

Brain Activation Induced by Estimation of Duration: A PET Study

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Abstract

Duration information about a visual stimulus requires processing as do other visual features such as size or intensity. Using positron emission tomography, iterative $H_2^{15}O$ infusions, and statistical parametric mapping, we investigated the neural correlates of time processing. Nine normal subjects underwent six serial rCBF. Three tasks were studied: (a) A temporal generalization task (D task) in which the subjects had to judge (by pressing one of two keys) whether the duration of the illumination of a green LED was equal to or different from that of a previously presented standard; (b) An intensity generalization task (I task) in which the judgment concerned the intensity of the LED; and (c) A control task (C task) in which the subjects had to press one of the two keys at random in response to LED illumination. A significant increase in rCBF during the D task, compared to that during the C task, was observed in right prefrontal cortex, right inferior parietal lobule, anterior cingulate cortex, vermis, and a region corresponding to the left fusiform gyrus. A significant increase in rCBF during the I task, compared to that during the C task, was observed in right prefrontal cortex, right inferior parietal lobule, right extrastriate cortex, anterior cingulate cortex, left inferior parietal lobule, vermis, and two symmetrical regions corresponding to the fusiform gyri. No significant activation was observed in the D task when compared to that in the I task. We propose that these cortical maps are best explained by the recruitment of visual attention and memory structures, which play a major role in prospective time judgements as indicated by behavioral studies. The data also suggest that the temporal dimension of a visual stimulus is processed in the same areas as other visual attributes.

INTRODUCTION

Duration may be the only parameter which enables us to discriminate two stimuli that otherwise are equivalent (reviewed in Lejeune and Macar, 1994; Richelle and Lejeune, 1980). Thus, duration requires processing as do, for instance, size, shape, intensity and spatial location. An important question is to determine whether distinct cerebral areas are activated while duration is processed, as has been demonstrated for other stimulus dimensions (Corbetta *et al.*, 1990; Zeki *et al.*, 1991).

This question has received little attention in the human brain mapping literature. However, several attempts to localize the anatomical correlates of time judgement have already been reported. When durations of a few seconds are concerned, electrophysiological studies have indicated that the frontal cortex is prominently involved, both in monkeys (Nicki and Watanabe, 1979) and in humans (Bruder *et al.*, 1992; Casini and Macar, 1993, submitted for publication; Elbert *et al.*, 1991). Subcortical structures have also been found to be involved in temporal estimation. Particularly the lateral cerebellum has been attributed a prominent role in motor and sensory temporal performances involving durations shorter than 1 s (Ivry 1993; Keele and Ivry, 1991). Recently Jueptner *et al.* (1995), using PET, suggested that the superior parts of the vermis and the adjacent hemispheres were specifically involved in timing functions.

However, at the functional level, a basic question remains unanswered. Whatever the structures considered, it is difficult to specify their function in temporal processing itself since these structures have also been implicated in other processes or functions. For instance, the cerebellum has long been allocated essentially motor functions. Recent data suggest its involvement in higher cognitive performances which require planning, memory (Schmahmann, 1991), or selective attention (Akshoomoff and Courchesne, 1992). The frontal cortex is admittedly a key structure for visuospatial working memory (Jonides *et al.*, 1993) and attention (Corbetta *et al.*, 1993; Fuster, 1989; Näätänen, 1992; Pardo *et al.*, 1991). Now, a number of models or studies in the field of psychological time have suggested that temporal judgements necessitate short- and long-term memory processes

(Church, 1984; Church and Broadbent, 1990; Meck, 1983; Wearden, 1993). Other studies have also emphasized how attention demanding these judgments may be (Block, 1992; Hicks *et al.*, 1977; Zakay 1989; Macar *et al.*, 1994).

The aim of the present PET study was to determine whether time processing would involve frontal and cerebellar areas and whether the pattern of cerebral activation would be specific to time processing, by comparing it to a luminance-based visual discrimination task.

METHODS

PET Acquisitions

PET acquisitions were obtained with a Siemens CTI 951 R 16/31 scanner (CTI, Knoxville, TN; in plane resolution: 8.7 mm; Degueldre and Quaglia, 1992), 10 mm above the OM line. The subject's head was immobilized using a thermoplastic face mask secured on the scanner head holder (Truscan imaging, Anapolis, MD). After a 20-min transmission scan, six scans were performed. Each consisted of a 60-s background frame followed by a 120-s frame. $H_2^{15}O$ (30 mCi/1110 MBq in 10 cc saline) was intravenously infused during 1 min. The infusion started just before the beginning of the second frame in order to observe the head curve rising between the 5th and the 10th second of the second frame. The tasks were begun 15 s before the second frame by the presentation of standard stimuli (see below). They were presented in a Latin square design and their order was counterbalanced over subjects. Two response buttons were fixed with adhesive tape to the scanner couch and were easily depressed by the subject's left or right thumb. A green LED centered on a mat black cardboard background (100 x 70 cm) was fixed at eye level 70 cm from the subject's head for stimulus presentation.

Tasks

During the scans, the subjects had to perform one of the following tasks by pressing their thumb on the right or left response button.

1. Duration Task (D)

This task was a temporal generalization task in which the subjects had to judge whether the illumination of the green LED (490, 595, 700, 805, and 910 ms) was equal to (right button press) or different from (left button press) that of a previously presented standard (700 ms, six successive presentations before the beginning of the task). Each duration, including the standard, was presented 20 times in random order (total: 100 trials per scan). The intensity of each signal was 15 cd/m². Interstimulus intervals lasted 1500, 1700, 1900, 2100, or 2300 ms (on average, 1900 ms) and were presented in random order.

2. Intensity Task (I)

This task was an intensity generalization task in which the subjects had to judge whether the intensity of the LED (3, 7, 15, 22, 29 cd/m²) was equal to (right button press) or different from (left button press) the previously presented standard (15 cd/m²). Each signal lasted 700 ms. Other conditions were identical to those of the duration task.

3. Control Task (C)

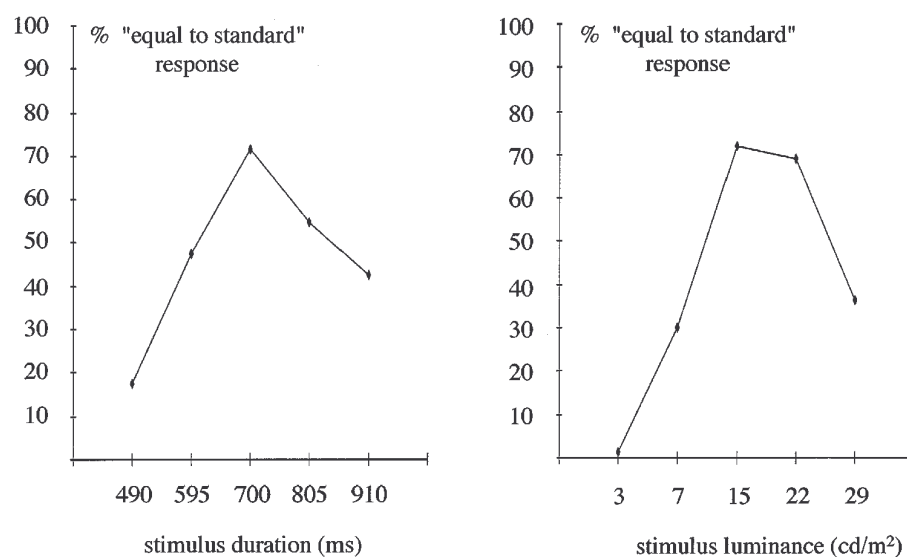
The LED signal (700 ms, 15 cd/m²) was presented 100 times to the subjects, with interstimulus intervals identical to those of the duration task. The subject had to press one of the two buttons at random, when the LED switched off.

The total energy consumed by the LED was 1500 cd/m² for the duration and intensity tasks and 1520 cd/m² for the control task. This similarity excludes sensory input as an explanatory variable of behavioral or neurophysiological differences between tasks, if any.

Selection of the Subjects

Nine subjects were selected from a group of 15 candidates. All of them were young (mean age 20; range 19 to 26), healthy, right-handed, nonsmoking males, with 20/20 vision without corrective lenses and without personal history of serious medical or psychiatric disease. All of them gave their written informed consent. The experiment was approved by the Ethical Committee of the University of Liège. Each candidate performed the three tasks successively in a room matching the dim ambient illumination (about 4 Lux) and the position of the subject in the scanner room. On the basis of the recorded responses (button presses), the subjects were selected if they produced clear-cut bitonic generalization gradients (as in Fig. 1), with the maximum located at or close to the standard. A further selection criterion was randomness of right and left button presses during the control condition.

FIG. 1. Average generalization gradients displaying the percentage of "standard" responses (ordinate) as a function of stimulus value (abscissa). (Left) stimulus duration gradient. (Right) stimulus intensity gradient.



Data Analysis

PET data were analyzed in the following way. First, the scans of each subject were realigned using the AIR package (Woods *et al.*, 1992). Then they were processed using the statistical parametric mapping (spm94) software (Wellcome Department of Cognitive Neurology, UK; Frackowiak and Friston, 1994) implemented in MATLAB (Mathworks Inc., Sherborn, MA). In short, data from each subject were again realigned using a least-square approach with the fourth scan as a reference (Friston *et al.*, 1995a). Following realignment, all images were transformed into a standard space (Friston *et al.*, 1995a; Talairach and Tournoux, 1988) and then smoothed using a 10-mm FWHM isotropic kernel. A design matrix was specified, including global activity as a confounding covariate (Friston *et al.*, 1990). Then, the condition and subject effects were estimated at each and every voxel, according to the general linear model (Friston *et al.*, 1995b; see also Friston *et al.*, 1991, 1994). To test hypotheses about regionally specific condition effects, the estimates were compared using linear contrasts. Three contrasts were evaluated:

	C	C	I	I	D	D
contrast 1	-1	-1	1	1	0	0
contrast 2	-1	-1	0	0	1	1
contrast 3	0	0	-1	-1	1	1

The resulting set of voxel value for each contrast constituted a map of the t statistic ($SPM\{t\}$). The $SPM\{t\}$ were transformed to the unit normal distribution ($SPM\{Z\}$) and thresholded at $P < 0.001$ ($z = 3.09$). The resulting foci of activation were characterized in terms of spatial extent [i.e., the probability that a region of the observed number of voxels could have occurred by chance; $P_{(n_{max} > k)}$] and in terms of peak height [i.e., the probability that the regional CBF variation could have occurred by chance; $P_{(Z_{max} > u)}$, which corresponds to a corrected P value] over the entire volume.

RESULTS Behavioral Data *D* and *I* Tasks

Average, generalization gradients obtained in duration and intensity tasks appear in Fig. 1, which relates the duration or intensity of the signal (abscissa) to the percentage recognition of the standard (ordinate). For instance, 10 identifications of a duration (out of 20) as the "standard" amounts to 50% on the ordinate. The individual data confirm that bitonic functions were obtained for each subject and that button presses were not made at random. Overall, the duration task was perceived as more difficult than the intensity task. The difference shows up in the data, with a steeper gradient in intensity discrimination. It also emerges from the fact that error scores (false identifications as the "standard") for the stimuli most remote from the standard were smaller for

intensity than for duration (mean score 18.8 vs 30.1, $P \leq 0.05$ Mann-Whitney U test).

C Task

The number of presses on the left or the right button remained in every case close to 50 (average on the left: 49 ± 7 ; on the right: 51 ± 7), matching the motor patterns recorded with the D and I tasks. No rule (such as alternation) was followed.

PET Data

Contrast 1: Increase during D Task versus C Task (Fig. 2, Table 1)

A significant increase in rCBF during the D task, compared to that during the C task, was observed in the following regions:

1. right prefrontal cortex, in an area encompassing most of Brodmann area 45, impinging on BA 47 and marginally on BA 44;
2. right inferior parietal lobule (BA 40);
3. anterior cingulate cortex in its dorsalmost part (BA 32), near the junction with premotor cortex (BA 6);
4. medial cerebellar structures including vermis and adjacent left cerebellar hemisphere;
5. a region, the coordinates of which correspond to the left cerebellar hemisphere but when displayed on the average mean normalized image (calculated on all experimental subjects and all conditions) appears to be located within the medial part of the left temporal lobe, in the fusiform gyrus.

Contrast 2: Increase during I Task versus C Task (Fig. 2, Table 2)

A significant increase in rCBF during the I task, compared to that during the C task, was observed in the following regions:

1. right prefrontal cortex (mainly BA 45, 47 and, marginally, 44);
2. an area located within the right inferior parietal lobule (BA 40) that spreads posteriorly toward extrastriate cortex (BA 19);
3. anterior cingulate cortex (BA 32), near the junction with premotor cortex (BA 6);
4. medial cerebellar structures including vermis and adjacent left cerebellar hemisphere;
5. left inferior parietal lobule (BA 40), impinging rostrally on BA 7 and posteriorly on BA 19;
6. two symmetric regions, the coordinates of which correspond to the lateral aspect of cerebellar hemispheres but when displayed on the average mean normalized image (calculated on all experimental subjects and all conditions) are located within the medial part of the left temporal lobe, in the fusiform gyri.

Contrast 3: Increase during D Task versus I Task No significant variations of rCBF were observed.

TABLE 1 Table of Regional Activations during the D Task versus the C Task, Characterized by the Corresponding Brodmann Area (BA), the Volume of Each Region (k), Its Significance Based on Spatial Extent [$P_{(nmax>k)}$], the Highest Z Value (u), Its Significance or $P_{(Zmax>u)}$, and the Location of Maxima

Region	BA	k	$P_{(nmax>k)}$	$Z(u)$	$P_{(Zmax>u)}$	x	y	z
Right prefrontal cortex	45 40	205 63	0.013 0.195	4.62 4.79	0.014 0.007	34 44	20 -52	4 40
Right inferior parietal lobule								
Anterior cingulate cortex	32	292	0.003	5.41	<0.001	2	10	48
Left fusiform gyrus		121	0.058	4.49	0.024	-42	-72	-24
Vermis/adjacent cerebellum		84	0.123	4.66	0.012	-2	-82	-24
				4.41	0.053	-16	-86	-28

FIG. 2. Statistical parametric map of the t statistic (after transformation to $spm\{Z\}$) corresponding to the increases in $rCBF$ during the D task (A) and the I task (B) compared to that in the C task. The anatomical space corresponds to the atlas of Talairach and Tournoux (1988). The SPMs were thresholded at 3.09 with a corrected $P < 0.025$. See the text.

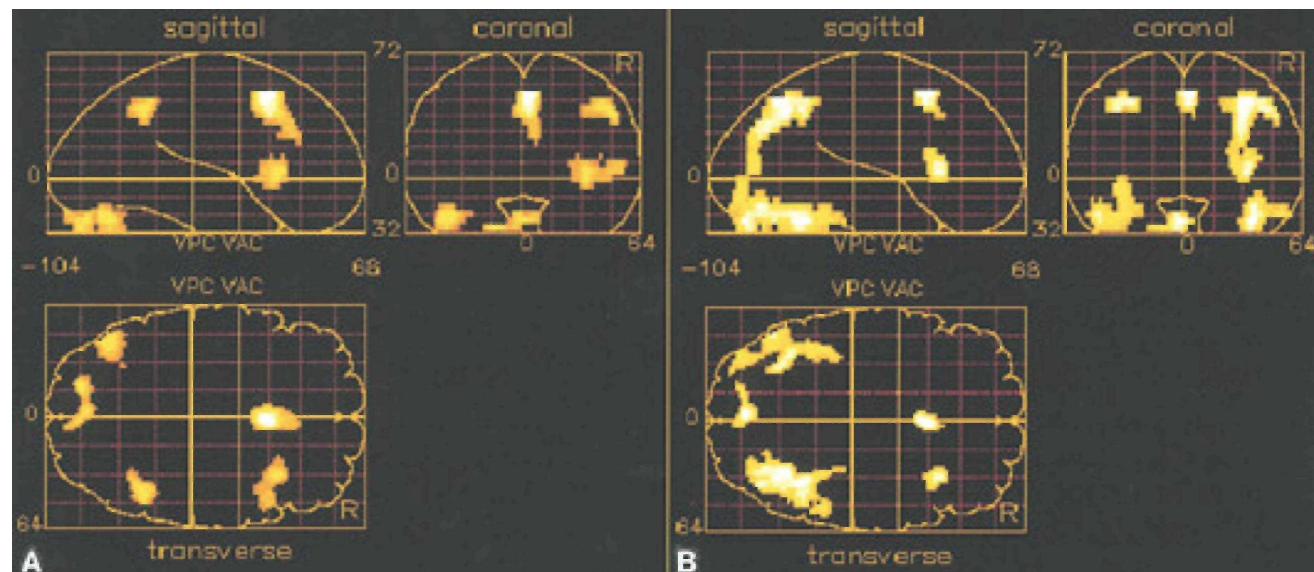


TABLE 2 : Table of Regional Activations during the I Task versus the C Task, Characterized by the Corresponding Brodmann Area (BA), the Volume of Each Region (k), Its Significance Based on Spatial Extent [$P_{(nmax>k)}$], the Highest Z Value (u), Its Significance or $P_{(Zmax>u)}$, and the Location of Maxima

Region	BA	k	$P_{(nmax>k)}$	$Z(u)$	$P_{(Zmax>u)}$	x	y	z
Right prefrontal cortex	45	133	0.046	4.69	0.010	32	20	4
				4.45	0.028	36	16	12
Right inferior parietal lobule	40	345	0.002	4.68	0.011	44	-52	40
Right extrastriate cortex	19			4.62	0.014	32	-62	40
				4.58	0.016	28	-70	32
Anterior cingulate cortex	32	54	0.238	4.39	0.036	0	12	48
Left inferior parietal lobule	40	55	0.233	4.34	0.044	-36	-60	40
Right fusiform gyrus		238	0.008	4.84	0.005	38	-76	-20
				4.72	0.009	36	-52	-24
Left fusiform gyrus		145	0.037	4.16	0.086	-44	-70	-20
Vermis/adjacent cerebellum		76	0.146	5.31	0.001	-2	-82	-24

DISCUSSION

Using PET in a generalization paradigm in which the subject had to compare the relevant stimulus cue (luminance or duration) to a standard one presented at the beginning of the scanning period, we explored whether specific cerebral areas were involved in the estimation of short durations. Our results show that during both D and I tasks, a distributed network of cerebral areas was activated, which shared in common the following regions: right prefrontal cortex, right inferior parietal lobule, anterior cingulate cortex, vermis, and a region most probably located in the left fusiform gyrus (although coordinates point to the cerebellar hemisphere in the Talairach and Tournoux stereotaxic space).

Extrastriate Areas

Our experimental protocol consisted of a delayed "same-different" visual task. In good agreement with previous reports based on the same principle, we observe an activation in extrastriate visual cortices (Corbetta *et al.*, 1991; Dupont *et al.*, 1993). These areas, activated during both D and I tasks, are known to participate in the detection of visual stimuli on the basis of some parameters such as luminance (Gulyas *et al.*, 1994).

Right Inferior Frontal Area

In addition, and in contrast to the papers previously quoted, we also found a significant activation of the right inferior prefrontal cortex. The function of this cortical area is not precisely known (Roland, 1993). In our task, its activation may depend on the decision to press the left or the right response button. However, we favor the suggestion that this right inferior frontal activation is especially related to memory processes. First, the estimation of duration implies its memorization in a short-term store and its comparison to a reference stored in long-term memory (Church, 1984). The same might be said for intensity. Second, the design of our task puts a particular load on memory processes since the standards, which were presented six times before the beginning of the task, had to be retained for the 120 s of the scan and recalled during the task at each LED lighting. On the one hand, this 120-s delay exceeds the storing capacity of the working memory system. The standard stimulus encoding in long-term memory stores and its iterative retrieval cannot be ruled out. On the other hand, it may be argued that the standard stimulus attribute was probably rehearsed from one LED lighting to the next and maintained in working memory. In consequence, the relative load of working and long-term memory stores on the final statistical maps cannot be determined. Third, several PET activation studies reported an activation of inferior frontal cortices during working memory tasks. In an early study engaging both temporal judgement and working memory, the discrimination of tone rhythms in a delayed "same-different" paradigm induced an activation of inferior frontal cortices (Roland *et al.*, 1981). More recently, Paulesu *et al.* (1993), exploring the verbal component of the working memory slave systems, observed a bilateral activation of Broca's area (BA 44). They suggested that the subvocal rehearsal system of the phonological loop is located in these areas. Jonides *et al.* (1993), exploring the visuospatial component of the working memory system, observed a right inferior prefrontal activation. It is noteworthy that the location of our right inferior frontal activation ($x: 34; y: 20; z: 4$) lies only a few millimeters more rostrally than the region reported by these authors ($x: 35; y: 19; z: -2$).

Admittedly, in our paradigm, memory load cannot be dissociated from attention. According to our volunteers, both D and I tasks required significant attentional effort. Prospective time judgements are indeed known to depend critically on attentional resources, which are the core of prominent psychological models of time perception (Thomas and Weaver, 1975; Zakay 1989). Many studies have documented the systematic errors which are observed in dual-task paradigms when the subject's attention is not allocated to the temporal parameters (e.g., Block, 1992; Hicks *et al.*, 1977; Macar *et al.*, 1994). It is also well known that the right prefrontal cortex is involved in attentional tasks using somatosensory or visual stimuli (Pardo *et al.*, 1991). However, the location of activation described by Pardo *et al.*, seems more widely spread over the dorsolateral prefrontal cortex (involving areas 8, 9, 44, and 46) than in the present experiment.

Right Inferior Parietal Lobule

Likewise, the activation of the inferior parietal lobule may be explained in several ways. It has been reported during delayed visuospatial tasks where the comparison stimuli follow the standard after a delay (Dupont *et al.*, 1993; Jonides *et al.*, 1993). These results suggest that this polymodal cortical area is involved in a visuospatial working memory network. Alternatively, the inferior parietal lobule has been considered a specialized extrastriate area processing visual attributes such as speed (Corbetta *et al.*, 1991), a selected visual feature that, interestingly, also implies a temporal dimension.

The parietal activation observed during both I and D tasks was clearly located within the inferior parietal lobule (Brodmann area 40). This activation focus may thus be differentiated from the sites reported in many visual attention tasks, which involved the superior parietal lobule (BA 7; Posner, 1990; Pardo *et al.*, 1991; Corbetta *et al.*, 1993). However, a superior parietal activation cannot be ruled out because of the limited field of view of the scanner in the z axis (we scanned rather low to explore the cerebellum).

Anterior Cingulate Cortex

Activation of the anterior cingulate cortex has been found in various tasks including visual selection (Corbetta *et al.*, 1991; Pardo *et al.*, 1990), recognition of visual patterns (Roland *et al.*, 1990), motor planning (Deiber *et al.*, 1991), and verbal fluency (Frith *et al.*, 1991). This area is also considered to play a pivotal role in attention (Posner, 1990). More precisely, it seems preferentially activated when the appropriate motor output has to be adapted to an unpredictable significant stimulus (Devinky *et al.*, 1995; Pardo *et al.*, 1990; Paus *et al.*, 1993), as was the case in our paradigm, in contrast to conditions where a well-established response is predefined (Corbetta *et al.*, 1993; Pardo *et al.*, 1991). A more global interpretation, however, based on the fact that the anterior

cingulate cortex is part of the limbic system, is that it handles the interactions between neuronal systems involved in emotions, attention, and working memory (Damasio, 1995).

Cerebellum

The cerebellum has direct reciprocal connections to many associative areas, among which are the prefrontal cortex, the inferior parietal lobule, and the anterior cingulate cortex. It has been implicated in motor function but also in sensory tasks, in oculomotor control (Ito, 1992), in temporal processing (Ivry, 1993; Keele and Ivry, 1991; Jueptner *et al.*, 1995), and, more recently, in higher order cerebral functions as well (Ito 1992). Whether these cerebellar activations reflect only the transsynaptic influence of related cortical areas or the genuine implication of cerebellar circuitry in these performances is still under investigation. It is clear that cerebellar activation is not specific to prospective judgements of time, since it was observed in both I and D tasks. It is, however, possible that the cerebellar activation found here was related to other timing aspects that are present in a number of studies, such as the time locking of the motor response to the stimulus or the more or less periodic distribution of stimuli (every 1500 to 2300 ms). Such timing aspects do not require any judgment from the subject: they do not necessitate the temporal discrimination which was the key factor of the D task. Therefore, our conclusion concerning the cerebellum contradicts the interpretation proposed by Jueptner *et al.* (1995). These authors observed a similar cerebellar activation focus with PET in a temporal discrimination task and concluded that their results "demonstrate the involvement of the cerebellum in time-critical perception." However, it is of major importance to consider the nature of the task that is contrasted with the temporal paradigm. We used two tasks involving discrimination judgements (D and I) and a control task requiring only the motor components also present in D and I. Jueptner *et al.* contrasted their temporal discrimination paradigm with a control task similar to ours and a rest condition (with closed eyes and no finger movements). In both studies, similar cerebellar activations were found when the temporal task was contrasted to the control. However, our data revealing no differences between the D and the I tasks demonstrate that the cerebellar activation is due to processes shared by discrimination tasks in general or by the casual timing aspects mentioned above, rather than to time processing itself.

Topographic Comparisons between Tasks

The sets of cerebral areas activated in the I and D tasks were very similar to each other. The spatial extent of the foci of activation appeared somewhat larger during the I task (activation of left inferior parietal lobule, of right fusiform gyrus, and of right extrastriate BA 19) than during the D task. However, the direct comparison between I and D tasks did not yield any difference. Admittedly, the clear overlap in the activation patterns observed in D and I tasks, when compared to that in the C task reduces the statistical power of the direct comparison of D and I. However, this negative finding suggests that, under the present experimental conditions, the cognitive resources necessary for the discrimination of any visual attribute activate a similar set of cerebral structures. Our delayed "same-different" visual paradigm does not allow any conclusion regarding the estimation of duration per se. Indeed, one cannot exclude that cerebral areas specific to the estimation of time were activated but did not appear on our statistical maps because the temporal stimuli were very short.

CONCLUSIONS

The present study addresses the issue of brain correlates of timing mechanisms with PET scan technology. It demonstrates that, in the context of a delayed "same-different" paradigm, the estimation of the temporal dimension of a stimulus can activate a distributed set of cerebral structures involved in attention and memory processes. This activation pattern is not specific to time judgement, but is also induced by the discrimination of other attributes such as luminance.

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