortex). Activity in the auditory rehearsal network correlated with memory distortion. Our results support the independence of systems that mediate interval encoding and decision processes. The results also suggest that distortions in memory for time may be due to strategic processing in cortical systems involved in either encoding or rehearsal.

Theme: Neural basis of behavior
Topic: Cognition

Keywords: Timing; Memory; Decision making; Basal ganglia; Cerebral cortex; Cerebellum

1. Introduction

Interest in how the brain processes temporal information has grown over the years, due to its importance in everyday activities that depend upon anticipating events and flexibly adjusting behavior to changing temporal goals. Information processing theories of temporal cognition maintain that multiple processes determine our ability to time events [20,33], including a metaphorical "clock" that represents time through the accumulation of pulses emitted from a timekeeper mechanism. The level of attention devoted to the passage of time is thought to influence the operation of the timekeeper, perhaps by mediating the starting and stopping of pulses. Once a representation of time is formulated, it is encoded into memory, and then decision processes compare the current representation of time from the clock process with those stored in memory to decide when and how to respond. The interaction among these component processes gives rise to our perception of time.

The present study investigated the neural representation of processes associated with encoding intervals and making decisions about their durations. The neural underpinnings of

* Corresponding author. Psychology (116B), New Mexico Veteran's Affairs Health Care System, 1501 San Pedro SE, Albuquerque, NM 87108, USA. Tel.: +1-505-265-1711x2389; fax: +1-505-256-5498.
E-mail address: dharring@unm.edu (D.L. Harrington).

0926-6410/$ - see front matter © 2004 Elsevier B.V. All rights reserved.
doi:10.1016/j.cogbrainres.2004.01.010

temporal information processing remain controversial, largely due to the difficulty in distinguishing between systems that specifically support timekeeping mechanisms and systems that regulate other processes, such as decision making. Focal lesion studies in humans have shown that damage to the basal ganglia, cerebellum and cerebral cortex all disrupt the ability to perceive and/or reproduce time intervals or perform other behaviors that appear to depend upon accurate timing [8,21–23,25,35,39]. The reasons for performance impairments remain controversial, because it is unclear how a deficient timekeeper should affect temporal processing proficiency (e.g., accuracy, variability) relative to impairments in other processes such as attention [55] or motor dysfunction in the performing limb [18]. Adding to this problem, functional imaging research has focused on motor timing or used blocked-trial designs, which make it difficult to distinguish the role of central timing mechanisms from sensorimotor or other processes.

In an earlier study, we addressed some of these limitations by using the temporal resolution capabilities of functional magnetic resonance imaging (fMRI) to study activation in neural systems associated with different components of a time perception task [45]. In this task, two tones separated by 1200 ms (defining the standard interval) were presented, followed by a comparison interval. Subjects judged whether the comparison interval was longer or shorter than the standard. We showed that activation in the basal ganglia (bilateral caudate and putamen) and right inferior parietal cortex developed in association with encoding the standard interval. This contrasted with activation in the right dorsolateral prefrontal cortex (DLPFC), which developed later in association with comparing the two intervals and making a decision about their relative duration. These results were consistent with the respective roles of the basal ganglia and the right inferior parietal cortex in timekeeping [36] and attention [23] components of the clock process and the right DLPFC in executive components of working memory [43].

Despite converging evidence supporting the striatum and dopamine neurotransmission in hypothetical clock processes [22,32,36,38,39], other research suggests that the caudate nucleus is intimately involved in working memory [29,42]. This proposal suggests that early caudate activation in our study could be due to actively maintaining the same representation of a single standard interval across trials, rather than encoding the interval on each trial. We addressed this issue in the present study by randomly presenting two different standard intervals (1200 or 1800 ms) to encourage subjects to encode the standard on each trial. If the caudate is involved in formulating representations of time, we predicted that activation should be seen within 4 s after the onset of the standard interval.

A second focus of the study was to investigate the neural systems that support decisions about two temporal events. Decision processes are involved in comparing pulse counts from the clock process with those stored in memory, but little is known about the nature of these processes. Theoretically, decisions take into account a threshold for determining whether a comparison interval exceeds the duration of a standard interval [20]. This assumption is consistent with a study showing that decision thresholds can be biased by manipulating payoff contingencies for detecting correct or incorrect responses [56]. In this study, selective attention to reinforced responses affected decisions about temporal events, but not their timing, implying a functional independence of the clock and decision components of timing. Selective attention has been implicated in making decisions about time in electrophysiological studies [9,10]. Here, the amplitude of slow cortical potentials in the prefrontal cortex is greater for incorrect than correct responses, ostensibly reflecting the lower level of attention paid to time when intervals can be easily discriminated. Still, the precise source(s) of the electrophysiological responses is (are) unknown, as is the role of other neural systems. Additionally, electrophysiological responses distinguishing correct and incorrect trials could also reflect the quality of interval encoding, rather than decision processes per se. Complicating the identification of decision processes is the fact that decisions closely follow the processing of information that must be acted upon. It is therefore not clear whether neural activity associated with selecting a response is due to the goodness of encoding an interval, decision making, or both. For these reasons, we examined the effect of time discrimination difficulty on brain activation during the decision-making phase of a trial to evaluate regions involved in decisions more directly. This aspect of the study also allowed us to test the independence of neural systems that support clock and decision components of temporal information processing. We predicted that decision difficulty should not influence activation in systems that are principally involved in timekeeping operations, if these processes are independent [20,56].

A related issue pertains to the role of memory in interval encoding and decision processes. Timing theory assumes that output from the clock process is encoded into memory and then retrieved for decision making, suggesting that the medial temporal lobes (MTL) should participate in temporal processing, given their role in memory [7]. It has been speculated that the MTL is crucial for keeping memory traces active and accessing them for decision making [7,47]. However, controversy remains as to whether MTL lesions in animals disrupt timing [13,40]. Functional imaging studies have not found MTL activation during timing, although this could be due to the use of "control" conditions that subtract out activation. Another explanation relates to the use of a single standard interval across blocks of trials, which could minimize memory demands during temporal processing. This possibility is suggested by the "migration" of temporal estimates when subjects are trained on two different intervals [30]. When different intervals are tested together, shorter intervals are overestimated and longer ones underestimated relative to when they are tested separately. This

appears to reflect a mixing of memories for the two intervals rather than a decision bias, because the latter should produce a distortion in the same direction for both standard interval conditions, which does not occur. In the present study, we expected that the use of two randomly presented standard intervals would place greater demands on memory processes, resulting in MTL activity in association with interval encoding and decision making.

Finally, while we assumed that clock and decision-making processes were operating primarily during the standard interval encoding and decision phases of a trial, respectively, other processes are likely ongoing at the same time during both phases. To better define the functional significance of activity during these two phases of a trial, we correlated brain activation with different behavioral measures of time perception to better identify systems that were preeminent in interval timing. Whether patterns of brain activation during temporal processing can be distinguished by measures that have different theoretical significance is not known. Although the bisection point, a measure of accuracy, reflects clock speed [20], we did not expect it to correlate with timekeeping systems in our study since the rate of the clock should be the same for both standard intervals. The point of bisection might correlate, however, with activity in systems that encode and retrieve representations of different intervals. We expected the difference between the bisection points, a measure of the migration or distortion in memory for intervals [30], to correlate with activation in systems associated with memory processes. Finally, we predicted that the coefficient of variation, a measure of temporal processing efficiency or sensitivity [20], would correlate with activity in systems previously associated with timing in lesion studies including the basal ganglia [22,39], right middle-frontal and inferior parietal cortex [23] and cerebellum [25].

2. Methods

2.1. Subjects

Study participants were 24 right-handed healthy adults between the ages of 21 and 53 (mean = 30.6, S.D. = 10) with no history of neurological or psychiatric disorders. Only nonsmokers were studied due to the effect of nicotine on the dopamine system. Participants were asked to refrain from drinking alcohol 24 h prior to their scanning session. Study procedures were approved by the Human Research and Review Committee at the University of New Mexico Health Sciences Center. Informed consent was obtained from all participants.

2.2. Procedures

Event-related fMRI was conducted on a 1.5-T Picker scanner at the New Mexico Veteran's Affairs Health Care System in Albuquerque. Subjects performed time discriminations as they underwent fMRI scanning. Prior to imaging, subjects practiced the task outside the scanner. Throughout the scanning session, subjects were instructed to maintain fixation on a green cross in the center of a screen. One second before the onset of each trial, the fixation cross changed color (white) for 500 ms, signaling the subject to get ready for the trial. Fig. 1 (top) diagrams the trial events.

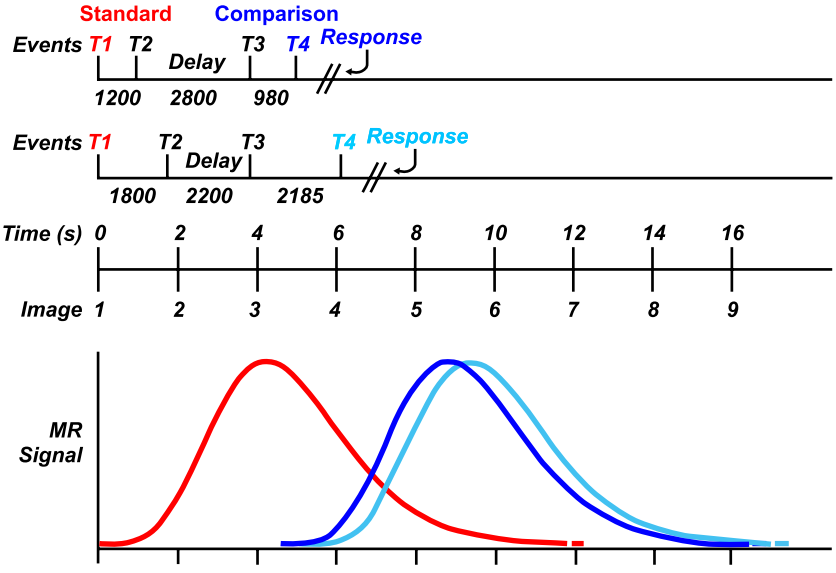

Fig. 1. Trial events, image acquisition and theoretical hemodynamic response associated with interval encoding and decision phases of a trial. The first scan was acquired at the onset of the first tone (T1). Responses for shorter trials (1200-ms standard interval condition with a "shorter" comparison interval) were made within 6-s posttrial onset, whereas responses for longer trials (1800-ms standard and "longer" comparison interval) were made within 7-s of trial onset. The three hypothetical time course functions illustrate the expected MR signal response associated with standard interval encoding (red) and decision phases (blue, light blue) of a trial.

At the beginning of a trial, two tones (T1 and T2) separated by 1200 or 1800 ms (standard interval) were randomly presented, followed by a 2800-ms (1200-ms standard) or 2200-ms (1800-ms standard) delay, and then two more tones (T3 and T4; comparison interval) that were separated by a longer or shorter amount of time than the standard interval. Subjects indicated whether the comparison interval was longer or shorter than the standard interval by pressing one of two keys using their right index or middle finger. For each standard interval condition, there were four longer and four shorter comparison intervals that incremented logarithmically beginning at ± 5% of the standard interval duration. Reaction time (RT) and accuracy were recorded. To generate temporal discrimination gradients, accuracy data were converted to the percent longer responses associated with each comparison interval.

Subjects rested supine in the scanner with their head secured by chin and forehead straps, and foam padding to limit head motion in the head coil. Tone stimuli were binaurally delivered to subjects via air conduction through plastic tubes that passed through earplugs, which attenuated background scanner noise. Background scanner noise consisted of approximately 500 Hz pulses occurring every 205 ms throughout an imaging run. Visual stimuli were presented using an Avotec Silent Vision goggle system. A non-ferrous key-press device was positioned directly under the subject's right hand to record responses. Stimulus presentation, synchronization of stimulus events with the MRI scanner and the collection of behavioral data for offline analyses were achieved using RTStim software (www.rtstim.org).

2.3. fMRI procedures

Images were acquired using a single-shot, blipped gradient-echo echo-planar pulse sequence (21 contiguous sagittal 6-mm slices, TE = 36 ms, TR = 2.0 s, 90° flip angle, FOV = 256 mm, 64 × 64 matrix). Before functional imaging, high-resolution 3D spoiled gradient recalled at steady-state T1 anatomic images were collected (TE = 5 ms, TR = 24 ms, 40° flip angle, NEX = 1, slice thickness = 1.2 mm, FOV = 256 mm, 256 × 256 matrix) for anatomic localization and co-registration.

Fig. 1 shows that image acquisition was synchronized to the onset of the first tone (T1) and the comparison interval. Because different delays were pegged to each standard interval, image acquisition coincided with the onset of the comparison interval in both conditions. Each run consisted of 24 trials for a total of 96 experimental trials. There were 48 trials for each standard interval condition, with 6 trials per comparison interval. For each run, a minimum of six images was collected per trial (i.e., 144 images for 24 trials). Another 42% of these images (i.e., 60 images) consisted of "blank" (resting) scanning intervals that were included as a baseline control condition and randomly inserted at the end of trials (i.e., one to four images) to introduce jitter in the time series. This procedure helps differentiate activation trials from baseline activation [6]. Subjects completed four imaging runs. An additional four images were added to the beginning of each run to allow the MR signal to reach equilibrium; these images were discarded in the data analyses. Another four images were added to the end of each run to accommodate the delayed rise of the hemodynamic response. In total, 212 images were acquired per run, and each run lasted approximately 7 min.

Fig. 1 shows the expected hemodynamic response in relationship to the encoding and decision phases of a trial. We expected that the 2- and 4-s posttrial onset-scanning intervals should reveal brain activation patterns specific to encoding time intervals. We expected that activity associated with decision making would be evident during the 8- and 10-s scanning intervals. This assumption was based on the observation that discrimination responses for shorter trials (e.g., 1200 ms standard and "shorter" comparison intervals) were made within about 6 s of trial onset, whereas responses for longer trials (e.g., 1800 ms standard and "longer" comparison intervals) were made within 7 s of trial onset. In addition, peak activity in the contralateral (left) primary motor cortex occurred 8- and 10-s posttrial onsets, in association with the right finger key-press responses. We reasoned that the analyses of decision difficulty would then separate regions specifically associated with decision making from those involved in encoding the comparison interval or other processes.

2.4. fMRI analysis

Functional images were generated using Analysis of Functional NeuroImages (AFNI) software [11]. Time-series images were spatially registered in three dimensions to minimize effects of head motion. A deconvolution analysis was used to generate impulse response functions (IRFs) of

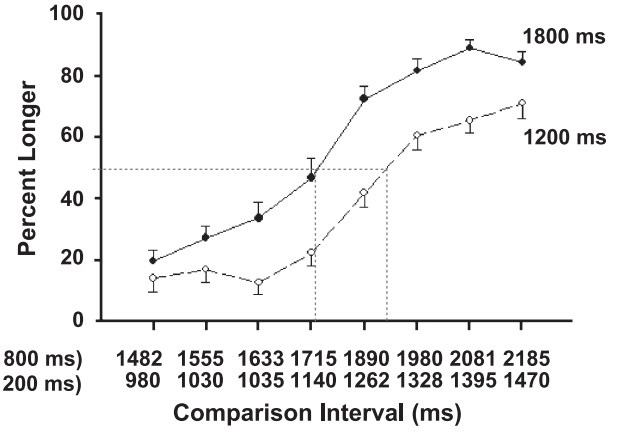

Fig. 2. Percent longer responses for the 1200- and 1800-ms standard interval conditions. Data are plotted as a function of the comparison interval. Open circles denote the 1200-ms standard interval condition, and closed circles denote the 1800-ms standard interval condition. Dashed lines illustrate the point of bisection for the two standard interval conditions (1299 and 1730 ms for the 1200- and 1800-ms standard intervals, respectively).

the fMRI signal on a voxel-wise basis. This analysis produced an estimate of the hemodynamic response for each condition (i.e., standard interval, discrimination difficulty) relative to a baseline state (rest) without making a priori assumptions about 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 and blurred using a 4-mm Gaussian full-width, half-maximum filter to compensate for intersubject variability in anatomic and functional anatomy. Activation foci were delineated using the Talairach atlas for the cerebral cortex [51] and the Schmahmann atlas for the cerebellum [48].

To examine regions associated with encoding the standard interval, a mixed-model analysis of variance (ANOVA) treating subjects as a random factor tested the within-subjects effects of encoding (2- and 4-s images) and standard interval condition (1200 and 1800 ms). In these analyses, the main effect of encoding reflects brain activity that was significantly greater than baseline activity during the 2- and 4-s epochs. To reduce false positives, the threshold for statistical significance was a *p*-value of 0.005 and a minimum cluster size of 200 μl [17]. A second analysis examined regions associated with making decisions about the relative duration of the two intervals. Due to the small number of observations for each comparison interval, several approaches were taken to gain adequate statistical power. First, we collapsed across standard interval condition. Second, we omitted comparison interval conditions that fell between those that were the closest and furthest away in physical time (i.e., longer and shorter by the same amount) from each standard interval. This was done because time discrimination functions are often asymmetrical with respect to the physical distance of the comparison interval from the standard, especially when two or more standard interval conditions are randomly presented. In our data, within-subject error variance was reduced, and the greatest differences in accuracy were obtained by taking the average of the comparison intervals that were the closest and furthest in physical time from the standard interval as an index of

Table 1
Regions showing signification activation during the encoding phase of a trial

Left hemisphere	Talairach coordinates			Volume (μl)	Right hemisphere	Talairach coordinates			Volume (μl)
	x	*y*	*z*			*x*	*y*	*z*	
Main effect of encoding									
Medial frontal and cingulate									
Increased activation									
Anterior cingulate (24)	− 11	16	25	239	Medial frontal (9)	1	41	35	431
					Posterior cingulate (23)	7	− 40	23	358
Decreased activation									
Medial frontal (9)	− 3	52	22	423	Pre-SMA (6)	7	11	55	1666
Frontal									
					Inferior frontal (44,45)	51	10	21	552
Temporal									
Superior temporal (22,41,42)	− 54	− 30	12	1228	Superior temporal (21,40[a],41,42)	54	− 28	9	11,412
Parietal									
Superior parietal (7)	− 35	− 64	43	370	Precuneus (7)	4	− 51	61	516
Angular gyrus (39)	− 44	− 60	35	253	Precuneus (7)	6	− 81	35	3624
Inferior parietal (40)	− 48	− 45	41	297	Inferior parietal (40)	40	− 48	40	2298
Occipital									
					Lingual gyrus (18)	10	− 88	− 10	258
Basal ganglia									
Caudate (body) and putamen	− 16	4	22	1829	Caudate (body)	14	− 1	17	1184
Caudate tail	− 36	− 34	− 1	217	Caudate (body)	10	16	3	774
Putamen	− 29	3	3	306					
Cerebellum									
Declive (lobule VI)	− 11	− 75	− 15	526	Declive (lobule VI)	40	− 61	− 20	3335
Pyramis (lobule VIIB)	− 12	− 70	− 29	730					
Tuber (lobule VII)	− 35	− 57	− 28	1938					
Main effect of standard interval									
Medial frontal									
Superior frontal (9)	− 4	53	34	225					
Temporal									
					Parahippocampus (36) and hippocampus	31	− 17	− 17	219

Numbers in parentheses refer to Brodmann areas.
[a] Post-central gyrus.

discrimination difficulty (i.e., hard and easy decisions). This resulted in 24 trials for the easy and 24 trials for the hard discriminations (i.e., 12 trials for each standard interval condition). A mixed-model ANOVA treating subjects as a random factor was applied to the IRF estimates for hard and easy conditions to test the effect of decision difficulty 8 and 10 s posttrial onset. Because this analysis contained only half of the total number of experimental trials, we adopted a less conservative significance threshold of $p = 0.01$ and used a minimum cluster size of 200 μl.

3. Results

3.1. Behavioral results

A repeated-measures ANOVA tested the main effects of standard interval, comparison interval and their interaction for RT and percent longer responses. The Huynh-Feldt correction was used to adjust for heterogeneity of variance. In the analysis of the RT data, there was a main effect of comparison interval [$F(5.3,161) = 3.49$, $p < 0.01$], showing that RTs were generally longer for comparison intervals closer than further away in physical time from the standard interval. RTs in the 1200-ms condition (mean = 1055, SDerr = 62.6) did not differ significantly from those in the 1800-ms condition (mean = 1021, SDerr = 65.9). No other effects were significant.

Fig. 2 displays the percent longer responses for each standard interval condition as a function of the comparison interval. The standard × comparison interval interaction [$F(5.8,161) = 3.2$, $p < 0.01$] suggests that subjects overestimated time in the 1200-ms condition and underestimated time in the 1800-ms condition. This was confirmed by a subsequent analysis that estimated the bisection point (i.e., point in time at which 50% of responses are "longer"), which reflects timing accuracy. Here, a linear regression was applied to each subject's data, and then estimates were derived for the bisection point (timing accuracy) and difference limen (timing variability). The dashed lines in Fig. 2

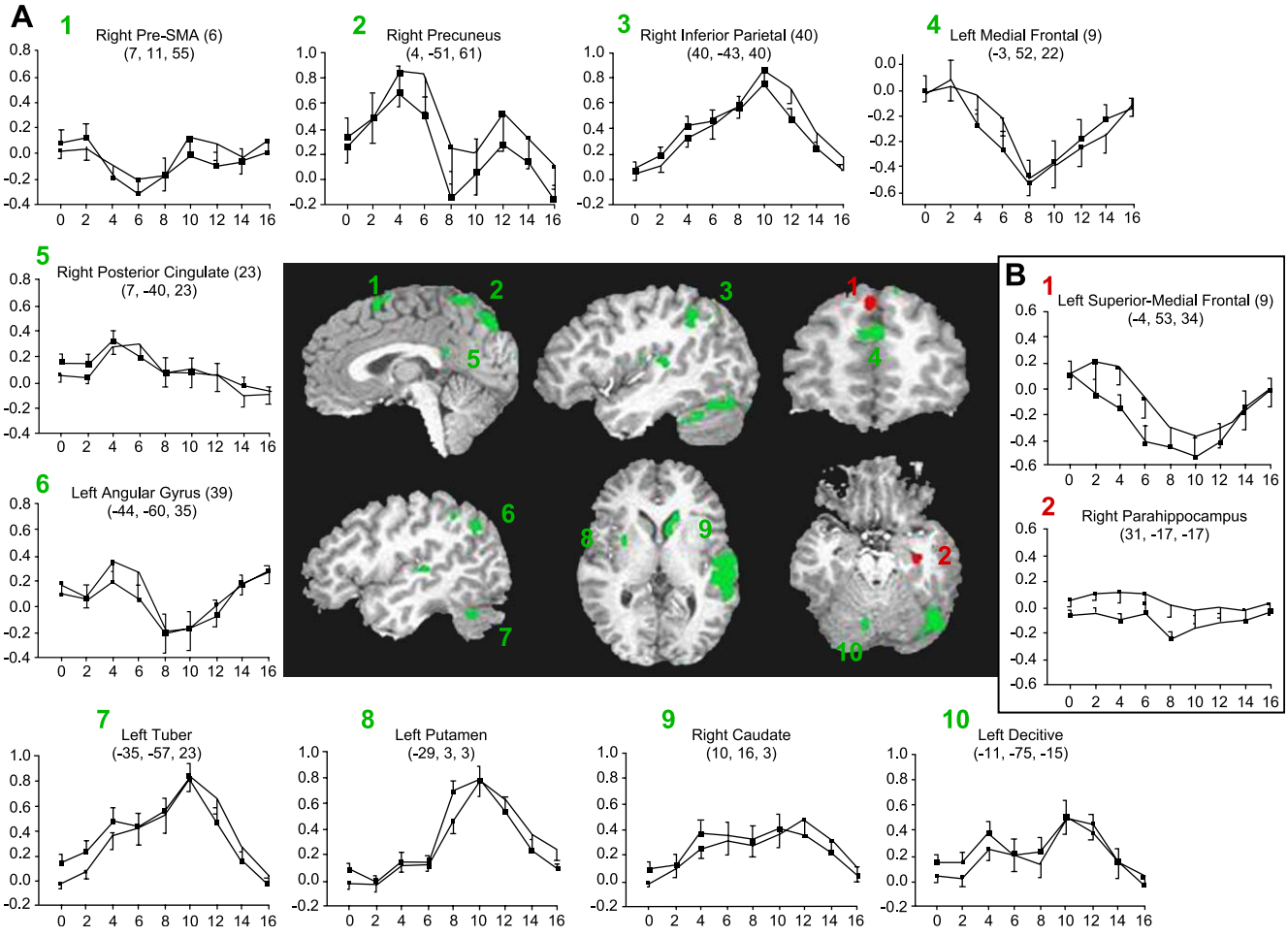

Fig. 3. Percent signal change in selected regions showing a main effect of encoding (A) and standard interval condition (B) in association with the presentation of the standard interval (2- and 4-s epochs). The time course of the MR signal change is graphed for the entire 16-s trial. Open circles and dashed lines denote the 1200-ms standard interval condition, and closed circles and solid lines denote the 1800-ms standard interval condition. Activation foci displayed in green designate areas showing a main effect of encoding, and foci in red designate areas showing a main effect of standard interval condition.

illustrate the point of bisection for the 1200-ms (mean = 1299, SDerr = 23) and 1800-ms (mean = 1730, SDerr = 26) standard interval conditions. Next, we computed a measure of memory migration or distortion by subtracting the 1200-ms bisection point from the 1800-ms bisection point. Larger values indicate greater differentiation between the two standard interval conditions. On the average, subjects showed some merging of their memories for the two intervals as indicated by the mean difference of 431 ms (SDerr = 30). Finally, the coefficient of variation was computed by dividing the difference limen (1200-ms standard: mean = 237, SDerr = 21.5; 1800-ms standard: mean = 315.3, SDerr = 27.4) by the bisection point. Timing was scalar or in proportion to the timed interval as demonstrated by the similar coefficients of variation for the 1200-ms (mean = 0.182, SDerr = 0.015) and 1800-ms (mean = 0.183, SDerr = 0.018) standard interval conditions.

To directly compare performance on easy and hard trials, a repeated-measure ANOVA tested the effects of standard interval, decision difficulty (easy, hard) and their interaction. For RT, a main effect of decision difficulty [$F(1,23) = 10.5$, $p < 0.01$] showed that responses were faster for easy (mean = 949 ms, SDerr = 62) than hard decisions (mean = 1098 ms, SDerr = 69). For percent correct, a main effect of decision difficulty [$F(1,23) = 41.4$, $p < 0.0001$] demonstrated that easy discriminations (mean = 80.4, SDerr = 2.9) were more accurate than hard discriminations (mean = 61.3, SDerr = 1.7). No other effects were significant.

3.2. fMRI results

3.2.1. Encoding phase

Table 1 lists the regions showing significant main effects of encoding (2 and 4 s posttrial onset) and standard interval condition (critical $F = 9.629$). A main effect of encoding was found in distributed brain regions in association with the presentation of the standard interval. Fig. 3A displays the time course of the MR signal change across the entire trial

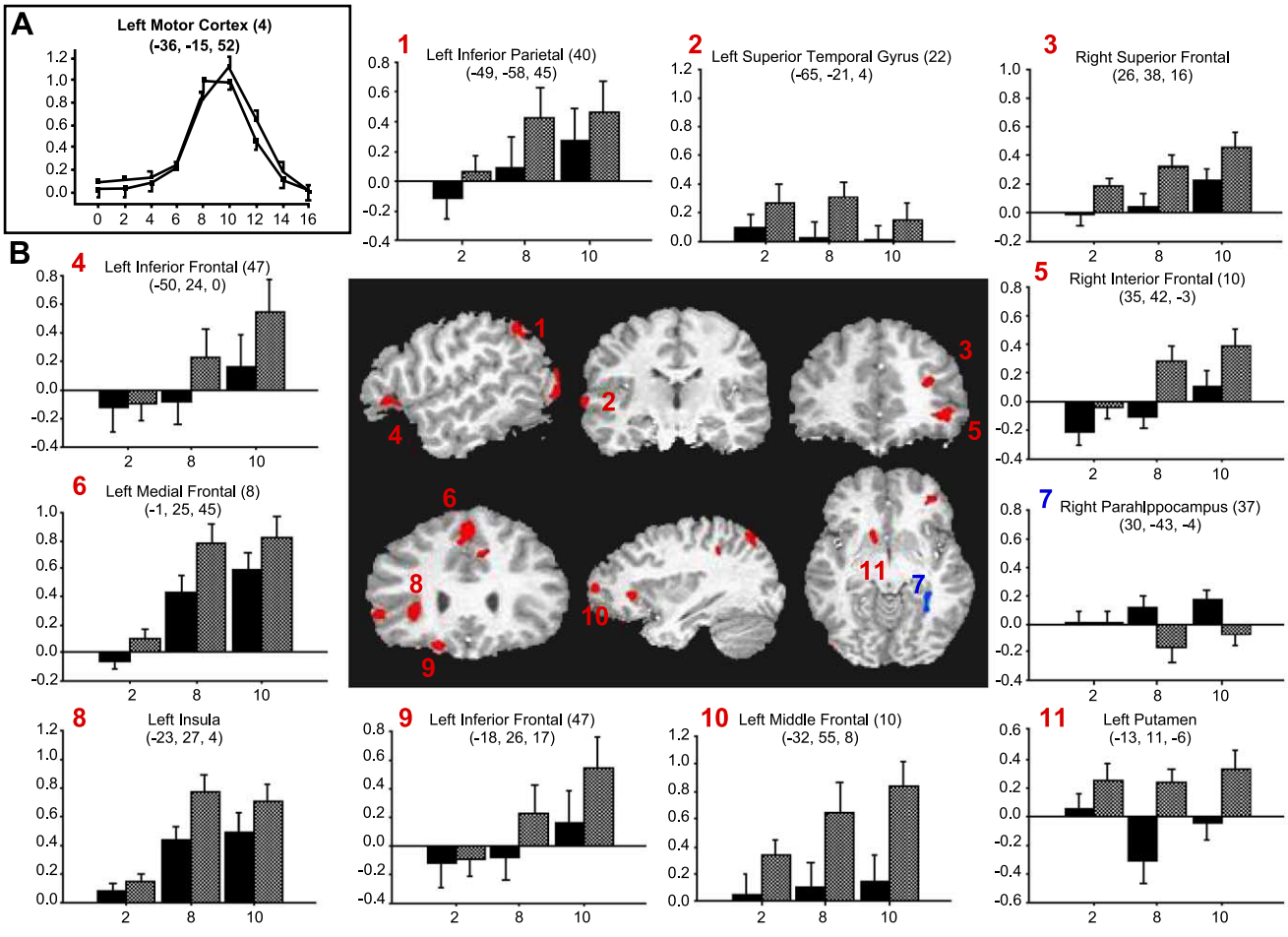

Fig. 4. Percent signal change in selected regions showing a main effect of time discrimination difficulty during the decision-making phase of a trial (8- and 10-s epochs). (A) graphs the percent signal change in the left motor cortex as a function of the time posttrial onset. (B) graphs the effect of discrimination difficulty in selected regions. The bar graphs contrast the percent signal change in an epoch associated with interval encoding (2-s posttrial onset), which showed no effect of discrimination difficulty, with the epochs associated with the decision-making phase (8- and 10-s posttrial onset). Black bars denote easy, and gray bars denote hard interval discriminations. Activation foci displayed in red designate regions showing greater activation for harder than easier interval

for selected regions. This figure shows that activation decreased below baseline during the encoding of the standard interval in the left medial frontal cortex (BA 9) and right pre-SMA. In both regions, activation did not return to baseline until the end of the trial. In contrast, activation increased above baseline in the right medial frontal cortex (BA 9; not shown) and the anterior and posterior cingulate areas. In all remaining regions, activation increased above baseline during the encoding phase of the trial. These regions included the bilateral superior temporal cortex, distributed areas of the parietal cortex (bilateral BA 40, left BA 7, left angular gyrus, right precuneus), right lingual gyrus, basal ganglia (bilateral caudate body, left caudate tail, left putamen) and lobules VI and VII of the cerebellum (bilateral declive, left pyramis, left tuber).

Table 1 shows that a main effect of standard interval was found in two regions: the left medial superior-frontal cortex and the right parahippocampus, both of which showed greater activation during the 1800-ms than the 1200-ms standard interval condition (see Fig. 3B).

3.2.2. Decision phase

To establish the epochs associated with the decision phase of a trial, a region of interest analysis was performed for the primary motor cortex contralateral to the performing hand, testing for the standard interval × time posttrial onset interaction (2–12-s posttrial onset) (critical $F = 4.669$, $p = 0.005$). Fig. 4A graphs the significant interaction. This figure shows that peak activation in the 1200-ms condition occurred from 8 to 10 s posttrial onset, whereas peak activation in the 1800-ms condition occurred 10 s posttrial onset. These results suggest that the 8- and 10-s epochs represented the decision-making phase of the trial, since response implementation closely follows a decision. This assumption is supported by the RT findings, which show that decision and response implementation processes are carried out within approximately 1 s after the offset of the comparison interval.

Table 2 lists regions showing significant main effects of discrimination difficulty at the 8- and 10-s posttrial onset epochs (critical $F = 2.655$), and Fig. 4B graphs the percent signal change in some of these regions. Greater activation for hard than easy decisions was found in the left medial frontal cortex (BA 8), bilateral prefrontal cortex (BA 10, 45, 47), left superior temporal cortex, left superior (BA 7) and inferior parietal cortex (BA40), left middle occipital cortex (BA 19) and the putamen and nucleus accumbens. In contrast, greater activation for easy than hard discriminations was seen in the right parahippocampus. To verify that activation was specific to the discrimination difficulty during these epochs, post hoc *t*-tests compared the percent signal change for easy and hard decisions, 2 s posttrial onset, when the decision stage had not yet begun. No effect of discrimination difficulty was found during this epoch.

Table 2
Regions showing significant effects of discrimination difficulty during the decision phase of a trial

Left hemisphere	Talairach coordinates			Volume (μl)	Right hemisphere	Talairach coordinates			Volume (μl)
	x	*y*	*z*			*x*	*y*	*z*	
Medial frontal									
Medial frontal (8)	−1	25	45	1538					
Frontal									
Middle frontal (10)	−32	55	8	324	Superior frontal	26	38	16	299
Inferior frontal (47)	−18	26	−17	236	Inferior frontal (10)	35	42	−3	418
Inferior frontal (47)	−50	24	0	230	Inferior frontal (45,47)	45	20	5	278
Temporal									
Superior temporal (22)	−65	−21	4	234					
Insula	−28	27	4	713	Parahippocampus (37)	30	−43	−4	331
Parietal									
Superior parietal (7)	−27	−66	53	851					
Inferior parietal (40)	−49	−53	45	322					
Inferior parietal (40)	−34	−41	41	241					
Occipital									
Middle occipital (19)	−46	−77	10	907					
Basal ganglia									
Putamen, nucleus accumbens	−13	11	−6	530					

Activation was greater for hard than easy discriminations in all regions except the parahippocampus, where activation was greater for easy than hard discriminations. Numbers in parentheses refer to Brodmann areas.

3.3. Correlation of behavioral and fMRI data

To identify regions associated with behavioral measures of time discrimination, Pearson correlations analyzed the relationship between three different indices of time discrimination (bisection point, memory migration, coefficient of variation) and area under the curve in regions identified in the encoding (2- and 4-s epochs) and the decision (8- and 10-s epochs) phases in the above analyses. Due to the exploratory nature of these analyses, an uncorrected p level of 0.05 was the criterion for significance. Table 3 shows that during the encoding phase, larger coefficients of variation (poorer processing efficiency) were associated with greater activation in the right inferior parietal, right caudate, left declive and left tuber. In contrast, increases in the bisection point correlated with greater activation in the right parahippocampus, whereas a greater memory migration effect was associated with greater activation in the right precuneus. During the decision phase, a greater memory migration effect was associated with less activation in the left superior temporal cortex.

To explore whether brain activation during the decision phase related to response preparation processes, Pearson correlations examined the relationship between RTs for easy and hard discriminations and the area under the curve for regions showing an effect of decision difficulty. Longer RTs were associated with greater activation in the left superior parietal (− 27, − 66,53) and inferior parietal (− 49, − 53,45) cortices ($r = 0.30$, $p < 0.05$ for both analyses).

Table 3
Correlations of timing proficiency with area under the curve in regions associated with encoding and decision phases of a trial

	Talairach coordinates			Estimates of timing proficiency		
	x	*y*	*z*	Bisection point[a]	Memory bias[b]	Coefficient of variation[a]
Encoding phase: main effect of time						
Right inferior parietal	40	− 48	40			0.31*
Right precuneus	4	− 51	61		− 0.44*	
Right caudate	14	− 1	17			0.30*
Left declive (lobule VI)	− 11	− 75	− 15			0.36**
Left tuber (lobule VII)	− 35	− 57	− 28			0.32*
Encoding phase: main effect of standard interval						
Right parahippocampus	31	− 17	− 17	0.40***		
Decision-making phase: main effect of time						
Left superior temporal	− 65	− 21	4		0.44*	

All tabled correlations based on two-tailed significance tests where *$p < 0.05$, **$p < 0.025$ and ***$p < 0.01$.
[a] $df = 48$.
[b] $df = 24$.

4. Discussion

4.1. Interval encoding

The results showed that distributed regions of the basal ganglia, cerebellum and cerebral cortex were activated during the standard interval encoding phase of a trial. However, activation correlated with behavioral measures of time discrimination in only some of these regions including the right caudate, right inferior parietal cortex and precuneus, right parahippocampus and hippocampus and left cerebellum. Damage to most of these regions produces timing deficits [22,23,25,40], which further supports their preeminence in interval timing. The results were also in keeping with a right hemisphere bias for time perception processes [23,45]. It was notable that different behavioral measures of time discrimination were associated with activity in different neural systems during this phase of the trial. This result supports timing theory, which assumes different measures express functionally distinct processes.

Encoding-related activity in the caudate nucleus and putamen extends our previous fMRI results [45] by demonstrating this effect under conditions when subjects were encouraged to encode the standard interval on each trial. Thus, it appears that basal ganglia activation in our earlier study was not due to rehearsing the same interval throughout the experiment. Importantly, greater activation in the right caudate was associated with reduced timing sensitivity, which suggests this area is more specifically involved in the clock process. This result is consistent with research in animals demonstrating that the binding affinity of D2 receptor antagonists predicts clock speed [36] and that striatal neurons fire in response to specific durations during a temporal estimation task [34]. The positive association between caudate activity and the coefficient of variation suggests that clock processes are more effortful in individuals who are less proficient at interval timing.

The above result is relevant to findings in people with Parkinson's disease who were tested "on" and "off" their dopamine replacement therapy as they performed a temporal estimation task, in which different durations were tested across different blocks of trials [30,31]. Temporarily stopping dopamine therapy produced an increase in the coefficient of variation and a migration effect (i.e., overestimation of shorter and underestimation of longer intervals), relative to when patients were taking their normal therapy. Because working memory demands were presumably minimized in this paradigm, the results were attributed both to a slowdown in memory storage and deficient inhibition of competing memories during retrieval [31]. This contrasts with our study, in which memory migration might be more related to trial by trial variability in working memory processes. Still, because caudate activity did not correlate with the migration effect during encoding or retrieval of interval representations in our study, the memory distortions in Parkinson's disease are not likely due to basal ganglia dysfunction per se, but perhaps

more directly related to reduced cortical functioning in this disorder.

Caudate activation during interval encoding was accompanied by activity in two areas of the right parietal lobe that appear to subserve distinct functions. Like the caudate, activation in the right inferior parietal cortex correlated with timing sensitivity. This finding is consistent with our previous fMRI study, which showed that caudate and right inferior parietal activity were unique to timing events, rather than more generally related to making sensory discriminations [45]. These results are also in agreement with disturbances in time perception after damage to the inferior parietal cortex of the right, but not the left hemisphere [23], which correlate with deficits in attention. Collectively, these findings strengthen evidence for the right inferior parietal cortex in modulating attention during interval encoding, perhaps by regulating the starting and stopping of pulses from the timekeeping mechanism [20]. A recent study provides physiological support for this proposal, showing that neurons in the posterior parietal cortex of monkey (which are not specific to a hemisphere) respond to elapsed time during the performance of a time perception task similar to ours [28]. In the present study, it is noteworthy that activity in the right inferior parietal cortex did not correlate with decision difficulty, suggesting that the well-documented attention function of this region in humans was specific to interval encoding in our task.

In contrast to the right parietal cortex, encoding-related activity in the right medial-parietal cortex (precuneus) correlated with memory bias. Greater activation in the right precuneus was associated with a larger migration effect. The precuneus has dense interconnections with the MTL [53], consistent with its participation in memory encoding and retrieval [43]. Structural equation modeling of networks involved in working memory further demonstrate that the precuneus shares strong functional connections with extrastriate cortex, parahippocampus, anterior and posterior cingulate areas and inferior frontal cortex [26], all of which were activated during encoding in the present study. Although the specific function of the precuneus is not well defined, activity in this area is greater for imaginable than nonimaginable word-pair associates during retrieval [16]. These findings lead us to speculate that increased activity in the precuneus may reflect greater difficulty in accurately encoding intervals, possibly due to the use of visual strategies. A visual encoding of time might be more susceptible to memory distortion because temporal processing is more variable in visual than auditory modalities [46]. This proposal is compatible with our finding that memory distortion is reduced during decision making when there is greater activation in systems involved in auditory rehearsal (see below).

We also found activation in the right parahippocampus and hippocampus during interval encoding, which correlated with the bisection point, indicating that MTL processing was specifically sensitive to the temporal characteristics of the standard interval. This result is consistent with timing theory, which assumes that output from an internal clock is encoded and represented in memory [20]. Our results are also in keeping with a bias for the left MTL in verbal processing and the right MTL in nonverbal processing [52]. However, our results also suggest that damage to the MTL may not necessarily affect timing sensitivity [13], at least under conditions in which memory functions are minimized. MTL pathways also appeared to act interdependently with the lateral ventral prefrontal (BA 44, 45), medial frontal (BA 9, 23, 24) and parietal (BA 7) and superior temporal cortex to promote encoding [7], with some regions showing decreased activation (left medial 9, right preSMA) and others showing increased activation (cingulate areas, right medial 9, right precuneus, left inferior frontal, superior temporal). Of particular significance in our study was activation in the right inferior-frontal (BA 44, 45) and superior-temporal cortices, which constitutes an auditory rehearsal network [41,57] that may maintain standard intervals active in working memory for later decision making. Unlike the MTL, activity in frontal and temporal regions during encoding did not correlate with performance, perhaps indicating that rehearsal networks are not crucial early during the formulation of interval representations. Consistent with our earlier fMRI study [45], activation was also not observed in middle-frontal areas widely associated with executive functions of working memory, which strengthens our contention that activity during the 2- and 4-s epochs was largely a reflection of clock and memory encoding processes.

Temporal processing efficiency during encoding also correlated with activation in vermal and hemispheric lobules VI and VII of the cerebellum, which receive auditory and visual inputs (vermis) and afferents from the motor and prefrontal cortices (cerebellar hemispheres) [1]. In a previous fMRI study, we reported that cerebellar activation associated with encoding the standard interval was not significantly greater than a baseline sensorimotor control condition, leading us to conclude that it did not support timekeeping processes per se [45]. This conclusion is consistent with recent findings showing normal time-perception performance in patients with large cerebellar lesions due to stroke [24]. Why then does cerebellar activity correlate with timing proficiency in the present study? Insight into this question can be gained by first considering the work of Bruekelaar and Dalrymple-Alford [4], who reported that rats with large lesions to the lateral cerebellar hemispheres, but not the vermis, showed subtle time estimation deficits for intervals in the milliseconds (200–800 ms), but not in the seconds (2–8 s) range. Cerebellar hemisphere lesions also disrupted numerical discriminations. However, both timing and numerical discrimination deficits recovered with extended training, unlike lesions to the substantia nigra and caudate putamen, which other work suggests produce enduring timing deficits [22,36,39]. These results are inconsistent with a cerebellar timing hypothesis [25], which would predict more robust and long-term time estimation deficits, particularly after large cerebellar hemi-

sphere lesions. Bruekelaar and Dalrymple-Alford proposed that cerebellar damage adds a constant source of variability to time estimation that is masked in longer interval conditions, because it constitutes a relatively smaller proportion of the variance. Although the precise source of the variability is unknown, the cerebellum participates in a broad range of sensory and cognitive functions that have no apparent interval timing requirements including tactile discriminations, spatial learning and working memory [12,19,27]. One model suggests that this is due to the cerebellum's role in monitoring and adjusting input from the cerebral cortex [3], perhaps to signal discrepancies between an intended action and the actual sensory consequences [2]. By this account, timing sensitivity in our task may relate in part to the cerebellums' role in monitoring input from sensory (auditory) systems involved in encoding intervals and optimizing this input in accord with internal representations of the standard intervals stored in memory.

4.2. Decision making

Neural systems associated with timing sensitivity during interval encoding (right caudate, right inferior parietal cortex, left cerebellum) were not implicated in decision processes. Similarly, activity in regions related to making decisions did not correlate with timing sensitivity. These results supported the independence of clock (and perhaps other unspecified sensory processes) and decision processes, consistent with scalar timing theory [20].

Making decisions about interval durations was associated with activity in distributed regions that mediate working memory, including the frontal and posterior (parietal, temporal) cortices. Activation was greater for harder than easier discriminations, presumably reflecting the greater demands of more difficult decisions on processing resources. Although these results are in agreement with the assumption that decision processes compare pulse counts from the clock with a distribution of stored values [20], our results suggest decision and memory processes are more interdependent, because regions involved in working memory mediate decision making. This included the bilateral anterior middle-frontal cortex (BA 10) where activity was not found during epochs associated with interval encoding, in agreement with its role in executive functions of working memory [15]. In contrast, the time course of activation in auditory rehearsal networks (bilateral inferior frontal and left superior temporal cortices) began early during interval encoding and continued into the decision phase. Of particular importance was the correlation of memory bias with activity in the left superior temporal cortex, but only during the decision phase of the trial. This finding indicated that greater utilization of auditory rehearsal systems helped to distinguish representations of the two standard intervals. Thus, distortions in the representation of intervals appear to be associated with systems that mediate interval encoding (precuneus) and decision making (superior temporal cortex).

Though the prefrontal cortices seem to be more specialized in terms of the operations they perform (e.g., encoding, rehearsal, executive functions) [15], hemispheric biases in processing different types of information have been noted in the parietal cortex of humans. A bias for timing events in the right parietal cortex has been demonstrated in focal lesion and fMRI studies [23,45]. Our results extend these findings by showing that the right parietal cortex does not support attention mechanisms during decision making, which might be engaged to compare intervals. Rather, decision making was specifically correlated with activity in the left superior and inferior parietal cortex, with greater activation associated with longer RTs. This finding suggests the left parietal cortex plays a preeminent role in preparatory processes involved in decisions. Converging support for this proposal can be found in studies showing that the left parietal cortex is biased for processes related to mathematical calculations or making decisions about the magnitude (size, distance) of symbolic or nonsymbolic stimuli [14,50]. Altogether, these results seem to suggest that the parietal cortex may acquire sensory information from other regions for the purpose of accumulating evidence about stimulus properties (e.g., amount, size, duration), which is used in decision making. In humans, this function appears to be biased for left hemisphere processing, perhaps related to the lateralization of language functions.

In contrast to interval encoding, the right parahippocampus, but not the hippocampus was associated with decision making, consistent with its role in retrieval of nonverbal information [7]. However, unlike cortical activity, activation was greater for easy than hard interval discriminations, the latter of which showed deactivation or suppression relative to baseline. Though previous studies have not examined the role of the MTL in decision processes, reduced (but not suppressed) parahippocampus activation was reported for forgotten words relative to remembered words [5,54], implying that unsuccessful retrieval is related to how well information is encoded. Our results, however, appear to relate more to the difficulty of decisions, rather then the goodness of encoding, because accuracy for hard interval discriminations was close to chance. Memory processes associated with easy and hard interval discriminations may be more analogous to those involved in making decisions about solvable and unsolvable anagrams. Similar to our results for easy and hard interval discriminations, one study reported parahippocampus activity increased above baseline for a solvable anagram task, but decreased below baseline for unsolvable anagrams [49]. Though deactivation is difficult to interpret, our results suggest that parahippocampus activation may also be reflective of retrieval success during decision making.

Finally, the left putamen was associated with decision processes as well as interval encoding. However, unlike the caudate nucleus, activity in the putamen did not correlate with any behavioral measures of timing. One speculation is that the basal ganglia nuclei may contribute differently to

the perception and the reproduction of time. Previously, we reported putamen, but not caudate activation, in healthy adults during the reproduction of time intervals [44]. Though time perception is associated with activation in both nuclei [45], the present study suggests the putamen plays a nonspecific role, in contrast to the caudate. The possibility that the putamen and caudate mediate timing for different purposes (i.e., action vs. perception) is consistent with their neuroanatomically distinct pathways to motor and nonmotor areas of the prefrontal cortex, respectively [37].

4.3. Summary

The present study identified networks of brain activity that were associated with interval encoding and decision processes. The relationship between behavioral measures of timing competency and activity in these networks further delineated their functional specificity. It is noteworthy that timing sensitivity relates to activity associated with formulating representations of time, but not making decisions about their duration. This provides compelling evidence for the functional distinctions between these two components of our time perception task. During interval encoding, timing sensitivity correlated with activity in the right caudate and right inferior parietal cortex, in keeping with their association with ‘‘clock’’ processes. Though activity in the cerebellum also correlated with timing sensitivity, the subtle effects of cerebellar damage on timing together with its broader role in sensorimotor functions lead us to speculate that it plays a more primary role in monitoring and adjusting input from cortical systems involved in sensory processing and working memory. For the first time we demonstrated a role for right MTL in interval encoding (where it correlated with the bisection point) and decision making, which may be due to the greater demands in our task on memory processes. Our data also show that distortions in the memory for intervals relate to right precuneus and left superior temporal cortex activity, which may respectively reflect encoding and rehearsal strategies used to store and maintain information active in memory.

Acknowledgements

We thank Sally Durgerian, Alison Lindsay, Kim Paulson, Corby Dale, Gabrielle Mallory, Jennifer Hogan and Ting Lee for their research assistance. This research was supported by grants from the MIND Institute, the Department of Veteran’s Affairs and P01MH51358.

References

[1] G.I. Allen, N. Tsukahara, Cerebrocerebellar communication systems, Physiol. Rev. 54 (1974) 957–1006.
[2] S.J. Blakemore, C.D. Frith, D.M. Wolpert, The cerebellum is involved in predicting the sensory consequences of action, NeuroReport 12 (2001) 1879–1884.
[3] J.M. Bower, Control of sensory data acquisition, in: J.D. Schmahmann (Ed.), The Cerebellum and Cognition, Academic Press, San Diego, 1997, pp. 489–513.
[4] J.W. Breukelaar, J.C. Dalrymple-Alford, Effects of lesions to the cerebellar vermis and hemispheres on timing and counting in rats, Behav. Neurosci. 113 (1999) 78–90.
[5] J.B. Brewer, Z. Zhao, J.E. Desmond, G.H. Glover, J.D. Gabrieli, Making memories: brain activity that predicts how well visual experience will be remembered, Science 281 (1998) 1185–1187.
[6] M.A. Burock, R.L. Buckner, M.G. Woldorff, B.R. Rosen, A.M. Dale, Randomized event-related experimental designs allow for extremely rapid presentation rates using functional MRI, NeuroReport 9 (1998) 3735–3739.
[7] R. Cabeza, F. Dolcos, R. Graham, L. Nyberg, Similarities and differences in the neural correlates of episodic memory retrieval and working memory, NeuroImage 16 (2002) 317–330.
[8] L. Casini, R. Ivry, Effects of divided attention on temporal processing in patients with lesions of the cerebellum or frontal lobe, Neuropsychology 13 (1999) 10–21.
[9] L. Casini, F. Macar, Can the level of prefrontal activity provide an index of performance in humans? Neurosci. Lett. 219 (1996) 71–74.
[10] L. Casini, F. Macar, M.H. Giard, Relation between level of prefrontal activity and subject’s performance, J. Psychophysiol. 13 (1999) 117–125.
[11] R.W. Cox, AFNI: software for analysis and visualization of functional magnetic resonance neuroimages, Comp. Biomed. Res. 29 (1996) 162–173.
[12] J.E. Desmond, J.D.E. Gabrieli, A.D. Wagner, B.L. Ginier, G.H. Glover, Lobular patterns of cerebellar activation in verbal working-memory and finger-tapping tasks as revealed by functional MRI, J. Cogn. Neurosci. 17 (1997) 9675–9685.
[13] A. Dietrich, J.D. Allen, B.N. Bunnell, Is the hippocampus involved in temporal discrimination and the memory of short intervals? Int. J. Neurosci. 90 (1997) 255–269.
[14] W. Fias, J. Lammertyn, B. Reynvoet, P. Dupont, G.A. Orban, Parietal representation of symbolic and nonsymbolic magnitude, J. Cogn. Neurosci. 15 (2003) 47–56.
[15] P.C. Fletcher, R.N. Henson, Frontal lobes and human memory: insights from functional neuroimaging, Brain 124 (2001) 849–881.
[16] P.C. Fletcher, T. Shallice, C.D. Frith, R.S.J. Frackowiak, R.J. Dolan, Brain activity during memory retrieval. The influence of imagery and semantic cueing, Brain 119 (1996) 1587–1596.
[17] S.D. Forman, J.D. Cohen, M. Fitzgerald, W.F. Eddy, M.A. Mintun, D.C. Noll, Improved assessment of significant activation in functional magnetic resonance imaging (fMRI): use of a cluster-size threshold, Magn. Reson. Med. 33 (1995) 636–647.
[18] E.A. Franz, R. Ivry, L.L. Helmuth, Reduced timing variability in patients with unilateral cerebellar lesions during bimanual movements, J. Cogn. Neurosci. 8 (1996) 107–118.
[19] J.H. Gao, L.M. Parsons, J.M. Bower, J.H. Xiong, J.Q. Li, P.T. Fox, Cerebellum implicated in sensory acquisition and discrimination rather than motor control, Science 272 (1996) 545–547.
[20] J. Gibbon, R.M. Church, W.H. Meck, Scalar timing in memory, Ann. N.Y. Acad. Sci. 423 (1984) 52–77.
[21] D.L. Harrington, K.Y. Haaland, Sequencing in Parkinson’s disease: abnormalities in programming and controlling movement, Brain 114 (1991) 99–115.
[22] D.L. Harrington, K.Y. Haaland, N. Hermanowicz, Temporal processing in the basal ganglia, Neuropsychology 12 (1998) 3–12.
[23] D.L. Harrington, K.Y. Haaland, R.T. Knight, Cortical networks underlying mechanisms of time perception, J. Neurosci. 18 (1998) 1085–1095.
[24] D.L. Harrington, R.R. Lee, L.A. Boyd, S.Z. Rapcsak, R.T. Knight, Does the representation of time depend on the cerebellum? Effect of cerebellar stroke, Brain 127 (2004) 561–574.

[25] R.B. Ivry, S.W. Keele, Timing functions of the cerebellum, J. Cogn. Neurosci. 1 (1989) 136–152.
[26] J.B. Krause, J.G. Taylor, D. Schmidt, H. Hautzel, F.M. Mottaghy, H.W. Muller-Gartner, Imaging and neural modelling in episodic and working memory processes, Neural Netw. 13 (2000) 847–859.
[27] M.G. Leggio, M. Molinari, P. Neri, A. Graziano, L. Mandolesi, L. Petrosini, Representation of actions in rats: the role of cerebellum in learning spatial performances by observation, Proc. Natl. Acad. Sci. 97 (2000) 2320–2325.
[28] M.I. Leon, M.N. Shadlen, Representation of time by neurons in the posterior parietal cortex of the macaque, Neuron 38 (2003) 317–327.
[29] R. Levy, H.R. Friedman, L. Davachi, P.S. Goldman-Rakic, Differential activation of the caudate nucleus in primates performing spatial and nonspatial working memory tasks, J. Neurosci. 17 (1997) 3870–3882.
[30] C. Malapani, B.C. Rakitin, R. Levy, W.H. Meck, B. Deweer, B. Dubois, J. Gibbon, Coupled temporal memories in Parkinson's disease: a dopamine-related dysfunction, J. Cogn. Neurosci. 10 (1998) 316–331.
[31] C. Malapani, B. Deweer, J. Gibbon, Separating storage from retrieval dysfunction of temporal memory in Parkinson's disease, J. Cogn. Neurosci. 14 (2002) 311–322.
[32] A.V. Maricq, R.M. Church, The differential effects of haloperidol and methamphetamine on time estimation in the rat, Psychopharmacology 79 (1983) 10–15.
[33] M.S. Matell, W.H. Meck, Neuropsychological mechanisms of interval timing behavior, Bioessays 22 (2000) 94–103.
[34] M.S. Matell, W.H. Meck, M.A. Nicolelis, Interval timing and the encoding of signal duration by ensembles of cortical and striatal neurons, Behav. Neurosci. 117 (2003) 760–773.
[35] M.D. Mauk, J.F. Medina, W.L. Nores, T. Ohyama, Cerebellar function: coordination, learning or timing? Curr. Opin. Neurobiol. 10 (2000) R522–R525.
[36] W.H. Meck, Neuropharmacology of timing and time perception, Cogn. Brain Res. 3 (1996) 227–242.
[37] F.A. Middleton, P.L. Strick, Basal ganglia output and cognition: evidence from anatomical, behavioral, and clinical studies, Brain Cogn. 42 (2000) 183–200.
[38] I. Nenadic, C. Gaser, H.P. Volz, T. Rammsayer, F. Hager, H. Sauer, Processing of temporal information and the basal ganglia: new evidence from fMRI, Exp. Brain Res. 148 (2003) 238–246.
[39] D.J. O'Boyle, J.S. Freeman, F.W.J. Cody, The accuracy and precision of timing of self-paced, repetitive movements in subjects with Parkinson's disease, Brain 119 (1996) 51–70.
[40] D.S. Olton, W.H. Meck, R.M. Church, Separation of hippocampal and amygdaloid involvement in temporal memory dysfunctions, Brain Res. 404 (1987) 180–188.
[41] E. Paulesu, C.D. Frith, R.S. Frackowiak, The neural correlates of the verbal component of working memory, Nature 362 (1993) 342–345.
[42] B.R. Postle, M. D'Esposito, Dissociation of human caudate nucleus activity in spatial and nonspatial working memory: an event-related fMRI study, Cogn. Brain Res. 8 (1999) 107–115.
[43] V. Prabhakaran, K. Narayanan, Z. Zhao, J.D.E. Gabrieli, Integration of diverse information in working memory within the frontal lobe, Nat. Neurosci. 3 (2000) 85–90.
[44] S.M. Rao, D.L. Harrington, K.Y. Haaland, J.A. Bobholz, R.W. Cox, J.R. Binder, Distributed neural systems underlying the timing of movements, J. Neurosci. 17 (1997) 5528–5535.
[45] S.M. Rao, A.R. Mayer, D.L. Harrington, The evolution of brain activation during temporal processing, Nat. Neurosci. 4 (2001) 317–323.
[46] B.H. Repp, A. Penel, Auditory dominance in temporal processing: new evidence from synchronization with simultaneous visual and auditory sequences, J. Exp. Psychol. Hum. Percept. Perform. 28 (2002) 1085–1099.
[47] K. Sakai, J.B. Rowe, R.E. Passingham, Parahippocampal reactivation signal at retrieval after interruption of rehearsal, J. Neurosci. 22 (2002) 6315–6320.
[48] J. Schmahmann, J. Doyon, A. Toga, M. Petrides, A. Evans, MRI Atlas of the Human Cerebellum, Academic Press, San Diego, 2000.
[49] F. Schneider, R.E. Gur, A. Alavi, M.E. Seligman, L.H. Mozley, R.J. Smith, P.D. Mozley, R.C. Gur, Cerebral blood flow changes in limbic regions induced by unsolvable anagram tasks, Am. J Psychiatry 153 (1996) 206–212.
[50] O. Simon, J.F. Mangin, L. Cohen, D. Le Bihan, S. Dehaene, Topographical layout of hand, eye, calculation, and language-related areas in the human parietal lobe, Neuron 33 (2002) 475–487.
[51] J. Talairach, P. Tournoux, Co-Planar Stereotaxic Atlas of the Human Brain, Thieme, New York, 1988.
[52] E. Tulving, H.J. Markowitsch, Memory beyond the hippocampus, Curr. Opin. Neurobiol. 7 (1997) 209–216.
[53] B.A. Vogt, D.M. Finch, C.R. Olson, Functional heterogeneity in cingulate cortex: the anterior executive and posterior evaluative regions, Cereb. Cortex 2 (1992) 435–443.
[54] A.D. Wagner, D.L. Schacter, M. Rotte, W. Koutstaal, A. Maril, A.M. Dale, B.R. Rosen, R.L. Buckner, Building memories: remembering and forgetting of verbal experiences as predicted by brain activity, Science 281 (1998) 1188–1191.
[55] A.J. Wearden, "Beyond the fields we know. . .": exploring and developing scalar timing theory, Behav. Processes 45 (1999) 3–21.
[56] J.H. Wearden, R. Grindrod, Manipulating decision processes in the human scalar timing system, Behav. Processes 61 (2003) 47–56.
[57] R.J. Zatorre, A.R. Halpern, D.W. Perry, E. Meyer, A.C. Evans, Hearing in the mind's ear: a PET investigation of musical imagery and perception, J. Cogn. Neurosci. 8 (1996) 29–46.