Interval and Ordinal Properties of Sequences Are Associated with Distinct Premotor Areas

Ricarda I. Schubotz and D. Yves von Cramon

Max-Planck-Institute of Cognitive Neuroscience, Leipzig, Germany

Lesion and imaging studies have suggested that the premotor cortex (PMC) is a crucial component in the neural network underlying the processing of sequential information. However, whether different aspects of sequential information like interval and ordinal properties are supported by different anatomical regions, and whether the representation of sequential information within the PMC is necessarily related to motor requirements, remain open questions. Brain activations were investigated during a sequence encoding paradigm in 12 healthy subjects using functional magnetic resonance imaging. Subjects had to attend either to the interval or to the ordinal information of a sequence of visually presented stimuli and had to encode the relevant information either before motor reproduction or before perceptual monitoring. Although interval and ordinal information led to activations within the same neural network, direct comparisons revealed significant differences. The pre-supplementary motor area (preSMA), the lateral PMC, the frontal opercular cortex as well as basal ganglia and the left lateral cerebellar cortex (CE) were activated significantly more strongly by interval information, whereas the SMA, the frontal eye field, the primary motor cortex (MI), the primary somatosensory cortex, the cuneus as well as the medial CE and the thalamus were activated more strongly by ordinal information. In addition, serial encoding before reproduction led to higher activations than serial encoding before monitoring in the preSMA, SMA, MI and medial CE. Our findings suggest overlapping but different kinds of sequential representation, depending on both the ordinal and interval aspects as well as motor requirements.

Introduction

The processing of both ordinal and interval properties of time, i.e. temporal order and temporal duration, is a vital aspect of our everyday perceptual abilities and motor skills. This is especially obvious in the comprehension of events such as language (Shannon *et al.*, 1995) or music (Platel *et al.*, 1997; Patel *et al.*, 1998), that are characterized by temporal patterns, but also in the production of many skills like piano playing, typing (Grudin, 1982) and speech (Fowler, 1979), where behaviors must be both precisely timed and put in the proper order. Two main issues have been debated: first, whether the timing and the sequencing of motor acts are realized by different brain mechanisms; and second, whether time perception can be distinguished from motor action timing in terms of brain structures involved.

With regard to the first question, motor timing control appears to be partly independent of sequence representation. For example, when subjects are asked to speed up or slow down the production of a movement sequence they do so with near constancy in the relative timing of the single motion components (Carter and Shapiro, 1984). Thus, it is argued on the basis of such invariant temporal characteristics in typing (Terzuolo and Viviani, 1979), handwriting (Viviani and Terzuolo, 1980), speech (Tuller *et al.*, 1982) and locomotion (Shapiro *et al.*, 1981), that the timing of a movement can be changed without affecting the sequential order of the motion components (MacKay, 1987a,b). However, it is also proposed that both aspects rely on the same mechanisms. Rosenbaum (Rosenbaum, 1985) and Rumelhart and Norman (Rumelhart and Norman, 1982) argue that the specification of timing in motion planning defines at the same time the proper order of movement components. This is confirmed by simulation experiments that test the hypothesis that a single learning system would be capable of representing both serial and temporal structures of sequences. Perturbations in serial reaction time tasks occurring when the prelearned temporal structure is changed support the suggestion that temporal structure is an integral part of the sequence so that when it is altered the sequence also changes (Dominey, 1998). Finally, it is suggested that timing and sequencing are closely related but independent processes in the programming of movement (Schmidt, 1980; MacKay, 1985; Keele, 1987). This kind of 'coupling' between sequencing and timing appears to be especially evident in skills involving rhythmic timing structures (Summers *et al.*, 1984).

With regard to the second question, it is argued that, if the same internal timing mechanism or central clock underlies both motor and perceptual timing, then one ought to find correlations between motor timing and perceptual timing (Keele *et al.*, 1985; Treisman *et al.*, 1992). Accordingly, since the standard deviation of both motor timing and time perception was found to be linearly related to the square of the target intervals and the slope of this standard deviation function – conforming to a generalized form of Weber's law – appeared to be identical for motor performance and perception, Ivry and Hazeltine (Ivry and Hazeltine, 1995) suggested that temporal judgements and productions are based on an integrated internal representation of the target interval. A computational model of memory for temporally extended behaviors, the so-called broadcast theory (Rosenbaum, 1998), describes the relationship between the timing of perceived events and the timing of produced events as functional mirror images or instantiations of one and the same neural architecture.

As indicated by studies in both man and monkeys, brain areas found to be involved in the learning and control of sequential movement are the lateral premotor cortex (PMC) (Halsband and Freund, 1990; Mushiake *et al.*, 1991; Gordon *et al.*, 1995; Kettner *et al.*, 1996; Sadato *et al.*, 1996), its most medial part, the supplementary motor area (SMA) or SMA proper (Toni *et al.*, 1998), and the more anterior or rostral portion, the preSMA (Hikosaka *et al.*, 1996, 1998; Picard and Strick, 1996; Sakai *et al.*, 1998). The standard paradigm employed in these studies is the serial reaction time task (SRT) introduced by Nissen and Bullemer (Nissen and Bullemer, 1987), in which subjects are required to press a key corresponding to each visual cue presented according to a sequence (Grafton *et al.*, 1995; Rauch *et al.*, 1995; Doyon *et al.*, 1996; Hazeltine *et al.*, 1997; Sakai *et al.*,

1998). Usually, the SRT is used to investigate effects of implicit learning mechanisms.

However, the SRT in its classical application does not distinguish whether subjects learn the sequence of presentations (perceptual domain), the sequence of responses (motor domain) or the sequence of stimulus–response relationships (Keele *et al*., 1995). It is argued that the similarity of brain activations caused by stimulations using different sensory modalities implies that sequence processing does not occur solely in the sensory dimension (Grafton *et al*., 1995; Hazeltine *et al*., 1997; Honda *et al*., 1998). This is confirmed by a recent patient study that shows basal ganglia (BG) involvement for non-motor as well as motor sequence processing, using a modified version of the SRT (Vakil *et al*., 2000). However, since most SRT studies focus on motor sequencing rather than sequence processing *per se*, they usually require a kind of motor output. Although motor activation is supposed to be subtracted out by suitable baseline conditions in imaging studies, it cannot be ruled out that motor requirements have a general effect on the representation format of the sequences. In the SRT context, non-motor serial processing has not been investigated systematically.

Furthermore, while these studies focus on the temporal order of effectors to be moved, the processing of interval properties, i.e. the temporal duration of successive movements, is not investigated. To our knowledge, no attempt has been made to date to distinguish the ordinal and the interval properties of motor sequences experimentally. Prominent brain structures found to be involved in interval timing tested by interval perception or interval production paradigms are the BG (Hinton *et al*., 1996; Harrington *et al*., 1998; Turner *et al*., 1998) and the cerebellar cortex (CE) (Buonomano and Mauk, 1994; Jueptner *et al*., 1995; Ivry, 1996, 1997; Raymond *et al*., 1996; Gibbon *et al*., 1997; Penhune *et al*., 1998; Casini and Ivry, 1999). In addition, one cortical area involved in the processing of sequential movements, the lateral PMC, also seems to be engaged when temporal intervals have to be processed (Weinrich *et al*., 1984; Lang *et al*., 1990; Halsband *et al*., 1993; Rao *et al*., 1997; Rubia *et al*., 1998; Schubotz *et al*., 2000). However, since sequencing/ordinal tasks and timing/interval tasks were not tested within the same studies, no reliable statement can be made about functional dissociations of these abilities within the PMC.

Therefore, the present study set out to investigate two aspects of serial processing. First, whether the representations of ordinal and interval properties of serial information are supported by the same brain structures, especially within premotor areas. And second, whether motor requirements of the task have an effect on the neural representations of motor sequences to be memorized. FMRI was used to measure brain activities while subjects performed a temporal encoding paradigm. Subjects had to attend to either the interval or the ordinal properties of visually presented three-part sequences repeated several times. Subjects were aware of the specific task requirements during the encoding stage. Afterwards, memory performance was tested by either perceptual monitoring of further repetitions for serial deviants or by manual serial reproduction. Thus, the experimental design comprised four cells, resulting from crossing of two two-level factors, Property (interval, ordinal) and Domain (monitoring, reproduction): interval encoding before monitoring (IM), ordinal encoding before monitoring (OM), interval encoding before reproduction (IP) and ordinal encoding before reproduction (OP). Additionally, a baseline condition (CC) controlled for perceptual and attentional effects. Brain activations were analyzed only in the time range of encoding the relevant sequential information, so that the only differences between tasks were (i) the attentional focus on interval or ordinal information and (ii) the requirement to reproduce the sequence or to perceptually analyze further repetitions following encoding.

Materials and Methods

Subjects

Twelve healthy right-handed subjects (six male and six female, ages 20–27 years, mean age 23 years) participated in the study. Informed consent was obtained from each subject before testing. All experiments complied with German legal requirements. Immediately prior to the functional imaging session, subjects spent 20 min in the scanner, so that they could acclimate to the confinement and sounds of the magnetic resonance environment. The subject's hands were carefully stabilized with the four response fingers positioned on the response buttons in order to prevent postural adjustments.

Before participating in the functional magnetic resonance imaging (fMRI) experiment, all subjects were trained to a minimal performance level of 70% in each condition.

Stimulus Presentation

Subjects fixated at screen center but were required to attend to timing stimuli that appeared in four stimulus windows that were located at 3.3 and 8° of visual angle to the left and right of screen center (Fig. 1). Timing stimuli were colored circles. They were presented for multiples of 290 ms, namely 290, 580, 870, 1160 or 1450 ms. The selection of these interval durations was based on previous work (Schubotz *et al*., 2000). Three successive stimulus presentations always added up to 2320 ms, such that, within each trial, one out of 18 different rhythm types, like 290–580–1450, 290–1450–580 or 580–580–1160, was presented. Within a trial, a rhythm type was repeated three times. The encoding phase lasted 3 × 2320 ms = 6960 ms. The tasks were presented in random order

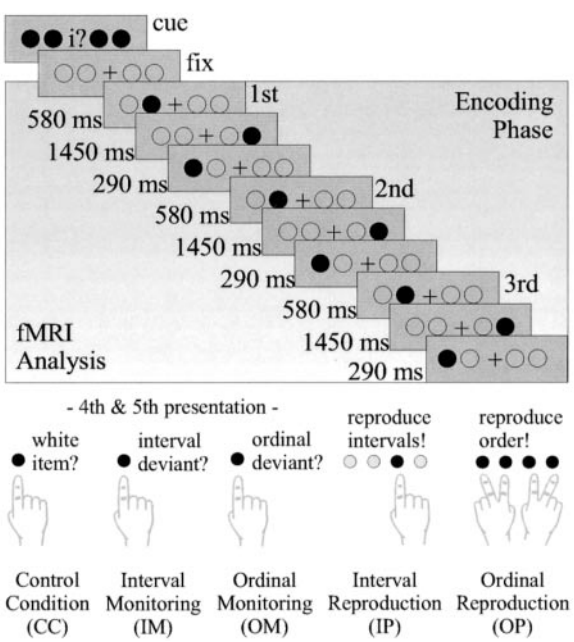


Figure 1. Illustration of the five experimental conditions. During each trial, subjects had to encode the task-relevant information of the first three stimuli (1st), which were repeated for further memory consolidation (2nd, 3rd). Brain activations were analyzed only during this encoding phase. Subsequently, subjects had to monitor two further repetitions of the sequence (4th, 5th) for either interval deviants (IM) or ordinal deviants (OM), or they had to reproduce manually the encoded intervals (IP) or the encoded order (OP). In the control condition (CC), subjects had to indicate color deviants.

and announced by verbal cues at the beginning of each trial. Subjects had to give their responses with the middle and the index finger of the left and the right hand on a four-button response box, corresponding to the four screen locations in the stimulus window. Before the experiment, participants performed in a training session to ensure proper task performance.

Task Procedure

Thirty-six trials were presented per condition. The inter-trial interval was 6 s. Each trial lasted 12 s and was preceded by a visual cue that announced the task to perform next. In order to provide a mnemonic aid, stimuli were colored differently in each task (IM, red; OM, yellow; IP, green; OP, blue; CC, white). During the encoding phase, subjects attended to different aspects according to the task demands, but the relevant features were physically the same for each task. Subsequently, subjects performed one of five tasks. A pilot study had shown that subjects found it much easier to perform the test phase immediately after the encoding phase than after a short temporal delay. Even an indication of the transition, realized by a small visual cue, was reported to irritate rather than to support the orientation. Accordingly, no transition cue was presented in the experiment. Since we were interested in the encoding phase rather than to make the test phase particularly memory demanding, the test phase followed the encoding phase without any temporal delay.

Task IM

In the IM task, subjects had to encode the interval properties (rhythm) of the sequence, i.e. the duration of each element in the set. Immediately afterwards, subjects had to monitor two further set presentations for rhythmical deviants. Fifty percent of all trials contained one deviant. If a deviant was detected, subjects had to press immediately a response key with the right index finger (go/no-go). Two further sets were presented rather than only one to ensure that the time on task should be equal in all tasks. A pilot study had shown that subjects needed longer to reproduce the order or the intervals of a stimulus set than to preceptually monitor the same stimulus set. A longer time on task can increase the bold response by linear addition (Dale and Buckner, 1997).

Task OM

In the *ordinal encoding before monitoring* task, subjects had to encode the ordinal properties (order) of the sequence, i.e. the order of the elements in the set. Immediately afterwards, subjects had to monitor two further set repetitions for order deviants. Deviants (one in 50% of all trials) were to be indicated by button press with the right index finger.

Task IP

In the *interval encoding before reproduction* task, subjects had to encode the interval properties of the sequence, just as in task IM. Then, subjects reproduced the studied rhythm with the right index finger [stimulus onset asynchrony (SOA) 0 ms, one time, four responses, with the last one to indicate the end of the third interval]. The response in this task only required an interval reproduction without confounding order information (responses with more than one finger).

Task OP

In the *ordinal encoding before reproduction* task, subjects had to encode the ordinal properties of the sequence, just as in task OM. Then, subjects reproduced the sequential order with the corresponding middle and index fingers of the right and the left hand (three responses). The response in this task only required an ordinal reproduction without confounding interval information (different response intervals).

Task CC

In the *control condition*, the stimuli were presented in the manner as in the other tasks, with the only difference that stimuli appeared in random colors and subjects had to indicate if a white item (one in 50% of all trials) was presented. Note that this condition had the same information content as the other tasks, but the temporal order and the temporal intervals had to be ignored.

Scanning Procedure

Imaging was performed at 3T on a Bruker Medspec 30/100 system equipped with the standard bird cage head coil. Subjects were supine on the scanner bed, and cushions were used to reduce head motion. They were provided with earplugs to attenuate scanner noise. In a seperate session, high resolution whole brain images were acquired from each subject to improve the localization of activation foci using a T1-weighted three-dimensional segmented MDEFT sequence (128 sagittal slices, 1.5 mm thickness, 265 × 265 pixel matrix). To align the echo planar functional images to the three-dimensional images, a set of two-dimensional anatomical images in plane with the functional images was acquired for each subject immediately prior to the functional experiment, using an IR-RARE sequence (TE = 20 ms, TR = 3750 ms, 512 × 512 pixel matrix). Functional images were acquired using a single-shot gradient echo-planar imaging (EPI) sequence (TE = 40 ms, 64 × 64 pixel matrix, flip angle 40°, field of view = 192 mm) sensitive to BOLD contrast. Slices were positioned parallel to the bicommissural plane (AC–PC), with one image covering the whole brain. Images were obtained continuously during the entire session from 16 axial slices (thickness 5 mm, spacing 2 mm) at the rate of 2 s per image (16 slices). The total number of images was 1620 (five conditions, 36 trials of 12 s, 6 s intertrial interval).

An important consideration is that the scanner noise can interfere with experimental tasks, particularly with rhythmic tasks. In our study, the gradient generated an isochronous background rhythm of 125 ms per beat (16 slices in 2 s, one beat per slice). Scans were time-locked with the start of the trial. However, since the stimulus onset times of the subsequent stimuli varied randomly from trial to trial, the temporal pattern composed of the mixture of the visual stimuli and the scanner beat was random. Moreover, since the scanner beat was very fast (125 ms per beat), subjects reported that they perceived the noise as a uniform, homogeneous stream rather than as a rhythm of distinct beats.

Data Analysis

The fMRI data were processed using the software package LIPSIA (Lohmann *et al.*, 1999). In the preprocessing, low-frequency signals (frequencies due to global signal changes like respiration) were removed by applying a 1/120 Hz highpass filter. Because low frequencies were removed, temporal filtering also effected a signal baseline correction. The increased autocorrelation caused by the filtering was taken into account during statistical evaluation by the adjustment of the degrees of freedom (see below). The anatomical registration was done in three steps: first, anatomical slices geometrically aligned with the functional slices were used to compute a transformation matrix, containing rotational and translational parameters, that register the anatomical slices with the three-dimensional reference T1-data set. In a second step, each individual transformation matrix was scaled to the standard brain size (x = 135, y = 175, z = 120 mm) (Talairach and Tournoux, 1988) by applying a linear scaling. Finally, these normalized transformation matrices were applied to the individual functional raw data. Slice-gaps were scaled using a trilinear interpolation, generating output data with a spatial resolution of 3 mm^3.

The statistical analysis was based on a least squares estimation using the general linear model for serially autocorrelated observations (fixed-effects model) (Winer *et al.*, 1991; Friston, 1994; Worsley and Friston, 1995; Aguirre *et al.*, 1997; Zarahn *et al.*, 1997).

The design matrix was generated with a boxcar function model and a response delay of 6 s (Hu *et al.*, 1997; Woolsey *et al.*, 1998). For each condition, the brain activations during a 6 s phase starting at the stimulus onset of each trial were analyzed, which included the first 6 s of the encoding phase (6960 ms). Thus, the last 960 ms of the encoding phase and the test phase were excluded from analysis, thereby ruling out that the analysis of memory encoding was confounded with any motor preparation or motor execution activation. Due to the rest period at the end of each trial, the hemodynamic response could return to baseline before the next trial. The design matrix and the data were linearly smoothed by multiplication with a matrix representing the hemodynamic response function, a Gaussian kernel of dispersion, of 4 s full width half maximum (FWHM). The model adjusts the degrees of freedom to include the effects of temporal autocorrelation. The output images, containing an estimation

for the slope of regression, were *F*-thresholded at a probability of $P = 0.0001$. The contrast between the different conditions was calculated using the *t*-statistic. Two kinds of task contrasts were analyzed. First, the control condition (CC) was used as a baseline in order to identify the general activation pattern during sequence and interval encoding. Second, in order to identify differences between the ordinal and interval tasks, direct task comparisons were computed. Subsequently, *t*-values were transformed to Z scores. As the individual functional datasets were all aligned to the same stereotactic reference space, a group analysis of fMRI data was performed by averaging individual *z*-maps and multiplying each *Z* value with the square root of *n* (*n* = number of subjects) (Bosch, 2000).

Results

Behavioral Performance

Behavioral performance was assessed by error rate (response times could only be assessed for the monitoring conditions, and thus where not informative). For the monitoring tasks (IM, OM), responses on a no-go-trial (false alarm) and missing responses on a go-trial (missing) were defined as errors. For the interval reproduction task (IP), an error occured when the durations between successive response onsets (reproduced rhythm) differed from the defined rhythm for that trial. Therefore, not absolute temporal durations were not decisive, but rather the relative durations (e.g. 'shortest–longest–middle') between the three reproduced intervals. For the ordinal reproduction task (OP), errors were defined as responses given with the wrong finger relative to the defined temporal order in a given trial. The error rates were 6.3% (OM), 2.8% (OP), 19.2% (IM) and 19.1% (IP) (Fig. 2*A*). A repeated measures ANOVA with the two level factors Property (interval, ordinal) and Domain (monitoring, reproduction) revealed no Property × Domain interaction and no main effect of Domain, but therer was a main effect of Property [$F(1,11) = 44.4$, $P < 0.0001$], indicating that task performance was better in the ordinal tasks than in the interval tasks. For the interval reproduction (IP), a repeated measures ANOVA with the five-level factor Interval (290, 580, 870, 1160, 1450 ms) showed a main effect [$F(1,4) = 124.6$, P 0.0001], suggesting that intervals were discriminated successfully on the motor output level (Fig. 2*B*).

MRI Data

Brain areas with significantly higher BOLD response during serial processing than during the control condition (CC) are shown in Figure 3*A*. As shown in Table 1 [for Talairach coordinates, see (Talairach and Tournoux, 1988)], all four contrasts (IM–CC, OM–CC, IP–CC, OP–CC) revealed similar modulations of a neural network including bilateral activations in the preSMA, SMA, frontal eye field (FEF), dorsolateral and ventrolateral PMC (dPMC, vPMC), frontal opercular cortex (FOP), BG, CE, thalamus (THA) and parietal lobule. Notably, direct comparisons between the serial processing tasks revealed significantly higher activations according to the specific contrast, as shown in Table 2 and Figure 3*B*. Thus, significantly higher activations during the interval tasks compared with the ordinal tasks (I–O) were found in the preSMA, dPMC, vPMC, FOP, BG and the left lateral CE. In contrast, higher activations during the ordinal tasks as compared to the interval tasks (O-I) were found in SMA, FEF, cuneus, medial CE and THA; additionally, the primary motor cortex (MI) and primary somatosensory cortex (SI) were activated. Serial encoding before reproduction (motor requirements) led to higher activations than serial encoding before perceptual monitoring (without motor requirements) (P > M) in preSMA, SMA, MI and right medial CE (Fig. 3*C*, upper panel). The reverse contrast (M > P) did not lead to higher activations in any brain area.

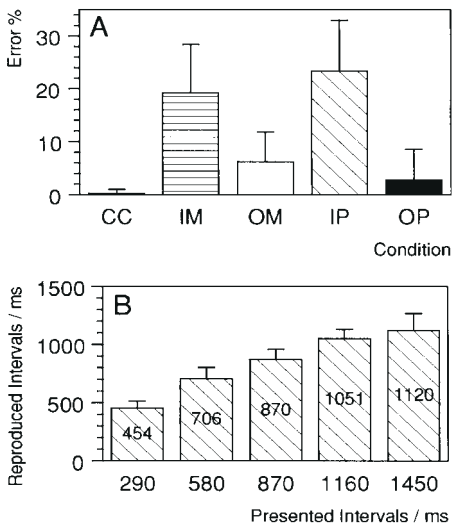


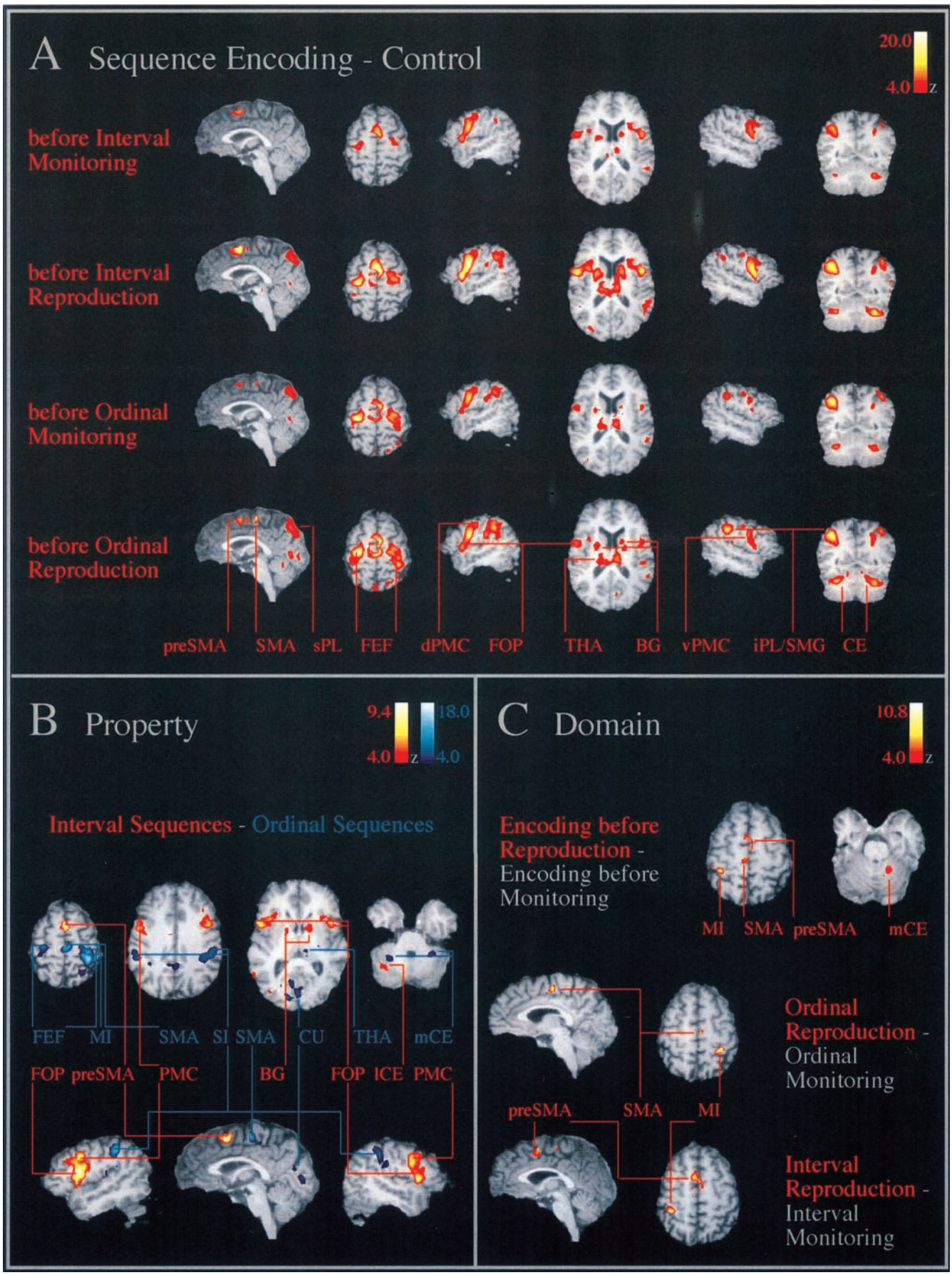
Figure 2. (*A*) Behavioral performance in the four sequencing tasks (IM, OM, IP, OP) and in the control condition (CC). (*B*) The mean durations of the reproduced intervals in relation to the durations of the presented intervals in the interval encoding before reproduction task (IM).

Because task difficulty can correlate with BOLD response intensity, we considered the following three aspects concerning the relationship between task difficulty and BOLD response: (i) behavioral performance was almost equal in IM and IP, whereas the corresponding *Z* scores (IM–CC versus IP–CC) do not show an overall similar activation pattern across different regions. (ii) The interval tasks (IM, IP) were more difficult than the ordinal tasks (OM, OP), but 10/20 areas considered here exhibited higher *Z* scores in the ordinal than in the interval tasks (all relative to CC). (iii) Descriptively, subjects performed better in the OP than in the OM task, whereas the BOLD responses were higher in the OP task for 16/20 areas analyzed here (all relative to CC). We take this pattern of results to indicate that higher BOLD activations cannot be attributed to unspecific higher task demands in general. Rather they reflect differences related to functional specializations of the corresponding brain areas.

Discussion

Medial Premotor Cortex: PreSMA and SMA

Two motor areas within the medial wall were functionally dissociated by experimental manipulations. These were the SMA proper, which is located posterior to the vertical line transversing the anterior commissure (VCA line), and the preSMA, which lies anterior to the VCA line (Stephan *et al.*, 1995; Picard and Strick, 1996). The SMA was significantly more activated during the order encoding, whereas the preSMA was significantly more activated during the interval encoding. SMA and preSMA belong to the mesial part of the PMC, which plays a major role in the preparation and processing of movement (Tokuno and Tanji, 1993; Tanji, 1994; Tanji and Shima, 1994, 1996). With respect to the tasks employed in our study, it is important to consider that both preSMA and SMA are particularly involved (i) in the temporal organization of movements (Clower and Alexander, 1998; Shima and Tanji, 1998) and (ii) especially of those movements that are internally guided and performed on the basis of memory (Goldberg, 1985;


A Sequence Encoding - Control
20.0
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z
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FOP
THA
BG
vPMC
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Encoding before Reproduction - Encoding before Monitoring
MI
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Ordinal Reproduction - Ordinal Monitoring
preSMA
SMA
MI
Interval Reproduction - Interval Monitoring

Table 1
Anatomical specification, mean Talairach coordinates and *Z* score of significant activated voxels detected in comparison between the sequencing tasks (IM, IP, OM, OP) versus the control condition (CC)

Anatomical area		IM–IC		IP–CC		OM–CC		OP–CC	
		x/y/z	*Z* score	*x/y/z*	*Z* score	*x/y/z*	*Z* score	*x/y/z*	*Z* score
preSMA		1/12/45	13.9	1/12/45	21.8	4/12/45	14.9	1/12/45	17.3
SMA		1/1/50	7.1	–2/–7/52	13.2	–2/–7/52	13.7	–2/–7/52	18.5
FEF	L	–29/–4/51	10.9	–29/–5/48	18.2	–29/–5/48	21.7	–29/–5/48	21.5
	R	28/–2/48	9.5	28/–2/48	12.9	22/–4/51	12.8	22/–4/51	12.8
dPMC	L	–47/–1/36	10.7	–47/–1/36	14.0	–47/–2/33	11.7	–47/–2/33	11.6
	R	40/–1/36	12.8	43/–1/36	14.5	43/0/36	12.1	43/–1/36	11.1
vPMC	L	–50/5/17	14.1	–50/5/17	20.8	–50/3/21	14.0	–50/3/18	16.4
	R	46/8/15	12.3	46/8/17	15.8	43/7/25	10.5	46/3/21	11.8
FOP	L	–47/11/2	11.7	–50/11/2	17.9	–53/7/11	10.4	–50/10/0	11.6
	R	46/12/4	11.7	46/12/4	16.4	46/8/11	8.3	46/12/4	10.2
iPL/SMG	L	–38/–45/46	13.1	–38/–45/46	18.0	–35/–43– 45	18.8	–38/–43/45	19.0
	R	43/–37/41	8.7	37/–39/47	11.9	37/–39/47	12.5	37/–36/46	14.0
sPL	L	–14/–66/50	11.2	–11/–66/50	15.9	–11/–66/50	14.9	–14/–66/50	15.5
	R	13/–57/51	10.0	7/–67/47	12.9	10/–62/55	13.2	10/–62/52	13.7
BG	L	–17/4/9	8.4	–23/6/8	11.9	–23/0/7	8.0	–23/0/7	9.3
	R	13/7/11	7.9	13/6/8	11.9	13/6/8	6.8	16/9/8	7.9
THA	L	–14/–17/11	6.9	–14/–17/11	12.6	–13/–20/11	10.7	–11/–20/11	11.9
	R	7/–14/10	8.9	7/–17/11	10.8	7/–17/11	12.8	7/–17/11	12.9
CE	L	–32/–66/–15	9.9	–32/–66/–15	13.8	–32/–57/–17	12.1	25/–57/–27	14.6
	R	25/–60/–17	12.0	25/–57/–17	16.0	25/–57/–17	11.0	–29/–57/–15	13.5

L, left hemisphere; R, right hemisphere; preSMA, pre-supplementary motor area; SMA, supplementary motor area; FEF, frontal eye field; d, dorsal; PMC, premotor cortex; v, ventral; FOP,frontal opercular cortex; i, inferior; PL, parietal lobule; SMG, supramarginal gyrus; s, superior; BG, basal ganglia; THA, thalamus; CE, cerebellar cortex.

Passingham *et al.*, 1989; Mushiake *et al.*, 1991; Halsband *et al.*, 1993). Recent data indicate, however, that the preSMA is involved in higher hierarchical roles in motor control than the SMA proper (Luppino *et al.*, 1990, 1993; Rizzolatti *et al.*, 1990, 1996; Matsuzaka *et al.*, 1992), whereas the SMA is more closely related to motor execution and effector-specific modulations (Wiesendanger *et al.*, 1985; Hummelsheim *et al.*, 1988; Dum and Strick, 1991a,b; He *et al.*, 1993; Tokuno and Tanji, 1993; Lu *et al.*, 1994). This difference is also reflected by the temporal succession in which preSMA and SMA engage in the movement coordination: the preSMA activation precedes activity changes in the SMA, which is more time-locked to movement onset (Alexander and Crutcher, 1990; Rizzolatti *et al.*, 1990; Matsuzaka *et al.*, 1992). Accordingly, imaging studies show that free selection and pure motor imagination is reflected by preSMA activation, whereas movement execution activates the SMA (Colebatch *et al.*, 1991; Deiber *et al.*, 1991, 1996; Playford *et al.*, 1992; Tyska *et al.*, 1994; Stephan *et al.*, 1995). Therefore, it seems appropriate to assume that the preSMA is a brain structure where movement or action is coded in a less determined state than in the SMA. In the present study, this functional hierarchy suggests that the rough temporal plot of a movement, which is (partially) represented within the preSMA, does not impose high restrictions on the order of the effectors to be used, which is (partially) represented within the SMA. In other words, a perceived interval sequence might be reproduced in several ways and with various effectors, whereas a perceived ordinal sequence of positions on a screen might more directly activate a concrete effector-specific (manual) representation. Accordingly, the representation of the more general interval structure would impose higher demands on the preSMA than on the SMA, whereas the representation of the more effector-related ordinal structure would impose higher demands on the SMA than on the preSMA.

Both the preSMA and the SMA were activated more strongly by encoding before reproduction than by encoding before perceptual monitoring. Thus, the intention to translate (later on) the task-relevant information of the perceptual input into motor response draws on those premotor areas that are mainly involved in the preparation of self-generated movement. Two factors suggest that these activations might reflect simple motor preparatory effects. First, the mean delay between the end of the encoding phase and the motor response was shorter in the reproduction task than in the monitoring task, because in the former subjects responded immediately after the encoding phase, whereas in the latter subjects had to detect deviants that occurred, on average, ~2.5 s after the end of the encoding phase. Second, all residual activation differences between the reproduction tasks and the monitoring tasks revealed by the same contrast point to motor preparation. These activations were located within the left MI and the right medial CE. Since the reproduction tasks required, on average, 4.5 right hand key presses and 1.5 left hand key presses more than the monitoring tasks, these activations are obviously due to motor preparation. However, since the contrast between interval and ordinal tasks had revealed a functional–anatomical dissociation between

Figure 3. Group averaged statistical maps ($n = 12$) superimposed onto an individual brain scaled to the standard Talairach brain size (Talairach and Tournoux, 1988). All anatomical abbreviations are listed in Tables 1 and 2. Axial slices show the top view, coronal slices show the back view, sagital slices show the left (right) hemisphere when the forehead is turned left (right) and all medial sagital slices show the right hemisphere (the left is removed). (*A*) Brain activations show task-dependent network modulations during sequence encoding before interval monitoring (IM, first panel), interval reproduction (IP, second panel), ordinal monitoring (OM, third panel) or ordinal reproduction (OP, lower panel) versus the control condition (CC). (*B*) Effects of the sequence property shown by direct contrast between encoding interval information (red scale) versus encoding ordinal information (blue scale). (*C*) Effects of the task domain shown by direct contrast between encoding sequential information before reproduction and before monitoring (upper panel). The middle panel shows the contrast between reproduction and monitoring only for the ordinal task (OP–OM), the lower panel shows the contrast between reproduction and monitoring only for the interval task (IP–IM).

Table 2
Anatomical specification, mean Talairach coordinates and *Z* score of significant activated voxels detected in direct comparison between the sequencing tasks

Anatomical area		Talairach coordinates			*Z* score
		x	*y*	*z*	
Interval versus ordinal sequences (I > O)					
preSMA		1	20	47	9.4
dPMC	L	–44	1	45	5.4
	R	37	–1	43	8.3
vPMC	L	–45	9	26	7.7
	R	46	9	23	8.8
FOP	L	–53	14	8	7.9
	R	43	13	17	9.3
BG	L	–17	5	7	4.2
	R	13	12	11	5.0
ICE	L	–35	–65	–9	4.1
Ordinal versus interval sequences (O > I)					
SMA		4	–5	55	11.0
FEF	L	–32	–7	56	10.0
	R	28	–10	57	12.0
MI	L	–35	–19	61	9.3
	R	31	–22	59	18.0
SI	L	–47	–26	43	9.3
	R	40	–22	47	18.0
CU		–2	–70	26	8.4
mCE	L	–17	–52	–3	10.0
	R	19	–49	–3	9.2
THA	L	–17	–26	17	5.5
	R	10	–21	16	6.9
Encoding before reproduction versus monitoring (P > M)					
preSMA		1	14	45	8.4
SMA		–2	–7	59	8.8
MI	L	–35	–22	59	10.8
mCE	R	16	–50	–6	7.3

l, lateral; MI, primary motor cortex; SI, primary somatosensory cortex; CU, cuneus; PCU, precuneus; m, medial. For other abbreviations, see Table 1.

preSMA and SMA, we additionally examined the contrasts between reproduction and monitoring within both the interval and the ordinal tasks (IP–IM, OP–OM). As shown in Figure 3*C*, these contrasts revealed motor preparatory effects within MI, since OP–OM showed a right MI dominance (reflecting more left hand key presses in OP than in OM) (middle panel) and IP–IM showed a left MI dominance (reflecting more right hand key presses in IP than in IM) (lower panel). However, the reproduction requirement led to stronger SMA-activation only in the ordinal task (OM–OP) (middle panel), whereas it led to stronger activation in the preSMA only in the interval task (IP–IM) (lower panel). Therefore, we conclude that these activations cannot be due to simple motor preparations. Instead, we suggest that encoding before reproduction causes higher demands than encoding before monitoring on exactly that part of the medial premotor region that is mainly involved in the processing of the task-relevant sequential, i.e. interval or ordinal, information. Thus, the requirement to put sequential information into motor output does not have any specific effect on the way that different properties of sequential information are represented. Rather, it stresses the regions involved in the preparation of movement according to the relevant property, i.e. either interval or ordinal characteristics.

With respect to anterior medial cortex activations, it is important to consider that tasks generating enhanced response competition and error detection are known to activate regions in the vicinity of the preSMA (Badgaiyan and Posner, 1998; Carter *et al.*, 1998, 1999). Since, in the present study, the interval tasks were more difficult than the ordinal tasks, an additional contrast was calculated in order to test if simple error detection might have caused the preSMA activation in the interval tasks. These contrasts, however, did not reveal any differences between correct and incorrect trials. Therefore, we suggest that the preSMA activation did not result from error detection.

Lateral Premotor Cortex

The lateral PMC was activated by all conditions relative to baseline. Direct task contrast, however, revealed a dominance in the interval task, independent of reproduction or monitoring requirements. This region, in contrast to the medial PMC, plays a major role in externally referenced, sensory guided motor behavior, as indicated both in monkeys (Halsband and Passingham, 1985; Mushiake *et al.*, 1991) and humans (Deiber *et al.*, 1991; Halsband *et al.*, 1994; Wessel *et al.*, 1997). Accordingly, we suggest that the lateral premotor activation found in our study reflects coding for movement parameters, such as velocity and spatial features. Since the interval task led to more activation in these areas than the ordinal task, we further suggest that interval processing, requiring coding of temporal durations, is more demanding on representational functions of the lateral PMC than other movement parameters, such as spatial features. Given the lateral premotor responsiveness to sensory events, the coding of temporal parameters might impose specific demands on this area, i.e. when movement preparation has to be synchronized precisely on several succeeding rhythmical events. In this context it is important to note that, even if the PMC is typically involved in motor preparation and execution, premotor activation is not necessarily linked to any simultaneous or subsequent motor output. Consequently, cells within the premotor areas are active regardless of whether a movement is executed or imagined (Wise and Evarts, 1985; Keller, 1993). In humans, imagining movements was found to activate premotor areas even more intensively than movement preparation (Stephan *et al.*, 1995).

A specific involvement of the lateral PMC in timing tasks is supported by several related imaging studies. In a recent fMRI study, the left vPMC was activated when subjects attended to time intervals (temporal orienting) as opposed to spatial positions (spatial orienting) (x = –44, y = 4, z = 20) (Coull and Nobre, 1998). Likewise, the monitoring of auditorily as well as visually presented rhythms activated the lateral PMC when compared with monitoring stimulus sequences for color or pitch deviants (Schubotz *et al.,* 2000). Recently, it was proposed that the left and the right PMC are differently involved in rhythm memory, with a dominance of the left hemisphere for integer ratio rhythms and of the right hemisphere for non-integer rhythms (Sakai *et al.,* 1999). However, such hemispheric differences were not found in the present study.

The lateral PMC activation was divided into a dorsolateral and a ventrolateral spot. Evidence for a functional differentiation of a dorsal and a ventral region within the PMC comes from cytoarchitectonic, histochemical and physiological studies in monkeys (Dum and Strick, 1991a; Kurata, 1991; He *et al.*, 1993; Lu *et al.*, 1994). In humans, a recent positron emission tomography study showed that the vPMC is activated during sequential finger movements, independently of the complexity and the length of the sequence to be executed. In contrast, the dPMC exhibited a linear increase of regional cerebral blood flow as the sequence complexity increased (Sadato *et al.*, 1996). The authors therefore implied an executive role in running sequences for the vPMC, but a storage function of motor

sequences and a role in the production of ongoing sequential movement with reference to that of buffered memory for the dPMC. However, in the present study both the vPMC and the dPMC showed significantly stronger BOLD responses during one and the same experimental manipulation, indicating either the presence of different functional contributions to the same task, or similar functions within the same task.

Frontal Opercular Cortex

As in the lateral PMC areas, the interval task also generated a higher BOLD response than the ordinal task in the inferiormost anterior extension of the PMC, clearly restricted to the pars opercularis of the inferior frontal gyrus (BA 44/FOP). Patient and imaging studies indicate that the FOP is engaged not only in linguistic functions, but also in actual and imagined movements of tongue, mouth and hand (Grossman, 1980; Fox *et al.*, 1988; Hamdy *et al.*, 1999; Nishitani and Hari, 2000). Accordingly, it is suggested that the FOP is best described on a general functional level, as specialized for the regulation of sequential activity in several different effector domains (Passingham, 1981; Lieberman, 1991; Fuster, 1995). Moreover, the FOP is particularly responsive to the perception and reproduction of rapid temporal patterns (Fiez *et al.*, 1995; Platel *et al.*, 1997; Rao *et al.*, 1997; Schubotz *et al.*, 2000). These findings suggest the FOP to be a common anatomical correlate for both linguistic and timing functions, or, as recently suggested, that rapid temporal integration is the core function of linguistic processes (Tallal *et al.*, 1993).

Frontal Eye Field

According to current reviews (Paus, 1996; Luna and Sweeney, 1999), we suggest that the most dorsal premotor region within BA 6 that was more strongly activated during the ordinal than during the interval task is best described as the FEF [mean coordinates: $x = \pm 30$, $y = -8.5$, $z = 56.5$, as compared with $x = \pm 31$, $y = -10$, $z = 54$ (Luna *et al.*, 1998); see also the mean stereotaxic coordinates reported in a meta-analysis by Paus (Paus, 1996): $x = \pm 32$, $y = -2$, $z = 47$]. The FEF is suggested to be involved in both visuomotor (executive) and cognitive (attentional) aspects of oculomotor control (Paus, 1996). Both covert detection and overt orientation towards visuospatial stimuli rely on FEF function, as indicated in monkeys (Latto and Cowey, 1971a,b; Rizzolatti *et al.*, 1983) and man (Bodis-Wollner *et al.*, 1997; Corbetta and Shulman, 1998). Several functions ascribed to the FEF are cognitive rather than oculomotor-related, e.g. visuospatial working memory (Courtney *et al.*, 1998; Zarahn *et al.*, 1999), predictive visual response to a future stimulus (Umeno and Goldberg, 1997), visual stimulus selection (Kodaka *et al.*, 1997) and visuospatial orientation (Scalaidhe *et al.*, 1997; Fujii *et al.*, 1998). We consider these findings to provide a straightforward explanation for our data, because the visuospatial properties of the sequential stimulation could be ignored during the interval task, but were the core information to be processed in the ordinal task. Here, subjects had to set up a representation of a visuospatial sequence during the encoding phase, in order to detect deviants during the test phase in the case of the monitoring task (OM), and in order to transcribe this visuospatial sequence to a motor program for the corresponding response fingers in the case of the reproduction task (OP).

Recently, a FEF involvement in ordered sequence performance for eye movements has been suggested (Schiller and Chou, 1998). In our experiment, however, subjects were carefully instructed to fixate the mark at screen center and to avoid visually pursuing the currently marked item. They followed the instruction successfully during the training session, where eye movements were controlled by monitoring the electrooculogram, and also reported to have done so during the fMRI study. Moreover, subjects reported after the training that fixation increased or facilitated their concentration, and thereby their performance level. However, due to technical reasons we did not control for eye movements during the scan. Thus, since the FEF is prominent in oculomotor control, one might argue that the FEF activation reflects eye movements. If the FEF activation were caused by overt eye movements, subjects must have executed more saccades during the order encoding than during the interval encoding. Although during training we did not observe a bias towards more eye movements during the ordinal than during the interval task, future imaging studies have to settle this question by eye movement control in the scanner. Recently, an fMRI study directly compared activations during eye movement with activations during a spatial working memory task (Courtney *et al.*, 1998), indicating similar brain regions in the vicinity of the FEF to be involved both in spatial working memory and eye movements. The average foci were $x = \pm 29$, $y = -6$, $z = 47.5$ for sustained spatial working memory and $x = \pm 31$, $y = -12.5$, $z = 45.5$ for saccades, showing that the mean FEF foci found in our study ($x = \pm 27$, $y = -3.8$, $z = 49$, all sequencing tasks relative to CC) are clearly more similar to the foci corresponding with the working memory manipulation of Courtney and co-workers [see also Zarahn and co-workers (Zarahn *et al.*, 1999): $x = 30$, $y = -3$, $z = 52$, for visuospatial memory]. Further evidence comes from an fMRI study on spatial attention that controlled very carefully for contributions of motor output, visual fixation, inhibition of eye movements, working memory and the conditional no-go component of responding (Gitelman *et al.*, 1999). Activations were reported in the FEF and two other cortical areas. The authors suggested that these areas form a network for spatial attention. Therefore, we suggest that the FEF activation in our study reflects predictive activity during the mental pursuit of the visuospatial sequence rather than mere eye movements.

Other Motor Areas

The anterior bank of the central sulcus, which is the likely site of MI (BA 4) in humans (Roland and Zilles, 1994; Geyer *et al.*, 1995), and adjacent spots in the SI (BA 1–3) were significantly more activated by the ordinal task than by the interval task. This is in line with the finding that mental representations of sequential finger movements during mental imagery as well as overt motor behavior are reflected by activations of the MI and SI (Porro *et al.*, 1996). In the present study, activations in these areas were more pronounced in the right hemisphere. However, this cannot be attributed to the left hand requirements in the sequence reproduction task, since the comparison between reproduction tasks and monitoring tasks revealed greater demands on the *left* MI. In contrast, the right hemisphere dominance of both MI and SI activation in the ordinal tasks seems to indicate greater visuospatial processing demands. This supports the idea of right hemisphere dominance for visuospatial information processing, as suggested by investigations of neglect patients (Halligan and Marshall, 1994) and by fMRI (Martinez *et al.*, 1997).

Cerebellum and Basal Ganglia

Both the ordinal and the interval tasks revealed activations of the CE and the BG, plausibly including activations of the mediating

structure, the THA. As revealed by direct comparisons, stronger activations in the preSMA co-occurred with higher activation in the left lateral cerebellar hemisphere during interval processing, whereas activations in the SMA covaried with activations in the paramedian cerebellum during ordinal processing. Modulations of cerebellar activation thereby parallel the functional dissociation found within the medial premotor areas and reflect different cerebrocortical projection patterns. Retrograde tracing in the monkey has shown that the general amount of cerebellar input is more extensive than the BG input for the preSMA, whereas the reverse is true for the SMA (Inase *et al.*, 1996; Matelli and Luppino, 1996). But also within the CE, a functional–anatomical dissociation is suggested that relates movement timing functions to the lateral CE, and movement execution functions to the paramedian CE.

On the one hand, both the preSMA and the lateral cerebellar hemispheres participate in the preprogramming of movements, which is also reflected by tasks that require pure motor imagery (Tyska *et al.*, 1994; Stephan *et al.*, 1995; Luft *et al.*, 1998). The lateral CE, in particular, is viewed as a provider of an internal substitutional representation of the external world that can temporarily eliminate the need for peripheral sensory input. In the case of motor learning processes, this feature allows one to increase the speed of the learned movement (Allen and Tsukahara, 1974). In the case of perceptual learning required in studies like the present one, the CE enables us to predict the temporal pattern of sensory events, as investigations of timing control and classical conditioning have demonstrated (Ivry, 1996, 1997). With respect to the view that the functional contribution of the lateral cerebellar cortex to preplanning specifically involves timing processes (Gibbon *et al.*, 1997), these findings might provide an explanation for the combined increase of preSMA and left lateral CE activation during interval processing (timing) as opposed to ordinal processing in our study. In a recent fMRI study, preSMA and CE function in sensory referenced response selection was investigated (Sakai *et al.*, 2000). When subjects were uncertain about when to give a response and thus sensory referenced timing adjustments were required, the CE was activated; in contrast, when subjects were uncertain about which of two reponse fingers was to be selected, the preSMA was activated. These findings, however, are not in conflict with the present findings, where both the preSMA and the CE were activated by the interval timing task. In the present study, subjects were required to set up an internal representation of the rhythm/order of events, i.e. to get independent from the perceived rhythm/order. According to the different responsiveness of medial and lateral premotor areas to sensory events (Goldberg, 1985), sensory referenced processes are mostly realized within lateral premotor areas, whereas internally referenced processes are mostly realized within medial premotor sites. The fact that our encoding paradigm required both an external sensory guidance and the set up of an internal representation is therefore supported by the finding that both lateral and medial premotor areas were involved during both encoding tasks.

On the other hand, as with the SMA, the functions of paramedian cerebellar areas seem to be more closely related to motor execution than the lateral cerebellar cortex (Allen *et al.*, 1997; Luft *et al.*, 1998). However, it is important to note that stronger paramedian cerebellar activations during the ordinal task as opposed to the interval task cannot be due to real motor execution or motor preparation. The mean number of key presses required to be prepared per trial are 2.25 (right hand) in the interval tasks and 1.0 (right hand) and 0.75 (left hand) in the ordinal tasks. If these differences of motor preparation were the cause of the paramedian cerebellar activations in the ordinal as opposed to the interval task, according to the subtraction logic of functional imaging, it would be reflected by a slight activation in the right paramedian CE and an activation decrease in the left paramedian CE in the ordinal–interval contrast. Instead, as shown in Table 2, this contrast reveals a balanced bilateral activation of the paramedian CE. Although this rules out a motor preparatory causation of the paramedian CE activation during the ordinal task, an adequate explanation for this effect is still missing; one possible explanation for our results might be that ordinal processing is more closely related to the imagination of movement than interval processing, since Luft *et al.* (Luft *et al.*, 1998) reported that motor imagination involves activation not only in the lateral CE, but also in the paramedian CE.

Bilateral BG activation was dominant in the interval task. This finding is in line with the notion that the BG are a core structure in timing functions. Studies with Parkinson's disease patients, who are impaired in BG function, have shown that the striatum plays an important role in rhythmic movement (Nakamura *et al.*, 1978; Freeman *et al.*, 1993). Recently, Harrington *et al.* (Harrington *et al.*, 1998) have shown that timing deficits following BG dysfunction are not restricted to motor timing, but also apply to time perception. Timing functions of the BG are also confirmed by animal lesion studies (Clarke and Ivry, 1997) as well as drug studies (Meck, 1996).

In general, cerebellar and subcortical activations, especially in the lateral CE and in the striatum, are confirmed by several imaging studies that investigate timing functions. The left lateral CE was activated during temporal orienting, as opposed to medial CE activations during spatial orienting (Coull and Nobre, 1998). A peak–interval timing task was found to activate the BG (Hinton *et al.*, 1996) or both the BG and the CE (Jueptner *et al.*, 1995), respectively. Likewise, rhythm reproduction was reported to activate both the lateral CE and the BG (Penhune *et al.*, 1998). Motor timing was investigated in a synchronization task and in a continuation task, leading to CE activation in both tasks and striatal activation during continuation, both relative to pitch discrimination (Rao *et al.*, 1997). The left putamen and the left cerebellar hemisphere were activated in both a synchronization task and a temporal generalization task (Lejeune *et al.*, 1997). Together, these imaging studies provide converging evidence for a substantial subcortical contribution to both time perception and motor timing, which is in line with the BOLD response during the interval tasks found in this study.

Anatomical Correlates of Interval and Ordinal Sequence Properties

To summarize, the results of the present study neither support the idea that ordinal and interval properties of sequential information are represented within exactly the same brain structures nor provide evidence for completely distinct neuroanatomical correlates. Although in principle both kinds of sequence processing require similar cortical networks, direct comparisons revealed characteristic modulations of different anatomical structures within this network. The striking differences, especially within premotor areas, suggest a functional–anatomical dissociation.

Ordinal functions, on the one hand, might be represented within areas that are more closely related to concrete behavioral output, as indicated by the SMA activation, and areas that are

prominent in spatially oriented representations, as reflected by activations in the FEF.

Interval functions, on the other hand, seem to be anatomically represented at a more abstract level of behavioral organization, as indicated by the preSMA activation, and are related to activation patterns that are less effector-specific, as reflected by extensive lateral premotor activations (PMC, including FOP), not restricted to specific motor effectors.

Furthermore, we found different brain activations depending on the purpose of sequential encoding, i.e. when subjects memorize sequences in order to reproduce them manually afterwards, or in order to carry out a perceptual monitoring on further presentations. The brain structures which are involved additionally in the representation of sequences if they have to be reproduced at a later time are those which are important in internally prepared and generated movements (preSMA, SMA, MI and mCE). However, the effects of reproduction preparation turned out to be information specific for the medial premotor areas. Thus, additional preSMA activation was revealed to be due exclusively to interval processing, whereas the SMA activation was caused only by the ordinal processing. We conclude that the requirement to reproduce a sequence is reflected by simple motor preparatory mechanisms (as indicated by MI and mCE activation), and additionally by information-specific and selective medial premotor activation.

Notes

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Address correspondence to Ricarda I. Schubotz, Max-Planck-Institute of Cognitive Neuroscience, PO Box 500 355, D-04103 Leipzig, Germany. Email: schubotz@cns.mpg.de.

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