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Internal and external modulation of parieto-premotor circuitry in voluntary motor control
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Chapter 2

Cerebral Representations of Space and Time

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2.1   Abstract

A Link between perception of time and spatial change is particularly revealed in dynamic conditions. By fMRI, we identified regional segregation as well as overlap in activations related to spatial and temporal processing. Using spatial and temporal anticipation concerning movements of a ball provided a balanced paradigm for contrasting spatial and temporal conditions. In addition, momentary judgments were assessed. Subjects watched a monitor-display with a moving ball that repeatedly disappeared. Ordered in 4 conditions, they indicated either where or when the ball would hit the screen bottom, where it actually disappeared or what its speed was. Analysis with SPM showed posterior parietal activations related to both spatial- and temporal predictions. After directly contrasting these two conditions, parietal activations remained robust in spatial prediction but virtually disappeared in temporal prediction, while additional left cerebellar- right prefrontal and pre-SMA activations in temporal prediction remained unchanged. Speed contrasted to the location of disappearance showed similar parietal decrease with maintained cerebellar-prefrontal activations, but also increased caudate activation. From these results we inferred that parietal-based spatial information was a prerequisite for temporal processing, while prefrontal-cerebellar activations subsequently reflected working memory and feedforward processing for the assessment of differences between past and future spatial states. We propose that a temporal component was extracted from speed, i.e. approximated momentary time, which demarcated minimal intervals of spatial change (defined by neuronal processing time). The caudate association with such interval demarcation provided an argument to integrate concepts of space-referenced time processing and a clock-like processing model.

2.2 Introduction

T EMPOROSPATIAL co-ordination is indissolubly linked with the preparation of purposeful movements in a dynamic environment. E.g., to catch a ball requires the computation of its location in nearby future, while such cerebral processing further prepares the hand to be at the right time in the right position (Lacquaniti and Maioli, 1989; Zago and Lacquaniti, 2005). The ball's behavior is anticipated by estimating its trajectory and speed (Brouwer et al., 2003). These parameters are inferred from the successive changes in the observed spatial relationships between the ball and its environmental features. This implies that the appropriate motor responses are based on a template of future dispositions, generated by the preceding (spatial) configurations. The application of such feedforward mechanism may be a general principle of brain function given the intrinsic constraint of processing speed in the nervous system that, more than in electronic computing devices, hinders real time adjustments to the actual environmental requirements. Such blurring of real-time action representation in the brain raises the question to what extent time is represented independent from spatial representations. This is the question we aimed to answer in the present study.

In visuospatial perception, spatial attention and overt visuomotor control, a dominant role of the parietal cortex has consistently been described in both human- and monkey brain studies (Mountcastle et al., 1975; Perenin and Vighetto, 1988; Goodale and Milner, 1992; Gitelman et al., 1999; de Jong et al., 1999a, 2001; Grefkes and Fink, 2005). Neuronal responses related to either observed spatial location, direction of perceived movement or the direction of actual reaching are particularly derived from areas centered along posterior parts of the intraparietal sulcus (Sakata et al., 1997; Wise et al., 1997). Such convergence of spatial characteristics, extracted from both sensory- and motor modalities, optimally enables transformations between multiple coordinate frames attuning upper limb-, head- and eye movements (Andersen et al., 1997). For the dorsal premotor cortex, electrophysiological recordings in monkey have demonstrated a similar multimodal representation of space, with firing patterns related to movement direction as well as target position (Boussaoud and Wise, 1993; Johnson et al., 1996; Shen and Alexander, 1997). Interconnectivity of distinct posterior parietal areas with visual- and dorsal premotor regions that show a selective neuronal responsiveness to orientation and direction, underscores the presence of a coherent cerebral network by which spatial representations are maintained (Zeki, 1978; Tootell et al., 1997; Johnson et al.,

1996; Wise et al., 1997; Galletti et al., 1997, 2001; Pesaran et al., 2006). A similar concerted dorsal parietal-premotor contribution to the spatial aspects of visuomotor performance has been demonstrated with functional imaging in the human brain (Grafton et al., 1996b; Toni et al., 1999; Prado et al., 2005; Clavagnier et al., 2007).

In contrast to the unequivocally demonstrated involvement of a parietal-premotor network in spatial processing, a consistent cerebral representation of time remains unproven. In order to understand this difference, it is crucial to conceive that spatial characteristics are already defined by the dimensions of static objects and sceneries, while judgment of time requires intervals that only emerge in a dynamic condition. Moreover, these intervals may concern intervals between stimuli, intervals between successive movements and stimulus-response intervals. This variation in experimental design partly accounts for divergent results of previous functional imaging- and patient studies that have addressed the localization of timing in the brain. Cerebral regions that have been implicated in timing include cerebellum, striatum, (pre-) Supplementary Motor Area (SMA) as well as (often right-sided) prefrontal and inferior parietal cortices (Jueptner et al., 1995; Rao et al., 1997; Harrington et al., 1998b; Brunia et al., 2000; Schubotz and von Cramon, 2001; Smith et al., 2003; Ivry and Spencer, 2004; Coull et al., 2004; Hinton and Meck, 2004; Pouthas et al., 2005; Livesey et al., 2007; Stevens et al., 2007)

Given the intrinsic differences between the physical natures of space and time, as indicated above, even more pitfalls may arise when time estimation and spatial orientation are to be treated as equivalent parameters in a single functional imaging design. Coull and Nobre (1998) approached this problem by using a cued attention task, which required matching pairs of either spatial locations or timed intervals, and found distinct parietal activations associated with either spatial or temporal attention. In their task, however, timing was restricted to the assessments required for comparing two fixed interstimulus intervals. Assmus et al. (2003) employed a collision judgment task and found a (left) inferior parietal role inferred to reflect temporo-spatial integration. Although their results pointed at a focus of interaction, the paradigm did not allow segregation between representations of time and space.

In the present fMRI study, we were able to contrast spatial and temporal judgments in a single paradigm that mimicked natural circumstances of active interaction with a dynamic environment. This direct contrast enabled the identification of overlap as well as segregation of underlying cerebral activation

patterns. The judgment conditions were optimally balanced for visual stimuli, motor responses and attentional demand. Such balance was reached by the introduction of anticipation. Subjects watched a display with a moving ball and had to predict either where or when the ball would touch the bottom edge of the screen (Fig. 2.1). They responded by pressing a button of a response box. Between trials, the stimuli varied with regard to start position, direction, trajectory length and speed. These characteristics were balanced for conditions. It is particularly important to notice that we thus avoided a bias between speed and the estimated time to reach the bottom edge of the screen. During the review proces of the present paper, an fMRI study of O'Reilly et al. (2008) appeared in which the principle of spatial and temporal prediction was applied in a way that strongly resembled our paradigm. The results of their study and the difference between the designs of the two studies will be treated in the discussion of this paper.

We hypothesized that spatial and temporal processing, optimally inferred from the two anticipation conditions, would be related with common parietal activation centered around the intraparietal sulcus. In addition, parietal activation evoked by specifically space estimation was expected to expand into the postero-superior parietal cortex, while the distribution of timing-specific activations was particularly thought to comprise the right posterior peri-Sylvian cortex, right ventral prefrontal cortex and cerebellum. Particularly the predicted right hemisphere activations in timing relied strongly on respectively the results of work from our own group (Brunia et al., 2000) and the cited human lesion studies (Harrington et al., 1998b). Our findings have previously been published in abstract format (Beudel et al., 2007).

2.3   Materials & Methods

Eighteen healthy right-handed subjects, mean age 27 (SD$\pm$ 8.4), 9 females, participated in this study. None of the subjects had neurological, ophthalmologic or upper extremity disorders. They signed an informed consent to a protocol approved by the medical ethics committee of the University Medical Center of Groningen. Procedures and task instructions were practiced briefly until the tasks were clearly understood. Such practice was one or two days before the experiment was performed and immediately prior to the experiment.

2.3.1   Experimental task equipment

During the acquisition of fMRI images, subjects watched a visual display of a black ball moving on a gray screen (monitor refresh rate 30 Hz). After judging specific temporospatial characteristics of the ball's behavior (see description of the experimental conditions), responses were made by pressing a button on a MR compatible response-box (fORP, Current designs, Inc. U.S.A.). For monitoring the way subjects responded in the various conditions, their response choices and reaction times were logged. A beamer (resolution 1024 × 768 pixels, Barco, Belgium) projected the computer-generated videos of the moving ball on the screen (display dimensions 44 × 34 cm). Subjects viewed the screen via a mirror placed at a distance of 11 cm from the face. The distance between mirror and screen was 64 cm. The middle of the bottom edge of the screen was marked by an arrow head. With blank intervals, the ball appeared at an uncued location and moved until it disappeared. It moved along a straight line, which was continued in a new direction after rebound from either the upper edge or one of the side-edges of the screen (Fig. 2.1). Stimuli were presented using the 'Presentation' program (Neuro Behavioral Systems, Inc. CA, USA).

A total of 72 stimuli was designed that varied with regard to ball directions and trajectory lengths. Each of these 72 trajectories was derived as part from one of 11 basic trajectories. They were balanced for both the time to virtually reach the bottom of the screen and the target side of arrival. Due to the constant 1000ms presentation time, differences in trajectory length resulted in speed differences. The stimulus presentation was designed such that by making the ball to move both over different parts of the basic trajectories and in opposite directions, the virtual arrival time at the bottom edge of the screen was dissociated from direction, trajectory length and speed. Indeed, a bias between particularly speed of the ball and the estimated time to virtually reach the bottom edge of the screen was thus avoided.

2.3.2   Experimental Procedure

The experimental paradigm was constituted by six stimulus-response conditions and one passive visual viewing task. In the latter, the ball remained at a fixed position in the centre of the screen. Subjects did not receive feedback on their responses. In conditions 1 and 2, subjects were instructed to extrapolate the ball's trajectory after its disappearance until it virtually touched the bottom edge of the screen. In condition 1 (visually instructed by 'place ahead'), they had to estimate whether the ball would touch either the left- or the right
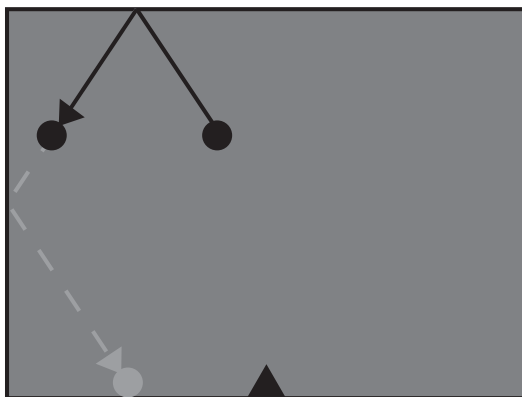
Figure 2.1: Display of the Stimulus Presentation. The solid line indicates one possible trajectory of the moving ball. The three balls point at the successive locations of respectively uncued appearance, stop and disappearance, and virtually touching the bottom edge of the screen. The dotted line indicates the extrapolated trajectory enabling the subjects to make either a spatial prediction in Condition 1 or a time estimation in Condition 2. The solid arrowhead (triangle) demarcates the middle of the screen. In Condition 1, subjects predicted whether the ball would touch either the left or the right side of the bottom edge. Responses were made by pressing one of two buttons of a response box. In Condition 2, subjects estimated whether the bottom edge was reached either within or after 3s.

side of the bottom edge, while in condition 2 ('time ahead'), they had to estimate whether this edge would be reached either within or after 3 s. Responses to such a two-choice demand were made by pressing one of two buttons with either the index- or middle finger of the right hand. In condition 3 ('place at stop'), subjects had to indicate whether the ball actually disappeared on the left- or right side of the screen. The subsequent response had to be given in a similar way as in conditions 1 and 2. The fact that this judgment concerned the spatial location of a moving ball underscores the dynamic character of the momentary spatial condition. This is further explained in the discussion. In condition 4 ('speed'), they had to distinguish between high and low speed. With regard to this distinction, one may assume a continuous adaptation of judgment based on preceding videos. In the base-line condition 5 ('press at stop'), subjects had to press always the same button at the moment the ball

disappeared, no additional choices needed to be made. In a sixth condition ('place at start'), which was not further analyzed in this study, the ball's start position had to be estimated.

The experiment consisted of a practice block (3 min) followed by two 15 min runs of task performance during functional imaging. In between these two runs, an anatomical T1 weighted scan (7 min) was made. The two runs contained 6 blocks each. Each block contained the 6 stimulus-response conditions, while the passive viewing task was placed in between blocks. The order of the conditions was randomized and balanced. In each block-segment, containing a single condition, the task was preceded by respectively a blank screen (500 - 3000 ms, jittering compatible), a visually presented task instruction (2000ms) and another blank screen (1000 ms). The subsequent task consisted of stimulus observation (1000ms) and a 2000ms interval in which a response had to be given. These stimulus-response trials were repeated six times in each 21 s segment. This amounted to a total of 72 trials per condition.

2.3.3   MRI characteristics

Data acquisition was performed using a 3 T Philips MR system (Best, The Netherlands) with a standard 6 channel SENSE head coil. A T1 weighted 3D anatomical scan was acquired to obtain high resolution anatomical information, matrix size = 256 × 256 in axial orientation. Functional images were acquired with a gradient-echo T2* Blood Oxygen Dependent Level (BOLD) contrast technique using the following scanning parameters: TR =3000 ms, TE = 35 ms, 41 slices, isotropic voxels 3.5 × 3.5 × 3.5 mm, axial orientation, 220 volumes per run. The first two volumes of each run were excluded from the analysis to reduce T1 relaxation artifacts.

2.3.4   Data Analysis

Image processing and statistical analysis were conducted with Statistical Parametric Mapping (Friston et al., 1995) version 5 (2005, Wellcome Department of Cognitive Neurology, London, UK; http://www.fil.ion.ucl.ac.uk/spm). Preprocessing with SPM included realignment and spatial normalization. To that end, a mean image of all volumes was created, to which individual volumes were spatially realigned by means of rigid body transformation. The resulting images were normalized to the Echo Planar Image (EPI) template of the Montreal Neurological Institute (MNI), and thus transformed into a standard

stereotactic space. After this, a Gaussian filter of 8 mm Full Width at Half Maximum (FWHM) was applied to smooth the data spatially.

Cortical activations were rendered onto the surface of a standard MNI brain. For the projection on brain slices, we used the standard MNI brain as well as the mean of the normalized anatomical images obtained from the studied subjects. For the statistical analysis of regional differences in cerebral activation, all conditions were modeled in a blocked design at subject level. To identify the distributions of activations related to cerebral processing beyond primary visuomotor control in the conditions 1-4, each of these four conditions was contrasted to the visuomotor control condition (5) at subject level, after which each contrast was separately analyzed at group level using one-sample t-tests. Differences between conditions 1-4 were analyzed by making comparisons at second level using a one-way repeated measures ANOVA (random effect analysis). To avoid confounding variance introduced by the visuomotor control condition, this simple stimulus-response condition was not treated in the ANOVA. The contrasts of the conditions 1-4 with the baseline task of passively viewing a stationary ball in the centre of the screen were used in the ANOVA. Conditions were assumed to be dependent and equally variant, whereas subjects were assumed to be independent and equally variant.

Behavioral differences between the 5 stimulus-response conditions, regarding response times and error rates during performance in the scanner, were analyzed by a one-way ANOVA using the means of single subjects for each condition. The reaction times concerned the interval between disappearance of the stimulus and the recorded response. Only for speed, error rates were not analyzed because the choice between high and low speed was a subjective distinction. In addition, subjects rated the difficulty of the conditions after performance in the scanner. The scale of this rating was from 1 to 10 in which 10 was most difficult. Differences in perceived difficulty between conditions were analyzed using a one-way ANOVA for repeated measurements.

2.4 Results

2.4.1 Behavioral Results

Analysis of the behavioral parameters revealed that the reaction times in the two anticipatory conditions (1 and 2) were similar [$F(1,17) = 0.03$; p=0.875] (Fig. 2.2 A). This confirmed the balance in the design with regard to par-

ticularly these two principal conditions. Such similarity was also found for the reaction times in 'place at stop' (condition 3) and 'speed' (condition 4) $[F(1,17) = 2.78, p=0.114]$. The anticipatory conditions, however, showed significantly longer reaction times compared to the momentary judgment conditions (Fig. 2.2 A). The fastest responses were made in the control condition 'press at stop' (5). Accuracy results indicated constant performance $[F(2,34) = 1,78; p=0.195,$ sphericity corrected] except for the visuomotor control condition. This was confirmed by contrasting the individual conditions with each other. In the probed experimental conditions, between 80 and 85% good responses were obtained while more than 95% of the responses were correct in the visuomotor control condition (Fig. 2.2 B). The subjective difficulty rating confirmed that the tasks were easily performed. Mean ratings were below 4 on the scale ranging from 1 to 10 (Fig. 2.2 C). The 'time ahead' condition was nevertheless judged significantly more difficult (3.9/10) than the other conditions, except for the 'speed' condition (3.7/10) $[F(1,17) = 0.46; p=0.508]$. The latter, on the other hand, was not rated significantly different from 'place ahead' (2.9/10) $[F(1,17) = 3.49; p=0.079]$. The 'press at stop' and 'place at stop' conditions were rated equally (1.4/10) and significantly more easy than the other conditions.

2.4.2   Functional imaging results

The comparisons of the anticipatory spatial and timing conditions (1 and 2) with the visuomotor control condition 'press at stop' (5) resulted in patterns of activation that were both dominated by a strong bilateral posterior parietal activation (Color Fig. 1 A/B on page 199, Tab. 2.1). In spatial prediction, the parietal maximum was at the junction between the dorsolateral extrastriate visual cortex (putative visual area V3A) and the angular gyrus, with extension along the intraparietal sulcus into the superior parietal cortex Color Fig. 1 A on page 199). Although the timing-related parietal activation largely overlapped with that of spatial anticipation, its maximum was located more lateral in the inferior parietal cortex, while it did not include visual cortex (Color Fig. 1 B on page 199, Tab. 2.1). In addition, spatial anticipation was related with activations in the dorsal premotor cortex and at a location ventral to putative visual motion area V5, while time estimation activated the posterior surface of the frontal operculum, the lateral prefrontal cortex, pre-SMA and cerebellum. A direct comparison between these two conditions, thus eliminating the effects of anticipation, revealed that the pattern for the spatial condition remained highly similar (Color Fig. 1 C on page 199). In contrast, when time estima-
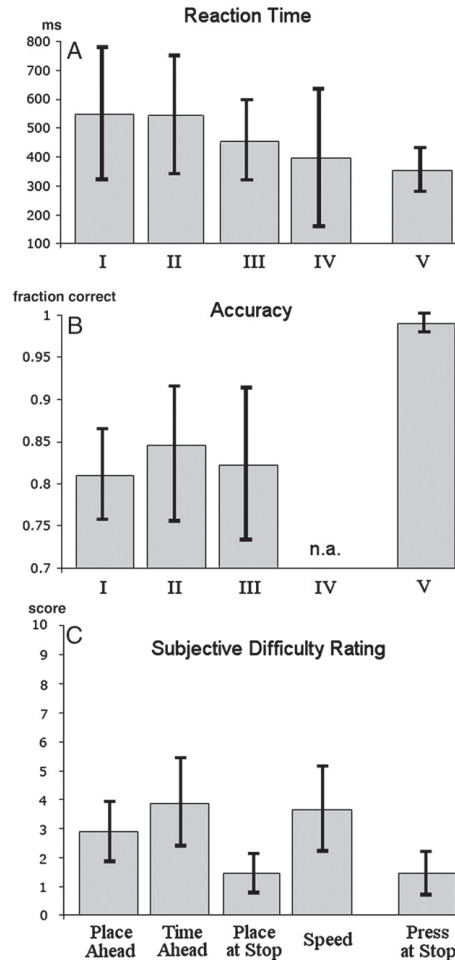
Figure 2.2: Behavioral Data. Reaction times (a) and accuracy of responses (b) obtained in the conditions during scanning. For each condition, the mean (±SD) of 18 subjects is presented, while each subject value is based on the mean of all measurements in a given condition. Only for speed, accuracy was not assessed because the choice between high and low speed was a subjective distinction. In addition, the subjective assessment of the conditions (c) is shown by the mean (±SD) score of the 18 subjects. After the scanning procedure, they rated the difficulty of the conditions with a range between 1 (easy) and 10 (difficult). Statistical analysis of differences between conditions was performed with a one-way ANOVA, of which the results are given in the text. I-IV represent the experimental conditions while V denotes the visuomotor control condition. These labels are fully described on the x-axis of 2c. n.a. = not assessed.

tion was directly contrasted to spatial estimation, the parietal contribution to the pattern of activations was strongly reduced. The time-specific activations were now restricted to the predominantly right frontal operculum and right anteroventral lateral prefrontal cortex, left cerebellum and the pre-SMA (Color Fig. 1 C on page 199, Tab. 2.1). The exact locations of the activated foci are specified in Table 1. In addition, these locations are illustrated by the projection of activations on anatomical brain slices in (Color Fig. 2 on page 200) .

The comparison of momentary spatial judgment (condition 3) with control 'press at stop' (5) showed a distribution of bilateral activations comprising putative visual areas V3A and ventral V5, postero-superior parietal cortex and dorsal premotor cortex. This pattern thus strongly resembled that of spatial anticipation (Color Fig. 1 D on page 199). A similar distribution was obtained from directly contrasting the anticipatory- to the momentary space condition (1 versus 3). Only activation of putative ventral V5 remained near absent (Color Fig. 1 E on page 199).

The strict temporal equivalent of momentary spatial judgment is virtually impossible to extract in a paradigm which is balanced for perceptual and motor features. Speed estimation makes use of time, but is necessarily based on preceding spatial changes. The comparison of such speed estimation (condition 4) with baseline press at stop (5) did, nevertheless, result in a distribution of activations highly resembling that of time anticipation, i.e. bilateral posterior frontal operculum, pre-SMA, right lateral prefrontal cortex, left cerebellum and bilateral parietal cortex (Color Fig. 1 F on page 199). Next, we contrasted speed to momentary spatial judgment (condition 4 versus 3). In this way, we reduced the effect of spatial information which enabled us to focus on the temporal component in speed, thus approximating momentary time estimation. This resulted in a major reduction of parietal activation, with residual involvement of only the right inferior parietal cortex (Color Fig. 1 G on page 199). The resulting pattern of cerebral activations related to momentary time approximation thus resembled the time-specific pattern extracted from the anticipatory conditions. In addition, bilateral activation of the anterior striatum, i.e. the head of the caudate nucleus was found (Color Fig. 1 H on page 199). The latter exclusively resulted from contrasting speed with momentary spatial judgment. This specificity is further supported by the absence of striatum activation after contrasting anticipatory time estimation to momentary spatial judgment (condition 2 versus 3).

Brain Region, Brodmann's Area(BA)								
		left				right		
	x	y	z	T.	x	y	z	T.
A. Place Ahead versus Press at Stop (1 vs 5)								
Dorsolateral extrastriate visual cortex, V3A (BA 19)	-34	-86	28	5.5	40	-84	22	5.7
Superior parietal cortex (BA 7)	-18	-60	52	4.6	32	-52	44	5.7
Putative ventral V5 (BA 19)	-44	-66	-12	4.4				.
Dorsal premotor cortex (BA 6)	-26	-8	60	5.3	28	0	60	4.7
Pulvinar	-22	-30	8	4.1	16	-24	8	3.4
Vermis				.	4	-76	-28	4.0
Inferior temporal gyrus (BA 37)				.	54	-52	-18	4.4
B. Time Ahead versus Press at Stop (2 vs 5)								
Frontal operculum (BA 47)	-30	24	-6	5.6	32	24	-8	5.5
Lateral prefrontal cortex (10,46)	-50	28	30	5.1	36	52	6	5.4
Pre-SMA (BA 32)				.	8	16	50	5.6
Cerebellar hemisphere	-28	-64	-40	5.8	26	-64	-38	5.7
Posterior intraparietal sulcus (IPS)	-44	-50	42	6.0	38	-52	46	5.6
Inferior temporal gyrus (BA 37)				.	56	-46	-18	3.9
C.1. Place Ahead versus Time Ahead (1 vs 2)								
Dorsolateral extrastriate visual cortex, V3A (BA 19)	-36	-84	26	4.7	40	-76	14	4.8
Superior parietal cortex (BA 7)	-18	-58	60	4.6	20	-58	56	5.1
Putative ventral V5 (BA 19)	-54	-68	-6	5.0				.
Dorsal premotor cortex (BA 6)	-24	-6	56	4.6	30	-4	60	4.8
Anterior inferior parietal cortex (BA 40)	-60	-26	38	4.5	36	-32	44	4.7
C.2. Time Ahead versus Place Ahead (2 vs 1)								
Frontal operculum (BA 47)	-48	18	-8	4.4	30	24	-4	5.0
Lateral prefrontal cortex (BA 10,46)				.	34	46	6	5.1
Pre-SMA (BA 32)				.	8	28	38	4.7
Cerebellar hemisphere	-40	-62	-46	4.5	38	-62	-48	4.1
Middle temporal gyrus (BA 21)	-50	-40	4	4.3	58	-46	0	4.3
Corpus callosum				.	8	-20	24	5.0
D. Place Stop versus Press at Stop (3 vs 5)								
Dorsolateral extrastriate visual cortex, V3A (BA 19)	-32	-82	26	4.4	42	-82	24	4.4
Superior parietal cortex (BA 7)	-26	-62	48	5.3	34	-48	54	4.9
Putative ventral V5 (BA 19)	-48	-66	-12	4.8	50	-54	-14	4.0
Dorsal premotor cortex (BA 6)	-20	0	52	5.4	20	-4	48	4.4
Pulvinar	-16	-28	14	4.1	22	-32	12	4.7
Vermis	-12	-68	-26	3.8	12	-76	-48	3.9
E. Place Ahead versus Place at Stop (1 vs 3)								
Dorsolateral extrastriate visual cortex, V3A (BA 19)	-32	-86	28	4.6	38	-78	26	5.8
Superior parietal cortex (BA 7)	-10	-68	56	5.3	14	-70	56	5.2
Dorsal premotor cortex (BA 6)	-26	-4	58	5.9	28	0	60	5.7
Anterior inferior parietal cortex (BA 40)	-58	-30	40	4.8				.
Putative ventral premotor cortex (BA 47)				.	50	8	34	3,9.
F. Speed versus Press at Stop (4 vs 5)								
Frontal operculum (BA 47)	-32	20	-4	4.9	30	22	-10	4.9
Lateral prefrontal cortex (BA 10,46)	-50	16	46	4.3	50	30	28	5.3
Pre-SMA (BA 32)				.6	16	48	5	5.
Cerebellar hemisphere	-36	-80	-34	4.2				.
Posterior intraparietal sulcus (IPS)	-30	-60	40	5.4	36	-56	44	5.4
G. Speed versus Place at Stop (4 vs 3)								
Frontal operculum (BA 47)	-34	22	-6	4.0*	34	22	-8	4.8
Lateral prefrontal cortex (BA 10,46)				.	42	52	12	4.9
Pre-SMA (BA 32)				.	8	28	44	4.9
Cerebellar hemisphere	-26	-80	-38	3.9				.
Inferior parietal cortex (BA 40)				.	44	-56	46	3.6
Caudate nucleus	-10	12	-2	4.2*	12	12	2	4.7*

Table 2.1: Condition-related Activations. Co-ordinates refer to the voxels of maximum activation within significant clusters (P< 0.05, whole-brain corrected at cluster level). In addition, three robust activations (at voxel-level) in anatomically small regions are reported for sub-threshold clusters (marked with *). Positive x,y,z coordinates (in mm) indicate locations respectively right, anterior and superior to the middle of the anterior commissure. The activations resulting from contrasts A-G are depicted in Color Fig. 1 on page 199.

2.5   Discussion

The applied paradigm enabled the successful distinction of cerebral activations related to both regional segregation and overlap in representations of space and time. By introducing anticipation, spatial and temporal judgments could be treated as equivalent parameters in conditions that were balanced for sensorimotor qualities and cognitive demand. The behavioral data supported this balance between the two main conditions 'place ahead' and 'time ahead'. Moreover, such balance reasonably sufficed for all stimulus-response conditions in which spatial, temporal or speed estimations had to be made. Only the visuomotor control task, that simply required pressing a button at the moment the ball stops, was easier. We think it unlikely that this easy task, with fast responses, included a specific element of temporal anticipation that might have led to false negative results in contrasting 'time ahead' to 'press at stop'. This view is supported by the results of the direct comparison between temporal- and spatial anticipation, at 2nd level, using passive viewing as baseline.

2.5.1   Parietal cortex centered function

The conditions that required spatial judgments, either in anticipatory- or in momentary mode, were consistently related with circuitry comprising putative V3A, postero-superior parietal cortex and dorsal premotor cortex. Particularly the involvement of extrastriate visual- and dorsal premotor cortices supports the notion that the cerebral construction of space is anchored with basic neuronal specializations such as processing orientation and direction, both at perceptual and pre-executional levels (Tootell et al., 1997; Pesaran et al., 2006)(see also Introduction). Similarity of the patterns related to respectively anticipatory- and momentary spatial judgment suggests that the extra demand of anticipation is dealt with by intensified processing within the same network. Only visual area coined putative ventral V5, which has previously been implicated in the perception of higher order visual motion (de Jong et al., 1994; Morrone et al., 2000), appeared to be an exception. This region was activated in both anticipatory- and momentary spatial judgment. Its near absence in the direct contrast indicates that it did not significantly contribute to wider aspects of anticipation.

When compared to the same visuomotor baseline task, activations related to time- and space anticipation largely overlapped in the parietal cortex. This suggests that the parietal cortex plays a prominent role in temporo-spatial

integration, which is consistent with the results of previous studies that have addressed temporal and spatial processing in a single design (Coull and Nobre, 1998; Assmus et al., 2003). We did, however, not find a convincing left parietal lateralization as reported by Assmus et al. (2003). On the other hand, an important difference with the referred studies is that our paradigm included active timing, i.e., subjects estimated when a ball would reach a given target. Coull and Nobre (1998) employed matching timed intervals, while Assmus et al. (2003) used the combination of temporal and spatial variables for judging if collision between two dots would occur or not. Absence of active timing may account for the absence of significant time-associated activations beyond the parietal cortex in their studies.

2.5.2 Space-referenced timing

Parietal activation related to time estimation was strongly reduced when this anticipatory condition was contrasted to spatial anticipation, which suggests that spatial information was a prerequisite for temporal processing. A similar reduction of parietal activation occurred when speed was contrasted to momentary spatial judgment. This supports our idea that the subtraction of spatial processing from speed estimation emphasized the temporal component of the latter, and thus provided an approximation of momentary time estimation. The resulting fronto-cerebellar distribution indeed demonstrated a strong similarity between the time-specific activations, extracted from either the anticipatory- or the momentary condition. This similarity is interesting, because time estimations in the anticipatory and momentary conditions thus appear to be accomplished with reference to respectively large and small intervals of spatial change.

The consistent pattern of time-associated activations, comprising predominantly right ventral prefrontal cortex, left cerebellum and pre-SMA, pointed at the additional processing of spatial reference information, recruited from circuitry centered on the parietal cortex. The functional coherence of particularly these regions may provide insight in general processing rules by which spatial reference information is used for temporal assessment. If one assumes that timing in dynamic visuomotor conditions includes the sequential fragmentation and ordering of past and possible future spatial states, the involvement of the (right) prefrontal cortex logically meets the requirements of spatial working memory and the capacity to compare past- and future frames (Jonides et al., 1993; Miller and Cohen, 2001). Cerebellar feedforward mechanisms particu-

larly facilitate the latter (Tesche and Karhu, 2000; Ohyama, 2003; Ramnani, 2006), while the maintained control of serial order, with an easy link to the optional onset of action, highlights the contribution of the pre-SMA (Coull et al., 2004; de Jong et al., 1996; Shima and Tanji, 2000). The pattern of crossed activations in respectively right prefrontal cortex and the posterior lobe of the left cerebellum, most prominently revealed by contrasting 'speed' to 'place at stop', supports the inference of functional coherence between the two (Gold and Lauritzen, 2002; Kelly and Strick, 2003; Makris et al., 2005b).

The time-related distribution of activations, comprising cerebellum, right fronto-parietal cortical regions and pre-SMA, is consistent with the results of O'Reilly et al. (2008). The results and experimental design of their fMRI study deserves special attention because, similar to our study, the distinction between temporal and spatial aspects of a moving target was reached by using anticipation. A difference with our study, however, was that judgment in the temporal condition of their study depended equally strong on spatial information as judgment in the spatial condition did. This was indeed acknowledged by coining it a temporal-spatial condition. In the O'Reilly study, spatial and temporal-spatial estimations were made as the target passed an occluded part of its trajectory, while after reappearance, subjects had to indicate whether the target either had changed direction (spatial judgment) or had traveled too far or not far enough (judgment of speed). This implied that in both conditions the same level of spatial accuracy was used to discern such change. In our study, subjects made a judgment (and subsequent response) already at disappearance of the moving ball. In the spatial condition, prediction of a highly specified location was asked for, i.e. the right or the left side of the screen bottom; while for time prediction, spatial accuracy was reduced because the whole screen bottom served as a target. This difference may well explain why O'Reilly et al. didn't find significant activations related to the spatial condition when contrasted to the temporal-spatial one. Indeed, in their temporal-spatial condition, increased activation was reported e.g. at a location (x 33, y 9, z 63) that was slightly anterior to the dorsal premotor activation related to spatial anticipation in our paradigm (28, 0, 60; see Table 2.1). The increase of this dorsal premotor activation remained significant when contrasted to time prediction. Their results, nevertheless, clearly provide support for the accuracy of our paradigm and thus strengthen the value of our additional results. Besides the pattern of activations specifically related to spatial anticipation, these results further included the activations related to the judgments in momentary mode. It is important to notice, in this respect, that in our paradigm there was no bias between temporal prediction and speed estimation, which en-

abled the task-specific distinction between cerebellar and striatum activations.

2.5.3   Clock-like measures

We proposed that in the dynamic conditions of our experiment, the cerebellar-prefrontal role in the perception of time particularly concerned the assessment of differences between multiple spatial frames. It was intriguing to see that the additional contribution of the caudate nucleus emerged in 'speed-derived' time approximation, which implies that such spatial intervals became exceptionally small, not to say virtually non-existing. This suggests that the caudate activation reflected timing without reference to external spatial change, i.e. non-contextual timing. In a similar way, such non-contextual timing may be assumed to occur in the planning of intervals between non-directional stimuli and responses (Rao et al., 2001; Buhusi and Meck, 2005). On the other hand, in the circumstance of exceptionally small spatial intervals, caudate activation may point at the assessment of change with reference to an internal interval defined by cerebral processing time. In other words, intervals of minimal spatial change are the consequence of cerebral processing time. Such association between caudate function and an internal time parameter comes close to the concept of a dopamine-related internal clock (Rao et al., 2001; Buhusi and Meck, 2005; Jahanshahi et al., 2006). Cerebral processing time indeed fractionates the flow of external change thus demarcating such intervals, which implies the construction of distinct spatial frames. In this way, a threshold is set at which the perception of e.g. a moving dot changes into the perception of a line. In other words, cerebral processing time eventually enacts the distinction between the perception of a dynamic and a static world (Bartels and Zeki, 2005).

With regard to contrasting the two momentary judgments, it is important to notice that speed estimation and the assessment of the location at which the moving ball disappeared (momentary spatial judgment) were both dynamic conditions. The dynamic character of the latter is illustrated by the 'flash-lag illusion'. This phenomenon implies that a moving object is perceived to be behind a spatially concurrent stationary flash before the two disappear (Nijhawan, 1994; Eagleman and Sejnowski, 2000; Roulston et al., 2006). If the delay is considered to reflect processing time required to construct a 'single spatial frame', one may speculate that this temporal measure is in the magnitude of 100 ms.

We thus argued that by defining the smallest intervals of perceptible change, cerebral processing intrinsically provides a measure of time. This is consistent with the model of cortical networks that are inherently able to tell time as a result of time-dependent changes in the network (Karmarkar and Buonomano, 2007). In this respect, the model of a single pulse-emitting oscillator has indeed changed into that of multiple cortical oscillators (Buhusi and Meck, 2005). In the latter, the basal ganglia have been proposed to play a role in the synchronization of such oscillators. The association we found between the caudate activation and particularly 'speed-derived' timing is therefore consistent with the role of the basal ganglia in providing an internal measure of time. The architecture of corticostriatal connections (Parent and Hazrati, 1995) enables each cortical processing node to emit a striatal efferent copy. This also implies that after an initial stimulus-induced activation, the temporo-spatial dispersion over the cortex is complemented by the induction of sequential regularity in the basal ganglia. One may hypothesize that this enforced regularity helps to maintain an oscillator function regarding the return of signals via the thalamus to the cortex (cartoon provided in Fig. 2.3).

2.6   Conclusion

To conclude, the task-specific modulation of activations in the parietal cortex, the consistent cerebellar-prefrontal activations related to temporal processing, and the increased caudate activation specifically associated with speed assessment contrasted to judging the actual site at which a moving ball disappeared, provided arguments to hypothesize a model that integrates concepts of space-referenced time processing and a clock-like processing model.
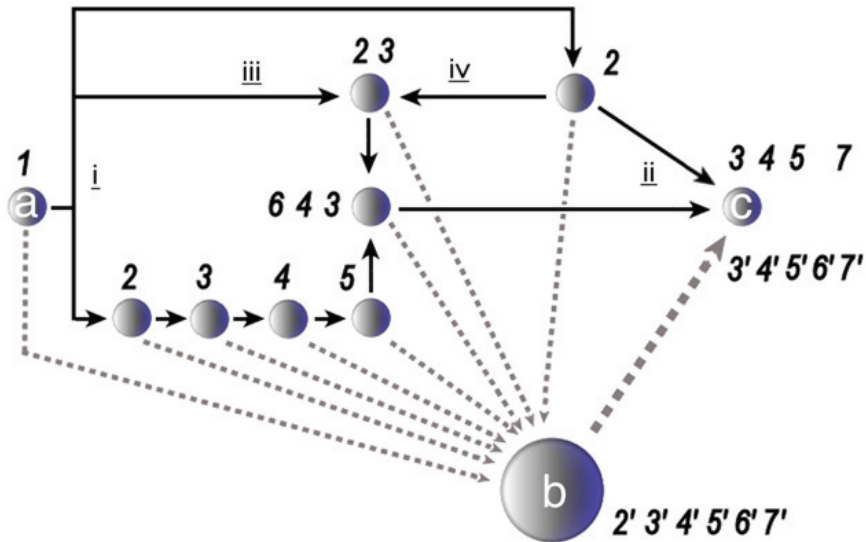
Figure 2.3: Stimulus Dispersion in Space and Time. Scheme of a simplified neuronal network to illustrate dispersion in space and time following the initial stimulus-induced activation (1) at locus A. Successive processing steps (indicated by the numbers 2-7) take place according to principles of functional segregation (i) and integration (ii), as well as bottom-up (iii) and top-down (iv) mechanisms. Delay by synaptic transmission at the indicated processing nodes may introduce sequence irregularity. At system-level, sequential regularity is maintained by the integration of efferent copies sent to locus B. The latter may act as an oscillator, providing a measure of 'processing-based' time at network locus C. E.g.: A = visual cortex, B = basal ganglia and thalamus, C = prefrontal cortex.