Neural Network Involved in Time Perception: An fMRI Study Comparing Long and Short Interval Estimation

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Abstract: In this study, long (~1,300 ms) and short duration (~450 ms) estimation trials in an event-related functional MRI (fMRI) study were contrasted in order to reveal the regions within a time estimation network yielding increased activation with the increase of the duration to be estimated. In accordance with numerous imaging studies, our results showed that the presupplementary motor area (preSMA), the anterior cingulate, the prefrontal and parietal cortices, and the basal ganglia were involved in the estimation trials whatever the duration to be estimated. Moreover, only a subset of the regions within this distributed cortical and subcortical network yielded increased activation with increasing time, namely, the preSMA, the anterior cingulate cortex, the right inferior frontal gyrus (homolog to Broca's area), the bilateral premotor cortex, and the right caudate nucleus. This suggests that these regions are directly involved in duration estimation. We propose that the caudate-preSMA circuit, the anterior cingulate, and the premotor-inferior frontal regions may support a clock mechanism, decision and response-related processes, and active maintenance of temporal information, respectively. *Hum Brain Mapp 25:433–441, 2005.* © 2005 Wiley-Liss, Inc.

Key words: timing; preSMA; caudate; anterior cingulate cortex; premotor; fMRI

INTRODUCTION

Although the temporal structure of events is essential information for framing our perception and understanding of the world, the way in which the human brain codes time is as yet little understood. Using event-related functional magnetic resonance imaging (fMRI), the present study was aimed at revealing the cerebral areas specifically involved in the perception of durations in the range of hundreds of milliseconds to less than 2 s.

Most information-processing models of temporal cognition differentiate three stages. A hypothetical clock mechanism, which consists of an oscillatory pacemaker emitting pulses and an accumulator counting them during the signal duration, provides the raw material for measuring time (clock stage). The output from the accumulator corresponding to the current time is stored transiently in a working memory system and/or permanently in a reference memory system (memory stage). Finally, a mechanism compares the current duration values with those in reference memory to decide on the adequate temporal response (decision stage). Brain imaging studies on motor and perceptual timing have suggested that these different processing stages involve sep-

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arate brain regions [see Macar et al., 2002, for a review], which may form several subnetworks of interconnected cortical and subcortical structures [Ferrandez et al., 2003].

In spite of converging data, it is still debated whether regions within this network are specifically recruited for timing actions and/or events, or subtend more general functions involved in many other perceptive and cognitive tasks. Some studies contrasting temporal and nontemporal processing [Belin et al., 2002; Ferrandez et al., 2003; Lejeune et al., 1997; Maquet et al., 1996; Nenadic et al., 2003; Rao et al., 2001] have suggested that the basal ganglia and the cerebellum may be the best candidates for subserving timekeeping operations, while a frontal-parietal network would be involved in attention to and memory of time. However, frontal and parietal lobes are known be implicated in attention and memory processes independently of the stimulus to be processed [Posner and Petersen, 1990].

Recent electrophysiological (EEG) studies have shown an increase in the duration and amplitude of event-related potentials (ERPs) associated with the increase in the duration of the stimulus and temporal judgments [Macar et al., 1999; Pfeuty et al., 2003; Pouthas et al., 2000]. Such findings suggest that an important property of any area specifically involved in time perception would be its sensitivity to the length of the duration to be judged. This assumption is compatible with the characteristics of pacemaker-accumulator models which postulate that brain activity increases with increasing time.

The goal of the present fMRI study was to reveal the regions within a time estimation (compared to no estimation) network in which activity is modulated when the duration to be estimated is varied. Such a modulation would provide strong support for the assumption that these structures play a crucial role in the perception of time. Durations were chosen so that they did not overlap. There is no agreement in the literature regarding categorization of durations as long or short: $>$ or $<$ 300 ms [Grimm et al., 2004; Michon 1967]; $>$ or $<$ 1 s [Ivry, 1996; Lewis and Miall, 2003]; $>$ or $<$ 2–3 s [Elbert et al., 1991; Pöppel, 1997]. However, following the review of data on the variability of interval timing in different duration ranges, Gibbon et al. [1997] suggested that coefficients of variation remain roughly constant for a given task between 0.1 s and about 1.5 s. Therefore, we chose two groups of durations within this range: one around 450 ms for the short-duration estimation condition and the other around 1,300 ms for the long-duration estimation condition.

Using a duration discrimination task we found a network largely consistent with that highlighted in previous studies, but only certain regions within this network showed greater activation for the discrimination of long durations than of short ones.

SUBJECTS AND METHODS

Subjects

Six healthy right-handed volunteers (three females, three males; mean age = 22 ± 3 years) participated in the study.

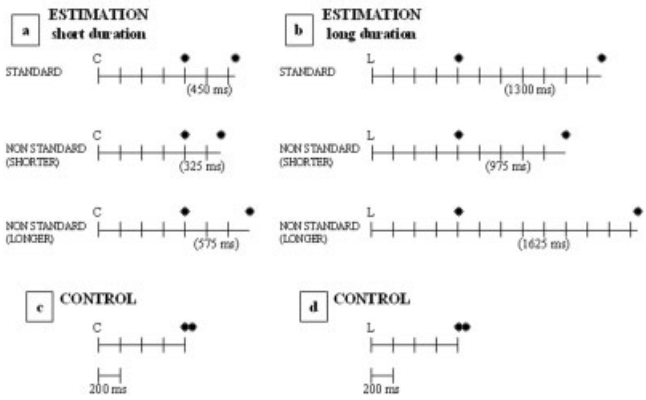

Figure 1.

Illustration of the experimental design. Each trial began with the presentation (200 ms) of the letter C (short duration) or of the letter L (long duration). The first LED flash (50 ms) appeared 800 ms after the letter onset and the second appeared after a variable duration depending on the trial type. There were four trial types: (**a**) short-duration (450/325–575 ms) estimation trials; (**b**) long-duration (1,300/975–1,625 ms) estimation trials; (**c,d**) control trials starting either with the letter C or the letter L and followed by two LED flashes (50 ms) separated by a fixed interval of 80 ms.

This research project was approved by the Ethical Committee from the La Salpêtrière Hospital, and all participants gave written informed consent.

Experimental Design

Training.

Before scanning, subjects were trained to discriminate two standard durations from slightly different nonstandard durations (Fig. 1): 1) a 450-ms standard interval (short duration) from shorter (325 ms) and longer (575 ms) intervals; and 2) a 1,300-ms interval (long duration) from shorter (975 ms) and longer (1,625 ms) intervals. All time intervals were delineated by two brief light-emitting diode (LED) flashes. Subjects gave standard/nonstandard responses by a two-alternative right/left button press. The letter "C" ("Court," French for short) was presented before the 450/325–575 ms trials (corresponding to the estimation of short-duration condition), and the letter "L" (Long) before the 1,300/975–1,625 ms trials (corresponding to the estimation of long-duration condition). Control trials with the letter "C" or "L" and requiring no estimation (80 ms interval between the two LED flashes) were also included (Fig. 1c,d). In this case, subjects had to press one of the two buttons at random.

Activation conditions.

Scanning trials were presented in randomized order in four runs of 48 trials: 8 for each standard interval, 4 for each nonstandard interval, and 16 control trials (8 C and 8 L). ITI lasted between 9–11 s to allow the hemodynamic response to return to baseline.

Image acquisition.

The event-related fMRI experiment was performed on a 3T Bruker (Ettlingen, Germany) scanner equipped with a head coil. Functional images were obtained with a T2*-weighted gradient echo-planar imaging sequence (TR = 2 s; TE = 35 ms, flip angle = 90 degrees, matrix 64 × 64, in-plane resolution 3.75 mm). Eighteen 6-mm thick axial slices were acquired to cover the entire brain, except the lower part of the cerebellum. We chose to scan relatively high for two reasons: 1) we assumed that the preSMA/SMA would be involved in the "timing network"; 2) our previous results [Ferrandez et al., 2003; Maquet et al., 1996] showed that activation of the cerebellum was not specific to the discrimination of stimulus duration. During each run, 265 volumes were acquired (four runs per subject, except for two subjects for whom only three runs were acquired). The first four volumes were discarded to take into account the T1 artifacts. Additionally, a high-resolution T1-weighted image (inversion-recovery 3D gradient echo sequence) was acquired to obtain high-resolution anatomical information (for each subject, voxel size = $1.5 \times 2 \times 1$ mm^3).

Data analysis.

Data were analyzed using the general linear model for event-related designs in SPM99 (Welcome Department of Cognitive Neurology, London, UK). Scans were realigned on the first volume after removal of the T1 artifacted volumes. The images were then spatially normalized to Talairach space using the reference template of the Montreal Neurological Institute. A spatial smoothing using an 8-mm full-width-at-half-maximum (FWHM) gaussian kernel was applied to the individual functional images (13 mm for the group analysis). The normalized functional images had voxels of $3 \times 3 \times 3$ mm^3.

The different types of individual events (time-locked to the letter presentation) were modeled by a synthetic hemodynamic response (latency = 5 s), allowing the lag in the BOLD response to be taken into account. Four critical conditions were modeled: Estim C (standard/nonstandard), Estim L (standard/nonstandard), Cont C, Cont L. Left- and right-hand motor responses were also included as two separate types of events to partial out the hemodynamic effect related to the motor responses. Accordingly, L vs. R and R vs. L hand comparison only yielded activation in the right and left (respectively) primary motor cortex and these events were not further analyzed in the comparisons of interest. Analysis of the data was performed using the general linear model to obtain parameter estimates of event-related activity at each voxel for each condition and each subject, and to generate statistical parametric maps of the *t*-statistics, which were then transformed to maps of the corresponding *Z* values.

The first aim of the statistical analyses was to identify the regions activated by temporal processing in all estimation trials relative to control trials. We then examined the regions that were sensitive to the duration to be estimated by taking a conservative approach using two inclusive masks. We contrasted long- and short-duration estimation trials, pooling standard and nonstandard stimuli, and masking this contrast by the main effect of estimation vs. control trials as well as by the interaction between estimation/control conditions and L/C cues (both masks set at $P < 0.01$). We concentrated on regions that survived at $P < 0.05$ corrected, but for thoroughness we also tabulated all regions that survived $P < 0.001$ uncorrected. Both fixed-effect and individual subject analyses were performed. For each activated brain region we reported the *Z* and *P* values of the fixed-effect group analysis, the number of voxels in each activated cluster, together with the levels of significance (in tables) and the effect size (in figures) for each individual subject analysis.

RESULTS

Behavioral Data

The mean percentage of correct responses did not differ between the short-duration estimation condition (74% ± 5%) and the long-duration estimation condition (80% ± 4%) ((t 5) = 1.26; $P > 0.10$). Subjects were slower when they judged short durations (1,486 ms ± 265 ms) than long durations (1,351 ± 260) ((t 5) = 2,92; $P < 0.05$).

Imaging Data

We first determined brain regions which showed activation when subjects had to estimate the duration of the interval between the two LED flashes, regardless of its duration, by comparing all estimation trials with all control trials. Significant activation was seen in the preSMA, the anterior cingulate cortex, bilateral ventrolateral prefrontal cortex in the vicinity of anterior insular cortex, right dorsolateral prefrontal cortex, right intraparietal sulcus, bilateral premotor cortex, and right caudate nucleus. All these areas were consistently activated across subjects (Table I, Fig. 2).

Second, we examined the effect of the duration to be estimated by comparing long- and short-duration estimation trials. To restrict this analysis to the regions constituting the time estimation network revealed by the comparison of estimation trials with control trials (Fig. 2), we used this former comparison as an inclusive mask. Moreover, in order to ensure that the duration effect could not be attributed to the presentation of the L/C letters initiating the trials, we also used as an inclusive mask the contrast testing for the interaction between the Estimation/Control conditions and L/C cues.

This stringent analysis showed that long- compared with short-duration estimation was associated with greater activation in the preSMA, anterior cingulate cortex, right inferior frontal gyrus, bilateral premotor cortex, and right caudate nucleus. No increase of activity was observed in the other areas of the time estimation network (Table II and Fig. 3).

TABLE I. Activation foci during all estimation trials compared to all control trials

Brain areas	Talairach coordinates			Z	P	Voxels (n)	Levels of significance in individual subjects
	x	y	z				
Pre-supplementary motor area	3	6	60	6.17	0.0001*	238	4 ++++ 1 +++ (1 +)
Anterior cingulate cortex	3	24	48	8.21	0.0001*		5 ++++ (1 +)
Right ventrolateral prefrontal cortex/insula	33	18	0	7.29	0.0001*	805	6 ++++
Right dorsolateral prefrontal cortex	39	33	15	6.80	0.0001*		5 ++++ (1 +)
Left ventrolateral prefrontal cortex/insula	−33	24	0	5.03	0.01*	135	5 ++++ (1 +)
Right intraparietal sulcus	39	−42	39	5.09	0.01*	103	4 ++++ (1 ++) (1 +)
Left lateral premotor cortex	−51	0	48	4.42	0.0001**	22	4 ++++ 1 +++ (1 +)
Right lateral premotor cortex	27	3	51	3.70	0.0001**	7	4 ++++ 1 +++ (1 +)
Right caudate nucleus	9	12	12	4.27	0.0001**	74	2 ++++ 3 +++ (1 +)

*Corrected; **uncorrected.
++++ $P < 0.001$ uncorrected;
+++ $P < 0.005$ uncorrected;
++ $P < 0.01$ uncorrected;
+ $P < 0.05$ uncorrected.

DISCUSSION

In the present study we used event-related fMRI to identify the network of regions showing activation during the estimation of brief durations, and to specify those whose activation was modulated by the duration to be estimated. We used a fixed-effect analysis of only six subjects, and the results are therefore acknowledged to be limited to this study. Nevertheless, even if these results cannot support conclusions about the general population, they are an important step in giving a prominent role in temporal processing to areas sensitive to the length of an interval to be judged.

First, when all estimation trials were contrasted with all control trials, the network found is compatible with previous brain imaging research, suggesting that time perception is mediated by a distributed neural network including frontal, mesiofrontal (preSMA) and parietal cortices, and basal ganglia. Some studies have indicated the involvement of the cerebellum in timing [Bengtsson et al., 2004; Ivry and Spencer, 2004; Jueptner, 1995, among others], but ours [Maquet et al., 1996; Ferrandez et al., 2003] suggest that this involvement is not specific to timing tasks. As the whole structure was not imaged in the present study, it will not be discussed further here.

The observed network showed a right hemispheric bias. This is consistent with previous EEG and neuropsychological work. EEG studies showed greater amplitude of electrical activity in the right than in the left hemisphere when time computations were required [Brunia et al., 2000; Monfort et al., 2000; Pouthas et al., 2000]. Harrington et al. [1998b], comparing temporal performances of patients presenting damage in either the left or the right frontal-parietal cortical regions, showed that only the latter exhibited time perception deficits.

Second, the principal finding from this study resulted from the contrast between the long- and short-duration estimation trials. More activation for long-duration estimation trials was found in the preSMA, the anterior cingulate cortex, a part of the right inferior frontal gyrus corresponding to Broca's area, the lateral premotor cortex bilaterally, and the right caudate nucleus. By contrast, there was no such significant enhanced activation in the ventrolateral prefrontal cor-

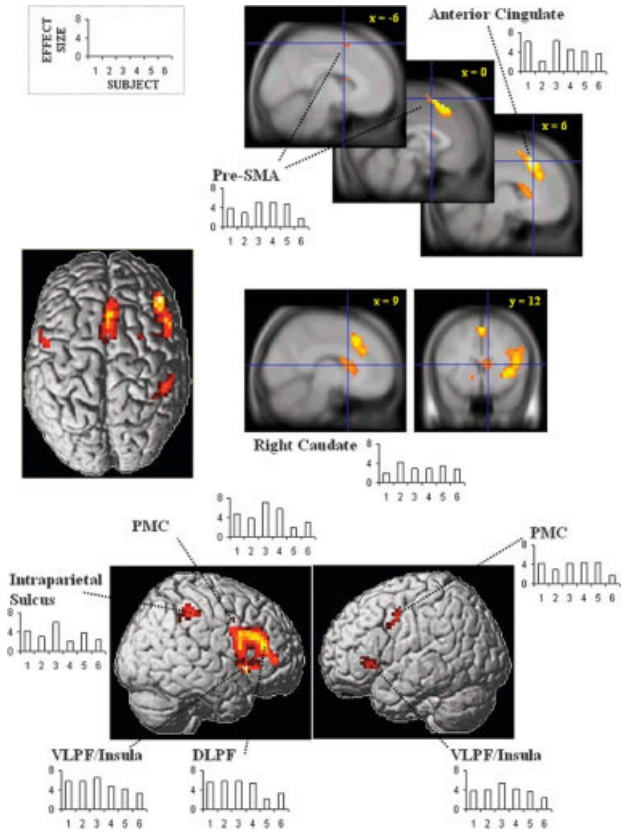

Figure 2.

Activations due to the time estimation effect. The activations revealed by the comparison between all estimation trials with all control trials are shown in top and lateral views of the brain as well as in selected sagittal and transversal slices for preSMA, anterior cingulate cortex, and right caudate nucleus. The size of the effect for each subject-specific maximum in the identified region (obtained from individual subject analyses) are plotted for every brain area.

tex/insula, the right dorsolateral prefrontal cortex, or the right intraparietal sulcus. Thus, although these regions may contribute to the timing process, it is likely that their involvement is not restricted to duration estimation but are related to general processes, such as allocation of attentional resources (parietal areas) and/or encoding and retrieval of information (frontal areas) [Belin et al., 2002; Courtney et al., 1997; Ferrandez et al., 2003; Nenadic et al., 2003]. On the other hand, the areas which show more activation with longer durations to be estimated point to a crucial role in temporal information processing, which we will now examine.

Network for Timekeeping Operations: PreSMA and Caudate Nucleus

It was noteworthy that the preSMA and the caudate nucleus, two structures which have a functional relationship, showed greater activation for the estimation of long than short duration. Evidence that the striatum is a likely candidate for subserving time coding in both motor and perceptive tasks has been provided by lesion and pharmacological studies in animals [for review, see Meck, 1996]. Neuropsychological studies in patients with Parkinson's disease [Harrington et al., 1998a; Malapani et al., 1998, 2002; Pastor et al., 1992] also indicate that the striatum plays an important role in interval timing. Thus, patients in these studies, who had decreased striatal functioning due to dopaminergic depletion, were impaired in their ability to reproduce and estimate time intervals. Furthermore, data from a recent study by Matell et al. [2003], using recordings of striatal and cortical ensembles in rats, suggest that neurons encode specific durations in their firing rate, which may reflect the output of clock mechanisms. Our results, showing an additional activation in the caudate nucleus for the long-duration estimation, are in line with this assumption and support the same mechanism in humans.

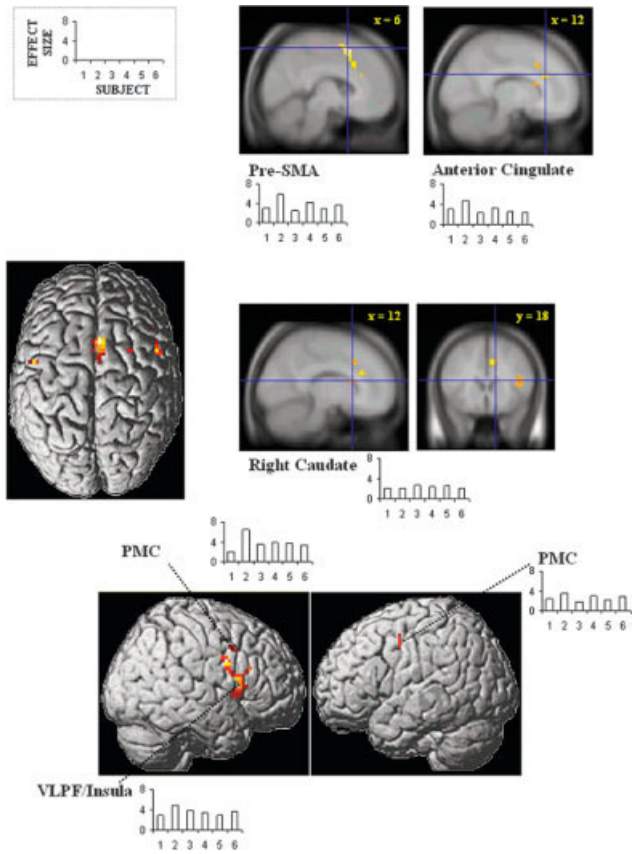

Figure 3.

Activations due to the length of duration to be estimated. These activations are shown in top and lateral views of the brain as well as in selected sagittal and transversal slices for preSMA, anterior cingulate cortex, and right caudate nucleus. The size of the effect for each subject-specific maximum in the identified region (obtained from individual subject analyses) are plotted for every brain area.

TABLE II. Activation foci during long duration estimation trials compared to short duration estimation trials

Brain areas	Talairach coordinates x	y	z	*Z*	*P*	Voxels (n)	Levels of significance in individual subjects
Pre-supplementary motor area	6	12	57	6.73	0.0001*	62	4 ++++ 1 +++ (1 ++)
Anterior cingulate cortex	12	30	27	4.62	0.01*		3 ++++ (2 ++) (1 +)
Right inferior frontal gyrus	51	12	15	4.48	0.0001*	77	4 ++++ 2 +++
Left lateral premotor cortex	−51	−3	48	3.89	0.0001**	7	1 ++++ 3 +++ (2 +)
Right lateral premotor cortex	51	9	42	3.82	0.0001**	4	5 ++++ (1 +)
Right caudate nucleus	12	18	15	3.44	0.0003**	3	2 +++ (4 +)

*Corrected; **uncorrected.
++++ $P < 0.001$ uncorrected;
+++ $P < 0.005$ uncorrected;
++ $P < 0.01$ uncorrected;
+ $P < 0.05$ uncorrected.

By contrast, the timing function of the preSMA/SMA still needs to be clarified. This area has long been implicated in motor execution and preparation. Focal lesions are uncommon in this region. Only one study has reported that patients with SMA lesions were impaired in reproducing rhythms in the absence of an auditory cue [Halsband et al., 1993]. Moreover, although SMA activation has been observed in various types of tasks involving either motor or perceptive timing [Kawashima, 2000; Rao, 1997, 2001], some control tasks also elicit its activation [see Macar et al., 2002, Tables 1 and 2; pp. 476–477]. This region has thus been attributed to a function related to working memory, not specific to timing [Rao et al., 2001]. Recently, converging evidence has established that, on the one hand, the SMA proper has an executive function in motor control and is one of the main generators of Bereitschafts potential preceding self-paced voluntary movements. On the other hand, the preSMA is thought to play a more important role in cognitive motor control, which involves anticipation of and preparation for forthcoming movements. Thus, the Akkal et al. [2004] study on monkeys showed that preSMA neurons were generally more active during the period preceding the movement than during the movement itself. These authors proposed that the gradual increase in preSMA activity might represent the neuronal substrate of the time accumulator system postulated in theoretical models of timing. In addition, even if studies have postulated a strong role of the preSMA/SMA in motor timing processes, more recent studies have shown that the timing functions of the preSMA also include pure time perception. EEG [Macar et al., 1999] and fMRI [Coull et al., 2004] studies using parametric analyses indicated that preSMA activity was greater when temporal processing was longer or when more attention was devoted to temporal processing. In the Macar et al. [1999] study, a positive relationship was found between subjective duration and brain activity, i.e., the longer the duration produced or judged to be so, the larger the ERP amplitudes recorded over the medial frontal-central electrodes. A parametric relationship between the strength of the hemodynamic response and the strength of attention to time has also been observed in a network including the preSMA [Coull et al., 2004]. Thus, the greater activation of the preSMA in long-duration estimation trials found in the present study provides further strong evidence of the timing function of this structure.

Neuroanatomically, the preSMA/SMA forms part of fronto-striatal pathways. It sends efferent connections to the neostriatum [Jurgens 1984; Saint Cyr et al., 1995; Cunnington et al., 2001], and receives information back via the globus pallidus and the thalamus [Alexander et al., 1986]. It is also connected to frontal and parietal cortical areas [Schell and Strick, 1984]. The present results show that activity increased in both the preSMA and the caudate nucleus when the duration to be estimated was longer. We suggest that the preSMA either provides the neural substrate of clock mechanisms commonly postulated in models of time processing, or that it receives output from these clock mechanisms located in striatal structures through striatal efferent pathways. An increase in the total amount of activation with the passage of time may reflect changes of activity in neural assemblies that may be due to an increasing firing rate of neurons or to the recruitment of more neurons.

Decision and Response Selection: Anterior Cingulate Cortex

Two separate foci were found for the preSMA and the anterior cingulate cortex (ACC). Signal increase was observed for long-duration estimation trials in both structures (Fig. 3). Several imaging studies have suggested the involvement of the ACC in tasks requiring attention or complex cognitive functions [see Paus et al., 1998, for review]. Encoding a temporal target necessitates sustained attention from the beginning to the end of the target [Macar et al., 2002]. Thus, it could be assumed that when the duration to be timed was longer, more attention was required and activity in the cingulate increased. However, this is at odds with some studies. In the Coull et al. [2004] study, in which levels of attention were manipulated, the results showed that more attention to time coincided with increased activation in various areas, but not in the cingulate. In Rao et al.'s [2001] study, timing and pitch discrimination tasks were contrasted. Although the extent of activation was found to be greater in the ACC for the timing task, the contrast between the two tasks did not reveal any significant effect. Moreover, in this latter study the activation of the parietal cortex specifically showed up in the timing task, whereas in our study, enhanced activation with the passage of time was only shown in the cingulate cortex and not in the parietal cortex. Therefore, we suggest that the inferior parietal cortex is involved in the allocation of general attentional resources to the duration discrimination task, and that the ACC subtends another aspect of attentional control related to response selection. Indeed, numerous studies have suggested that the ACC may have an evaluative role and be involved in response-related processes such as monitoring and resolving response conflict [Carter et al., 1999; Milham et al., 2003; van Veen et al., 2001; Woldorff et al., 1999], functions which are necessary for motor timing and distinguishing time intervals. Moreover, patients with lesions in the ACC show a failure to sustain attention to the task and deficits in planning and monitoring ongoing behavior [Peru et al., 2004; Swick and Turken, 2002, among others]. Moreover, using electrophysiological recordings in both monkeys and humans, Luu et al. [2000] have shown a linear increase in the amplitude of the centromedial frontal cortex activity with increasingly late responses, suggesting greater attentional demands for self-monitoring. Similarly in the present study, as time passed the ACC could have been more activated until a decision about the duration of the interval being timed was made.

Representing Temporal Information in Memory: Lateral Premotor and Right Inferior Frontal Cortices

The other areas which revealed an increased BOLD signal with longer durations were the lateral premotor cortex and the right inferior frontal gyrus (right-side homolog of Broca's area). In tapping and rhythmic tasks, lateral premotor activation (associated with SMA activation) has been attributed to a memory function, reflecting a process of transforming the visual or auditory rhythm input into a motor sequence, providing a reference structure for the mnemonic representation [Kawashima et al., 1999; Schubotz and von Cramon, 2001]. Similarly, in the Rao et al. [1997] study the activation of an area located in the right inferior frontal gyrus (whose coordinates are similar to those found in our study) was only present in a continuation condition (self-paced tapping) and not in a synchronization condition (tapping in synchrony with regularly spaced stimuli). The authors proposed that this area may subtend retrieval and rehearsal of (auditory) information in the absence of external stimulation. In our study, the observation of enhanced activation for long durations in the right inferior frontal gyrus and in the lateral premotor cortex is compatible with the fact that the rehearsal function might last longer for long durations than for shorter ones.

In conclusion, our results shed new light on the neural bases of timing mechanisms. Until recently, brain imaging studies have addressed this issue either by contrasting the areas activated in duration discrimination tasks with those activated in pitch, frequency, or intensity discrimination tasks [Ferrandez et al., 2003; Maquet et al., 1996; Nenadic et al., 2003], or by differentiating the time course activity of the areas involved in a time perception network [Rao et al., 2001]. By contrasting long- and short-duration estimation trials, we were able to differentiate neural systems whose role is crucial in time measurement from those subtending nonspecific attention and memory functions required for time estimation tasks. Structures subtending the latter systems, in particular the dorsolateral prefrontal cortex and the inferior parietal cortex, support a variety of computations not restricted to timing intervals. By contrast, the regions whose activation increases with increasing time are the key components of the network underlying timing proper. We propose that the preSMA, together with the caudate nucleus, is involved in the clock mechanism, the anterior cingulate cortex in sustained attention and response-related processes, and the lateral premotor cortex and the right inferior frontal cortex in the temporary maintenance of temporal information just retrieved from reference memory.

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