

# Dissociating brain regions controlling the temporal and ordinal structure of learned movement sequences

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## Abstract

We used functional magnetic resonance imaging to investigate if different brain regions are controlling the temporal and ordinal structure of movement sequences during performance. Human subjects performed overlearned spatiotemporal sequences of key-presses using the right index finger. Under different conditions, the temporal and the ordinal structure of the sequences were varied systematically in relation to each other, using a factorial design: COMBINED had a rhythm of eight temporal intervals and a serial order of eight keys; TEMPORAL had an eight-interval rhythm produced on one key; ORDINAL had an isochronous rhythm and an eight-key serial order; two control conditions had an isochronous pulse performed on one or two keys, respectively. Brain regions involved in rhythmic and ordinal control of the sequences were revealed by analysing main effect contrasts for the corresponding factors. TEMPORAL and ORDINAL were also compared directly to test for significant differences. A dissociation was found between largely the presupplementary motor area, the right inferior frontal gyrus and precentral sulcus, and the bilateral superior temporal gyri, involved in temporal control, and lateral fronto-parietal areas, the basal ganglia and the cerebellum, which were implicated in ordinal control. The vermis and the superior colliculus were the only regions with an activity increase specifically related to combining long temporal and ordinal sequences. We conclude that humans use different brain networks for temporal and ordinal sequence control, and that the performance of combined sequences activates both networks, the medial cerebellum, and the superior colliculus.

## Introduction

Successful performance of sequential motor skills often requires that both the serial order and the timing of the individual movements are correct. A typical example is the playing of a musical instrument. Recent data from learning transfer experiments suggest that the brain can form independent representations of the ordinal and the temporal structure of a sequence (Ullén & Bengtsson, 2003). We present here, for the first time, evidence of a corresponding dissociation of neural systems controlling the temporal and ordinal structure of learned movement sequences during performance.

A large number of human functional imaging studies have addressed learning (e.g. Clegg *et al.*, 1998; Hikosaka *et al.*, 2000; Sakai *et al.*, 2002) and performance (Sadato *et al.*, 1996; Boecker *et al.*, 1998; Catalan *et al.*, 1998; Grafton *et al.*, 1998; Harrington *et al.*, 2000) of motor sequences with varying ordinal structure. These studies show that a network of fronto-parietal brain regions, including lateral and medial premotor areas and the posterior parietal cortex, as well as the basal ganglia and the cerebellum, are activated fairly consistently during performance of learned movement sequences. These areas, as well as the superior temporal and inferior frontal gyri, are also often active during learning, encoding and performance of temporal sequences (Halsband *et al.*, 1993; Penhune *et al.*, 1998; Sakai *et al.*, 1999; Ramnani & Passingham, 2001; Schubotz & von Cramon, 2001; Penhune & Doyon, 2002; Ullén *et al.*, 2003). What has been lacking

until now is a study in which the same subjects perform sequences, the ordinal and temporal structures of which are varied independently, so that increases in activity specifically related to processing of either type of information can be revealed. Furthermore, little is known about the neural control of temporal and ordinal information in a combined sequence performance (Sakai *et al.*, 2002). We used functional magnetic resonance imaging (fMRI) to test the hypothesis that there is a dissociation of brain regions preferentially involved in temporal and ordinal control of spatiotemporal sequence performance, expecting specific involvement of superior temporal cortex and the mesial part of the superior frontal gyrus in temporal control (Halsband *et al.*, 1993; Ullén *et al.*, 2003) and parietal regions in ordinal control (Catalan *et al.*, 1998; Sakai *et al.*, 2002).

Subjects performed overlearned spatiotemporal sequences of key-presses at different locations where the length of the temporal and ordinal structure, i.e. number of temporal or ordinal elements in the sequence (see Materials and methods), was varied in different conditions. To reveal brain activity specifically associated with temporal and ordinal sequence control, main effect contrasts were defined in a  $2 \times 2$  factorial design. Second, we tested for significant differences between these main effect contrasts, to reveal brain areas more involved in temporal than in ordinal control, and vice versa. Finally, we investigated the control of combined sequences, i.e. sequences with long temporal and long ordinal structure. Combined sequences require the integration of a temporal and an ordinal sequential structure. We therefore also tested the possibility that certain brain structures show a particularly strong activity during combined sequence performance, by investigating the interaction term in the factorial design.

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## Materials and methods

### Subjects

Seven right-handed (Oldfield, 1971) healthy subjects – two females and five males (18–25 years old) – with no history of neurological disease participated in the study. No subjects were professional musicians or music students. All experimental procedures were undertaken with the understanding and written consent of each subject, conformed with The Code of Ethics of the World Medical Association (Declaration of Helsinki), and were ethically approved by the Karolinska Hospital Ethical Committee.

### Behavioural tasks

The experimental tasks consisted of rhythmic sequences of key-presses with the right index finger on three buttons aligned horizontally at a distance of 30 mm from each other (Fig. 1A). Both during training

and fMRI scanning the subjects were lying in supine position. The arm and hand were supported so that the subjects could execute the key-presses by moving the index finger and the wrist only, i.e. without arm movements. A plastic bite bar was used to restrict head movements during fMRI recordings. During performance of a task the sequence was repeated continuously by the subject (see Procedure).

Five different sequences were used, in which the length of the temporal and ordinal structures were varied systematically to allow analysis with a  $2 \times 2$  factorial model (Fig. 1B). The ordinal structure of a sequence had either eight elements, i.e. eight different key-presses in a particular serial order, or one element, i.e. the middle key was pressed repeatedly. (In the second of the two control tasks an ordinal structure of two elements was used; see below.) The temporal interval between consecutive key-presses could be 375 ms, 750 ms, 1125 ms or 1500 ms; all temporal intervals were thus even multiples (1, 2, 3 or 4; Fig. 1C) of 375 ms. The temporal structure of a sequence also had either eight elements, i.e. eight temporal intervals in a particular order (see below), or one element, i.e. an isochronous pulse with period of 750 ms. The sequences with a temporal structure of eight elements had a total duration of 6 s; during this time eight key-presses were performed in all tasks (Fig. 1C). The tasks were thus matched in terms of number of key-presses.

The different sequences are illustrated schematically in Fig. 1C. The first sequence, COMBINED, consisted of a series of eight key-presses (middle–right–middle–left–left–right–left–middle) and had a corresponding temporal structure of eight temporal intervals (375–375–750–1125–375–750–750–1500; all in ms). The second sequence, TEMPORAL, had the same temporal structure as COMBINED but was performed on the middle key only. The third sequence, ORDINAL, had the same serial order of key-presses as COMBINED but had a regular isochronous rhythm. Two control sequences were used: EVEN ONE KEY consisted of a regular pulse performed on the middle key and EVEN TWO KEYS had an isochronous rhythm performed on the two outer keys, alternatingly. The latter task was included to control for lateral wrist movements in ORDINAL and COMBINED. In addition to these five sequential tasks, a rest condition (REST) was included in which the hand of the subject was completely relaxed.

### Experimental procedure

All tasks were practised for about 1 h in one training session 1 or 2 days before the fMRI experiment. Subjects first learned the control tasks EVEN ONE KEY and EVEN TWO KEYS, thereafter TEMPORAL and ORDINAL, and finally the most difficult COMBINED task. The subject initially listened to the temporal structure of the task, which was presented repeatedly through headphones as a recorded sequence of drum beats. Subsequently, the task was practised repeatedly while listening to the recorded rhythm, i.e. in synchrony with the drum beats. Finally, the subject practised the task from memory, without listening to the prerecorded tape. The ordinal structure of key-presses in ORDINAL and COMBINED was presented verbally and was immediately memorized by all subjects. Training of a task was terminated when the subject could perform the task continuously while maintaining a conversation with the experimenter. In addition to this training session, an additional shorter rehearsal (30 min) took place immediately before the fMRI recordings, where it was verified that the subject was able to perform all tasks from memory while talking to the experimenter.

In the experiment the tasks were performed in epochs lasting 40 s. During the first 8 s of each epoch the subjects were given a verbal instruction on which task to perform (*c.* 3 s), followed by five beats of an auditory metronome at 80 beats per minute providing the

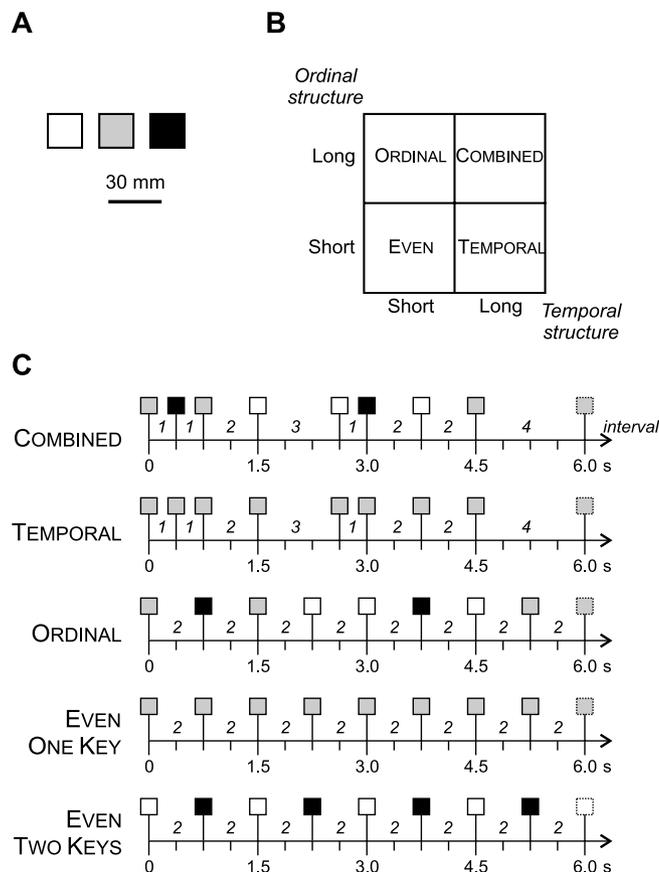


FIG. 1. Behavioural tasks. (A) Schematic drawing of the three response keys aligned horizontally at a distance of 30 mm from each other. The subjects produced rhythmic sequences of key-presses with the right index finger. (B) The experimental tasks were designed to allow analysis with a  $2 \times 2$  factorial model, with temporal and ordinal length as the two factors. Each factor had two possible levels, short (one or two elements; see text and C) and long (eight elements). (C) Schematic illustration of the five conditions. COMBINED consisted of a series of eight key-presses and had a corresponding temporal structure of eight temporal intervals; TEMPORAL had the same temporal structure as COMBINED but was performed on the central key only; ORDINAL had the same ordinal structure as COMBINED but a regular temporal structure (i.e. an isochronous pulse); EVEN ONE KEY consisted of a regular pulse performed on the central key; and EVEN TWO KEYS had an isochronous rhythm performed on the two outer keys, alternatingly. All sequences had a total duration of 4.5 s. The total number of movements was the same in the different conditions. In addition, a rest condition (REST) was included where the subject was completely relaxed.

correct tempo. After the metronome ceased, subjects repetitively performed the sequence for the remaining 32 s of the epoch. Data from this period were used in the subsequent analysis, whereas the 8 s of instruction and metronome were modelled as conditions of no interest (see below). Behavioural data, i.e. the identity and timing of all key-presses, was recorded continuously on a PC during the scanning, using the E-Prime software (Psychological Software Tools, Inc., PA, USA).

#### Data acquisition: fMRI

fMRI was conducted on a 1.5-T scanner (Signa Horizon Echospeed, General Electric Medical Systems, Milwaukee, WI, USA). At the beginning of each experiment a high-resolution, three-dimensional gradient echo T1-weighted anatomical image volume of the whole brain (voxel size  $1 \times 1 \times 1$  mm) was collected. Functional imaging data were then recorded as gradient-echo, echo-planar (EPI) T2\*-weighted images with blood oxygenation level-dependent (BOLD) contrast (Kwong *et al.*, 1992; Ogawa *et al.*, 1992). Image volumes of the whole brain were built up from contiguous axial slices ( $n = 30$ ). The following parameter values were used for the fMRI scanning: echo time, 60 ms; field of view, 22 cm; matrix size,  $64 \times 64$ ; pixel size,  $3.4 \text{ mm} \times 3.4 \text{ mm}$ ; flip angle,  $90^\circ$ ; slice thickness, 5.0 mm; repetition time ( $T_R$ ), 4 s; number of volumes per run, 122. The image volumes were collected continuously during separate runs, where all tasks were performed twice in the same order in each run. To reduce possible time and order effects, three different task-orders were used for different runs. We started each run by recording four 'dummy' image volumes that were not stored, to allow for T1 equilibration effects. Five runs were recorded from each subject. Two of the subjects made a mistakes in one run, i.e. one or more erroneous key-presses. In those two cases one additional run was recorded, to allow data from five error-free runs to be analysed. No subjects performed more than six runs.

#### Image processing and data analysis

Functional MR data were analysed using the SPM-99 software package (Wellcome Department of Imaging Neuroscience, London, UK). The volumes were realigned to correct for head movements using sinc interpolation and further unwrapped to correct for task-specific head movements (Andersson *et al.*, 2001). Subsequently, the volumes were coregistered to each individual's T1-weighted image and normalized to the stereotactic coordinate system of Talaraich and Tournoux (Talaraich & Tournoux, 1988; Friston *et al.*, 1995a), using the template brain of the Montréal Neurological Institute. Proportional scaling was applied to eliminate the effects of global changes in the signal. The time series were smoothed spatially with an isotropic Gaussian filter of 8 mm full width at half-maximum, and temporally with a Gaussian kernel of width 4 s.

The fMRI data were modelled with a standard linear regression model, as implemented in SPM-99, where we defined six conditions of interest corresponding to the periods in each epoch when the subjects performed the tasks without hearing the metronome (i.e. the last 32 s of the 40-s epochs). Six conditions of no interests were also modelled, corresponding to the first 8 s of each 40-s epoch when the subjects were listening to the task instruction and the metronome. The significance of the effects was assessed using *t* statistics for every voxel from the brain to create statistical parametric maps (SPMs), which were subsequently transformed into *Z* statistics. To increase the sensitivity of the analysis, we pooled the data from all subjects, performing a fixed-effects group analysis. Peaks of activity, i.e. local maxima that, after correction for the total number of comparisons for the whole brain volume, corresponded to  $P < 0.05$  on the basis of a test of peak height

(Friston *et al.*, 1995b) are reported. To focus only on brain areas that show more activation during the motor tasks than during rest, where the subjects produce no movements, we used the procedure of inclusive masks. This excluded the possibility that differences between the motor sequence conditions merely reflected a deactivation in one of the conditions. All masks used had an uncorrected *P*-value of 0.05.

The validity of the fixed-effects analysis was corroborated in two ways. First, we investigated the activation maps from the group analysis in individual subjects. The significance level of each activation peak was reported for each subject and is indicated with a letter from A to E as in Table 1 (A,  $P \leq 0.05$  corrected; B,  $P \leq 0.001$  uncorrected; C,  $0.001 < P \leq 0.01$  uncorrected; D,  $0.01 < P \leq 0.05$  uncorrected; and E,  $P > 0.05$ , not significant). This single-subject analysis represents a purely descriptive approach. Second, a second-level random effects analysis was performed. For each activity peak in the fixed-effect analysis we report whether the same peak was found at  $P < 0.001$ , uncorrected, in the random effects analysis (see Tables 1 and 2).

Neural activity related to the control of the temporal and ordinal aspects of the sequential tasks was analysed with a  $2 \times 2$  factorial design, with number of elements in the temporal and ordinal structure as the two factors (see Fig. 1B). The number of elements was either eight or, in the baseline conditions, one or two. The main effect contrast for long rhythmic structure was defined as [(COMBINED + TEMPORAL) - (ORDINAL + EVEN ONE KEY)], using (COMBINED + TEMPORAL - REST) as an inclusive mask. Similarly, the main effect of long ordinal structure was investigated with the contrast [(COMBINED + ORDINAL) - (TEMPORAL + EVEN TWO KEYS)], with (COMBINED + ORDINAL - REST) as an inclusive mask. In the latter contrast, EVEN TWO KEYS was used as a control task to match the lateral wrist movements in the ordinal tasks. These main effects contrasts thus reveal brain areas that are more strongly activated during performance of sequences with long ordinal and rhythmical structure as compared with their respective control tasks. For each main effect contrast, the two corresponding simple effect contrasts were also examined, i.e. TEMPORAL - EVEN ONE KEY and COMBINED - ORDINAL for long temporal structure, as well as ORDINAL - EVEN TWO KEYS and COMBINED - TEMPORAL for long ordinal structure (see Table 1).

Furthermore, we directly investigated which brain regions showed a significantly higher activity during performance of long ordinal structures than during performance of long temporal structures, and vice versa. For this purpose the contrasts TEMPORAL - ORDINAL, with TEMPORAL - REST as an inclusive mask, and ORDINAL - TEMPORAL, with ORDINAL - REST as an inclusive mask, were used. Note that these contrasts correspond to direct subtractions between the temporal and ordinal main effect contrasts. Finally, we performed an analysis to identify brain regions that showed higher activity in COMBINED as compared with the sum of the activities associated with TEMPORAL and ORDINAL. Thus we examined the interaction term in the factorial design using the contrast [(COMBINED - ORDINAL) - (TEMPORAL - EVEN ONE KEY)], with COMBINED - REST as an inclusive mask. In neurophysiological terms this interaction corresponds to activity increases associated specifically with performing a sequence in which a long temporal structure and a long ordinal structure are coupled.

Anatomical localizations of the activated regions were determined from an average image of normalized and intensity standardized T1-weighted images from all seven subjects (Duvernoy, 2000). Cerebellar activations were localized using the atlas of Schmahmann *et al.* (2000).

TABLE 1. Brain regions with significant<sup>†</sup> increases in BOLD contrast signal in the main effect contrasts for long temporal and long ordinal structure

Brain region	Side	Main effect, long temporal structure							Main effect, long ordinal structure								
		x	y	z	t-score	T-E1 <sup>a</sup>	C-O <sup>a</sup>	Single subjects <sup>c</sup>	RE <sup>f</sup>	x	y	z	t-score	O-E2 <sup>b</sup>	C-T <sup>b</sup>	Single Ss <sup>c</sup>	RE <sup>f</sup>
Frontal lobe																	
Medical frontal gyrus	R									24	39	27	4.99	**	–	AAABBCCD	+
Superior frontal gyrus (pre-SMA)	R	3	18	51	6.26	**	*	AABCCCD	(+) <sup>g</sup>								
Superior frontal gyrus (SMA/pre-SMA)	L	–6	3	60	8.76	**	*	AAABBBC	(+) <sup>g</sup>	–6	9	54	5.49	**	**	AAABBCE	+
Cingulate sulcus (CMA)	L									–12	15	36	5.79	**	–	BBBCCCE	+
										–3	3	42	6.54	–	**	ABCCCD	+
Inferior frontal gyrus/precentral sulcus	L	–60	9	18	4.76	**	*	AAACCCE	–	–60	12	9	5.65	**	–	AABBCCC	+
Precentral sulcus (PMV)	R	51	9	39	5.46	**	**	AABBCCCE	+								
Central operculum	L									–48	0	6	6.16	**	**	BBCCCC	+
	R									48	3	12	5.03	**	*	BBCCDD	+
Precentral gyrus/superior precentral sulcus (PMD)	L									–24	–12	66	12.82	–	**	AAAAABB	+
	R									21	–3	60	11.22	**	**	AAABBCC	+
Precentral gyrus (PMD)	L									–27	–9	48	16.14	**	**	AAAAAAB	+
										–39	–15	57	10.58	–	**	AAAAACD	–
	R									27	–6	45	12.25	**	**	AAAAABB	+
Parietal lobe																	
Subcentral gyrus	R									60	–15	21	5.42	–	**	AABBBC	+
Parietal operculum	L									–51	–21	18	7.12	–	**	ABBCCD	+
Postcentral gyrus/intraparietal sulcus	L									–45	–33	39	15.63	**	**	AAAAAAB	+
	R									45	–30	39	11.66	**	**	AAAAABB	+
Intraparietal sulcus	L									–39	–39	51	16.67	**	**	AAAAAAB	+
										–30	–57	57	19.20	**	**	BBBBBBB	–
Superior parietal gyrus	L									–18	–54	63	17.60	**	**	AAAAAAB	+
	R									21	–57	63	9.17	**	**	AAAAAAB	+
										15	–66	54	9.45	**	**	AAAABBC	–
Temporal lobe																	
Superior temporal gyrus	L	–57	–42	18	4.76	**	–	AABCCDE	(+) <sup>h</sup>								
Superior temporal gyrus, anterior pole <sup>d</sup>	R	51	12	–9	6.73	**	**	ABBCCCE	(+) <sup>h</sup>								
Insula	L	–42	9	–3	4.91	**	–	ABBCCCE	–								
	R	39	15	0	5.31	–	*	AABCCCE	–								
Basal ganglia																	
Putamen	L									–27	12	6	6.25	**	**	ABBCCD	+
	R									–24	–6	15	7.75	**	**	AABBDE	+
										27	12	3	6.13	**	*	ABBCCCE	–
										24	–6	18	7.15	**	*	AABBCE	+
Globus pallidus	R	15	0	6	4.69	**	*	BBBCDEE	–	12	–3	–3	4.64	**	*	ABCCDD	–
Caudate nucleus	L									–21	9	12	6.91	**	**	AAABBE	–
										–15	3	27	4.75	**	–	AABCCD	–
Cerebellum (vermis) <sup>e</sup>																	
Lobule V	R	6	–60	–9	4.71	–	*	AABBCEE	–	3	–60	–15	19.52	**	**	AAAAAAE	–
Lobule VIIIA–B	R									3	–72	–39	14.67	**	**	AAABBBC	+
Cerebellum (hemispheres) <sup>e</sup>																	
Lobule VI	L	–33	–63	–33	5.67	**	*	AABBCEE	–	–27	–51	–30	15.12	–	**	AAAAAAC	+
	R									30	–51	–30	20.78	**	**	AAAAAAA	+
										21	–66	–27	10.66	–	**	AABBCCD	+
Lobule VIIIA–B	L									–15	–60	–51	11.77	**	**	AAAABBC	–
	R									15	–63	–51	17.04	**	**	AAAAAAB	+
Thalamus and brain stem																	
Thalamus	L									–21	–27	12	7.81	**	**	AAABBCCD	+
	R									18	–18	12	7.61	**	**	AABBCCCE	+
Mesencephalon	L									–6	–27	–18	6.21	–	**	AABBCCD	+

<sup>†</sup> $P < 0.05$  corrected for multiple comparisons. The  $x$ ,  $y$  and  $z$  give the Talairach coordinates of the activity peak. Activations from the corresponding simple effects and in single subjects are indicated in separate columns. For details, see Methods. <sup>a</sup>For each active region in the main effect contrast, the level of activity in the same region in the simple effect contrasts with long vs. short temporal structure, i.e. TEMPORAL – EVEN ONE KEY (T-E1), and COMBINED – ORDINAL (C-O) is shown; \*\*peak at  $P < 0.05$ , corrected; \*peak at  $P < 0.001$ , uncorrected; –, no peak at  $P < 0.01$ , uncorrected. <sup>b</sup>Data as above in (a) for the two simple effect contrasts with long vs. short ordinal structure, i.e. ORDINAL – EVEN TWO KEYS (O-E2), and COMBINED – TEMPORAL (C-T). <sup>c</sup>The level of activity in the individual subjects, for each active region in the group analysis. Each subject is allocated a letter from A to E to indicate significance level (A,  $P \leq 0.05$  corrected; B,  $P \leq 0.001$  uncorrected; C,  $0.001 < P \leq 0.01$  uncorrected; D,  $0.01 < P \leq 0.05$  uncorrected) and 'E' indicates no significant activity at  $P < 0.05$ . The sequence of letters is by significance, not by subject. <sup>d</sup>The cluster extended into the insular and inferior frontal cortices. <sup>e</sup>Cerebellar lobules are given after Schmahmann *et al.* (2000). <sup>f</sup>A + indicates that the same peak was seen also in a random effects analysis (see text); a (+) indicates that a peak was found in the same brain region (see footnotes g and h); and – indicates that the peak was not seen. <sup>g</sup>A cluster was found in the pre-SMA with a peak of activity at  $x = 6$ ,  $y = 6$ ,  $z = 30$ . <sup>h</sup>Bilateral activity in the superior temporal gyri was found, with peaks of activity at  $x = 45$ ,  $y = -33$ ,  $z = 9$  and  $x = -51$ ,  $y = 9$ ,  $z = -12$ .

TABLE 2. Brain regions with significant\* increase in BOLD contrast signal in the contrasts TEMPORAL – ORDINAL and ORDINAL – TEMPORAL

Brain region	Side	x	y	z	t-score	RE <sup>†</sup>
Temporal vs. Ordinal						
Frontal lobe						
pre-SMA	Midline	0	18	48	5.98	+
	R	3	21	57	5.98	+
		3	3	60	6.76	–
Inferior frontal gyrus pars opercularis	R	54	15	12	4.76	–
Inferior precentral sulcus (PMV)	R	51	12	42	6.05	+
Temporal lobe						
Superior temporal gyrus (anterior pole)	L	–48	12	–12	7.05	+
	R	51	12	–9	8.03	+
Insula	R	42	3	–3	5.04	–
Superior temporal gyrus	L	–63	–36	15	4.68	–
Occipital lobe						
Middle occipital gyrus	L	–45	–75	18	5.3	–
Ordinal vs. Temporal						
Frontal lobe						
Central operculum	R	48	0	12	5.28	–
Superior frontal gyrus (PMD)	R	21	–6	60	7.21	+
Precentral gyrus (PMD)	L	–30	–12	63	20.61	+
		–27	–12	54	18.8	+
	R	30	–9	48	10.45	+
Cingulate sulcus (CMAc)	L	–9	–27	42	6.77	–
Parietal lobe						
Subcentral gyrus	R	57	–15	18	5.55	+
Postcentral gyrus	L	–48	–30	51	23.04	+
		–42	–36	57	23.97	+
	R	51	–24	39	11.48	+
Intraparietal sulcus	R	42	–33	39	12.62	+
Superior parietal gyrus	L	–18	–54	63	19.68	+
		–30	–57	57	19.84	+
	R	21	–57	63	10.49	+
Angular gyrus	R	51	–54	30	4.85	–
		48	–63	30	5.26	+
Occipital lobe						
Cuneus	L	–18	–75	12	4.64	–
	R	21	–90	6	5.0	–
Basal ganglia						
Putamen	L	–24	15	6	4.62	–
		–27	–6	12	6.61	+
	R	24	–9	18	5.53	+
Caudate nucleus	R	24	6	18	5.52	–
Cerebellum (vermis) <sup>†</sup>						
Lobule V	R	6	–60	–18	21.96	+
Cerebellum (hemispheres) <sup>†</sup>						
Lobule VI	L	–24	–51	–27	16.2	+
	R	30	–48	–30	25.57	+
		18	–66	–24	11.64	+
		33	–72	–15	6.02	–
Lobule VIIIA-B	L	–18	–60	–51	11.7	+
	R	15	–69	–51	19.72	+
Thalamus	L	–18	–21	6	8.39	+

\* $P < 0.05$  corrected for multiple comparisons.  $x$ ,  $y$  and  $z$  give the Talaraich coordinates of the activity peak. For details Methods. <sup>†</sup>Cerebellar lobules are given after Schmahmann *et al.* (2000). A + indicates that the same peak was seen also in a random effects analysis (see text); – indicates that the peak was not seen.

## Results

### Behavioural data

The behavioural data consisted of the identity and onset time of all key-presses performed during scanning. First, we confirmed that all tasks had been performed correctly. The ordinal structure of the sequences was reproduced correctly at all times by all subjects. Figure 2A–D shows the mean durations and standard deviations (SDs) for all subjects of the individual temporal intervals of the sequences in the different experimental conditions. The mean relative error, i.e. mean produced duration of each interval divided by its ideal duration for all subjects, was less than 7.3% for all conditions (Fig. 2A–D). The

temporal structure of the different sequences was thus reproduced with high accuracy.

Second, we investigated if there were any significant differences in temporal accuracy between conditions. For this purpose, all instances of a particular interval in a particular condition were first normalized to the mean duration of that interval, for all subjects. Thereafter, differences in variance between all conditions were investigated using  $F$ -tests, after correction for multiple comparisons. No differences in variance were found between the three isochronous conditions, ORDINAL, EVEN ONE KEY and EVEN TWO KEYS ( $P > 0.2$ ; Fig. 2). The two conditions with a long temporal sequence, TEMPORAL and COMBINED, had a significantly higher variance ( $P < 0.0001$ ) than

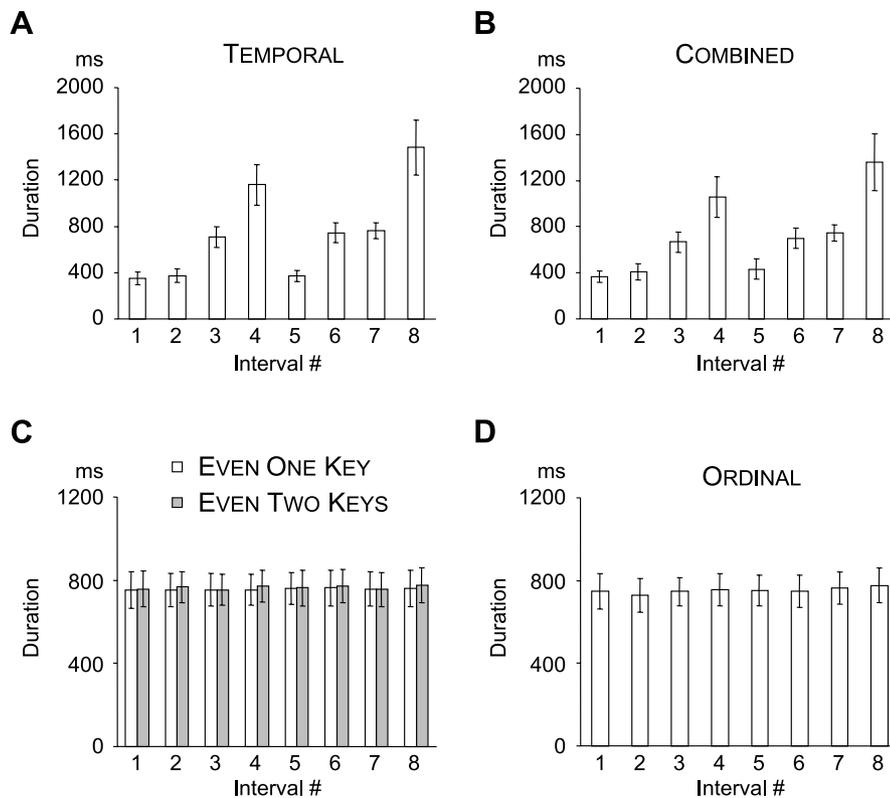


FIG. 2. Behavioural recording during the fMRI scans. Mean interval durations and SDs are shown for each temporal interval of the sequence. (A and B) The tasks with long temporal structure (COMBINED and TEMPORAL) were performed with similar temporal regularity. (C and D) A comparable level of temporal regularity was also seen in the tasks with an isochronous pulse (ORDINAL, EVEN ONE KEY and EVEN TWO KEYS).

the isochronous conditions, and COMBINED had a higher variance than TEMPORAL (Fig. 2; see Discussion).

Finally, we investigated if any significant improvement of performance took place during the scanning sessions. For this purpose a comparison of performance in the beginning and the end of the scanning was made. The SD and relative error, i.e. mean produced duration divided by ideal duration, of the temporal intervals produced in the ten first and ten last sequences of the experiment were calculated, for each condition and subject. Pooling together data from all subjects, no significant difference in SD was found for either condition (COMBINED,  $P=0.25$ ; TEMPORAL,  $P=0.82$ ; ORDINAL,  $P=0.06$ ; EVEN ONE KEY,  $P=0.65$ ; EVEN TWO KEYS,  $P=0.07$ ; paired  $t$ -tests without correction for multiple comparisons), nor in relative error (COMBINED,  $P=0.16$ ; TEMPORAL,  $P=0.63$ ; ORDINAL,  $P=0.80$ ; EVEN ONE KEY,  $P=0.70$ ; EVEN TWO KEYS,  $P=0.77$ ; paired  $t$ -tests without correction for multiple comparisons). In summary, all tasks were well learned and performed correctly without any significant change of behaviour during the scanning.

#### Main effect of long temporal and ordinal structure

Significant activations associated with the performance of long temporal and ordinal sequences, respectively, are presented in Fig. 3 and Table 1, as revealed by the main effect analyses. For each brain region showing activation in the main effects analyses, activity seen in the two simple effect contrasts and the neural activity in individual subjects are shown in separate columns (Table 1; see also Methods). The result from the latter analyses corroborated the results obtained from the main effect analyses and will not be described in detail in the text. Histograms in Fig. 3 show mean adjusted BOLD responses from local maxima of activation during the different conditions, with the mean activity during REST used as baseline. This mean is set to 100 and the values thus correspond to per cent signal change.

The main effect contrast for long temporal structure revealed a large cluster of active voxels located in the presupplementary motor area (pre-SMA) and the SMA. There were two peaks of activity: one located clearly in pre-SMA ( $y=18$ ) and one close ( $y=3$ ) to the tentative border between pre-SMA and SMA ( $y=0$ ; Picard & Strick, 1996). We denote this latter peak rostral part of SMA proper because it can be anatomically distinguished from the more rostral peak in pre-SMA, and in recognition of the fact that the exact border between pre-SMA and SMA is not known (Roland & Zilles, 1996; Vorobiev *et al.*, 1998). As can be seen from the BOLD signal histograms, increases in activity in SMA and pre-SMA were found during all motor conditions, where larger increases in the tasks with a long temporal sequence, i.e. TEMPORAL and COMBINED, were found in particular in the pre-SMA (Fig. 3). Activity was also seen in the bilateral superior temporal gyri (STG; Fig. 3, Table 1), extending into the bilateral insula and the right inferior frontal gyrus. Bilateral activity in the inferior part of the precentral sulcus was also seen (PMV/44; Table 1). Subcortical activations were found in the cerebellum: lobule V of the right anterior vermis and the left lobule VI of the hemisphere and in the right globus pallidus (Fig. 3, Table 1; Schmahmann *et al.*, 2000).

The main effect contrast for the long ordinal sequence revealed major bilateral activations in the dorsal premotor cortices (PMD), with local peaks in the precentral gyrus and in the cortex lining the precentral sulcus. In addition, activation of the posterior part of the superior frontal sulcus was observed (Fig. 3, Table 1). As revealed from the BOLD signal histograms, these activity increases were specific for the two conditions with a long ordinal structure, i.e. ORDINAL and COMBINED (Fig. 3). On the left side the activity extended into the medial wall of the frontal lobe with one peak of activity located in the cingulate sulcus, i.e. the cingulate motor area (CMA), and one peak located in the rostral part of the SMA proper (Table 1). Additional frontal activity was found in the bilateral central operculum, the left inferior part of the precentral sulcus and inferior

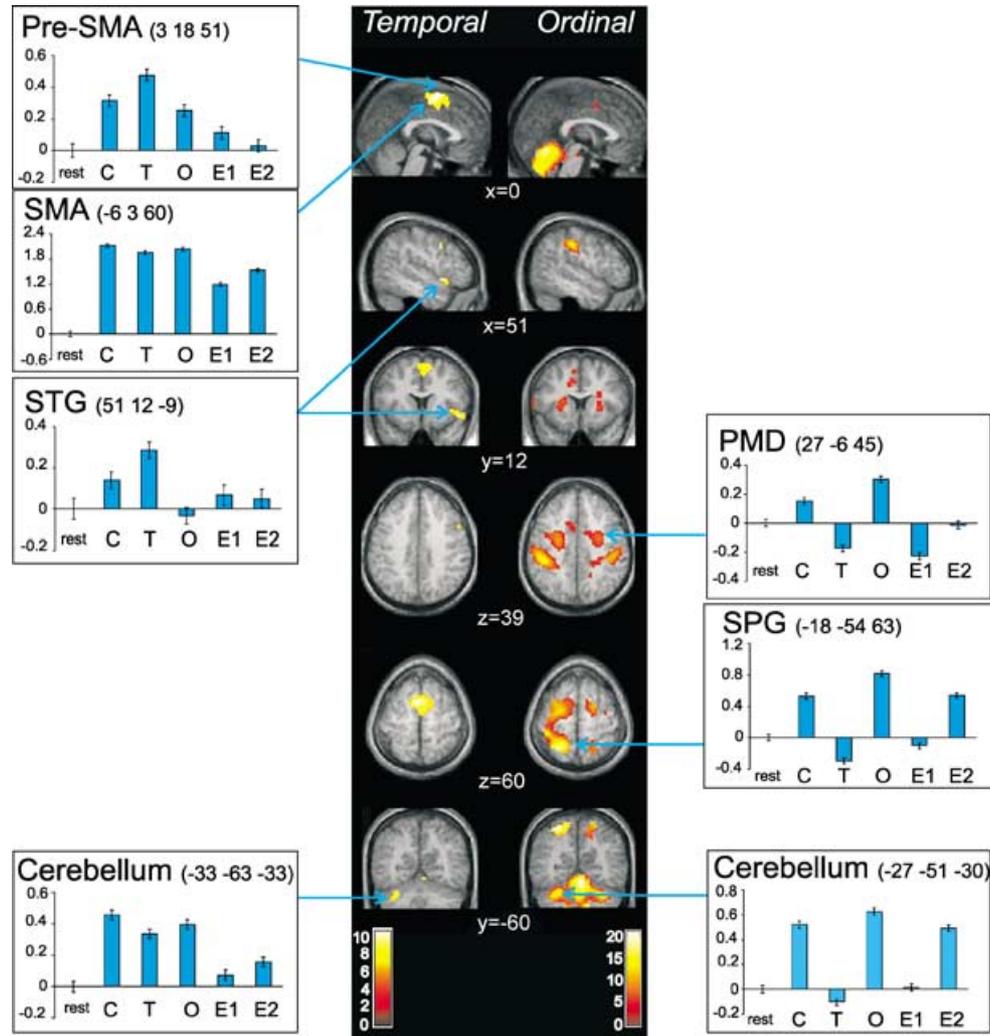


FIG. 3. The main effect contrasts for long temporal structure (left half) and long ordinal structure (right half). Dissociation between brain regions predominantly involved in the control of either aspect was observed. Activity maps of brain regions with significantly increased BOLD contrast signals ( $P < 0.05$  corrected) for the main effect of long temporal structure are shown for the SMA and pre-SMA (the slices  $x = 0$ ,  $y = 12$  and  $z = 60$ ), the right superior temporal gyrus (STG) ( $x = 51$ ,  $y = 12$ ), the right inferior part of the precentral gyrus (slices  $z = 39$ ,  $x = 51$  and  $y = 12$ ), and the left cerebellar hemisphere including vermis (slice  $y = -60$ ). For the main effects of long ordinal structure the maps illustrate responses in the dorsal premotor area bilaterally (PMD) (slices  $z = 39$  and  $z = 60$ ), the SMA/pre-SMA region (slices  $x = 0$  and  $y = 12$ ), the CMA (slices  $z = 39$  and  $y = 12$ ), the right subcentral gyrus (slice  $x = 51$ ), the basal ganglia (slice  $y = 12$ ), the bilateral superior parietal gyrus (SPG) and right intraparietal sulcus (slices  $z = 39$  and  $z = 60$ ), and the cerebellum including vermis (slices  $x = 0$  and  $y = -60$ ). The bars illustrate the adjusted relative haemodynamic response for each task in a local peak voxel (C = COMBINED, T = TEMPORAL, O = ORDINAL, E1 = EVEN ONE KEY, E2 = EVEN TWO KEYS). The colour scale shows Z-values.

frontal gyrus (PMV and area 44), and in the right medial frontal gyrus (Table 1). Extensive activity was seen in the parietal lobe: the bilateral superior parietal gyri (SPG), the left intraparietal sulcus (IPS), the left supramarginal gyrus, the postcentral gyri along the intraparietal sulcus, the right subcentral gyrus and the left parietal operculum (Fig. 3, Table 1). Furthermore, extensive activity was found in the cerebellum, including vermal lobules V and VIIIA-B, and bilaterally in lobules VI and VIIIA-B in the cerebellar hemispheres (Fig. 3, Table 1). Additional subcortical activity was found bilaterally in the thalamus and the putamen, and in the left caudate nucleus and right globus pallidus (Table 1).

In summary, major differences were seen in the patterns of brain activity in the two main effect contrasts. The main effect contrast for rhythmical sequence revealed prominent activations in the pre-SMA, the bilateral inferior part of the precentral sulcus, the bilateral inferior frontal gyrus and the bilateral STG. Less extensive activations were

seen in the basal ganglia and cerebellum. No specific activations were seen in the parietal lobes. By contrast, the performance of the ordinal sequence was associated with extensive fronto-parietal activations, including the SMA/pre-SMA, the CMA, the bilateral PMD, superior parietal cortex and the postcentral gyri, but no activations in the temporal lobes. Subcortically, widespread activity was seen in the cerebellum, the thalamus and the basal ganglia.

#### Direct comparisons of the conditions with long ordinal and rhythmical structure

The main effect contrasts suggested a dissociation between brain regions involved in temporal and ordinal sequence control. To test directly which of these regions showed a statistically significant difference in activation associated with either type of control, the temporal and ordinal sequences were directly compared using TEMPORAL – ORDINAL and ORDINAL – TEMPORAL contrasts (see

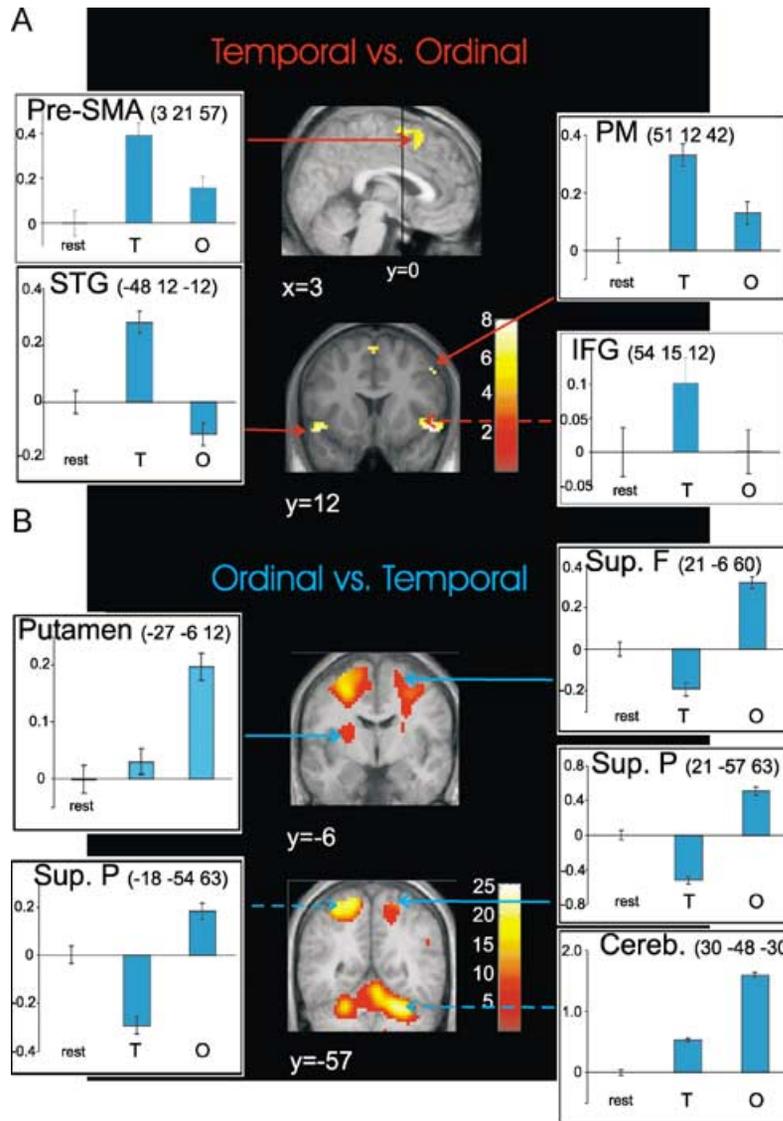


FIG. 4. Direct comparisons between rhythmic sequence and long ordinal sequence (see text). Activity maps of brain regions with significantly increased BOLD contrast signals ( $P < 0.05$  corrected) are shown. (A) TEMPORAL – ORDINAL. Activated brain regions included the pre-SMA ( $x = 3$ ), the bilateral superior temporal gyri (STG) ( $y = 12$ ), the inferior frontal gyrus pars opercularis (IFG) ( $y = 12$ ), and the right inferior part of the precentral sulcus (PM) ( $y = 12$ ). (B) ORDINAL – TEMPORAL. Activated regions included the bilateral dorsal premotor areas (SFG: superior frontal gyrus) ( $y = -6$ ), the putamen ( $y = -6$ ), the superior parietal cortex bilaterally (SPG) ( $y = -57$ ), the cerebellar hemispheres and vermis ( $y = -57$ ). The bars illustrate the adjusted relative haemodynamic response for each task in one local peak voxel (C = COMBINED, T = TEMPORAL, O = ORDINAL, E1 = EVEN ONE KEY, E2 = EVEN TWO KEYS). The colour scale shows Z-values.

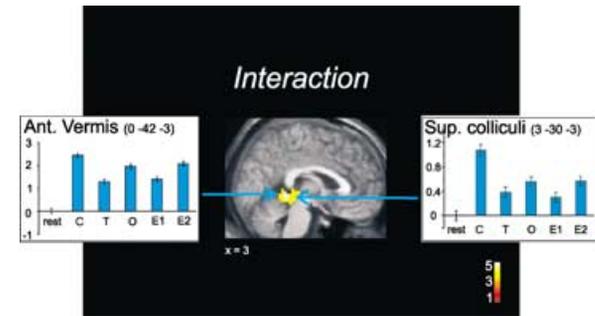


FIG. 5. Brain region showing stronger activation during COMBINED as compared with the sum of activities associated with TEMPORAL and ORDINAL (significant interaction in the  $2 \times 2$  factorial design). An activation was located in the lobule III of the anterior vermis and extended into the superior colliculi of the mesencephalon. We show the adjusted haemodynamic response for the two local maxima of the cluster (0, -42, -3) and (3, -30, -3) for each task; C = COMBINED, T = TEMPORAL, O = ORDINAL, E1 = EVEN ONE KEY, E2 = EVEN TWO KEYS. The colour scale shows Z-values.

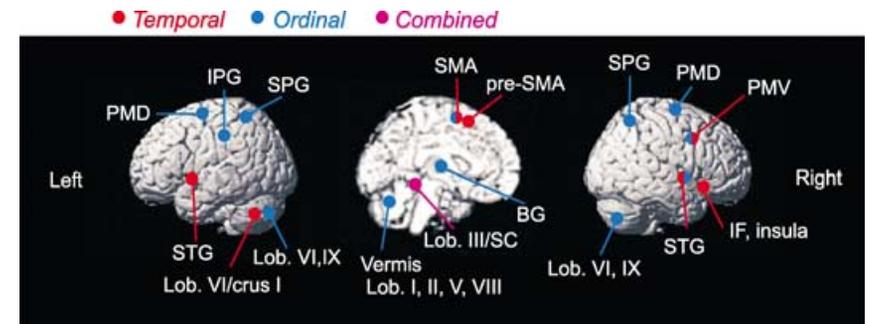


FIG. 6. Schematic summary of brain regions specifically involved in the control of rhythmical, ordinal and combined spatiotemporal sequences. For exact coordinates and a complete description of all activations, see Tables 1 and 2 and the text. Main activations are indicated with coloured circles. Blue circles indicate areas involved in rhythm control, red circles show areas involved in ordinal control, and the green circle indicates brain activity specifically related to the performance of a combined sequence.

Methods; Table 2, Fig. 4A and B). Notably, in this analysis, there is no influence by the control tasks. To corroborate the results from the fixed effects model, these contrasts were also investigated in a random effects model. Activity peaks that were also found in the random effects model ( $P < 0.001$ , without correction for multiple comparisons) are indicated in Table 2.

With a few exceptions, these contrasts revealed the same brain regions as seen in the main effect contrasts (Tables 1 and 2). In TEMPORAL – ORDINAL activations were seen in the pre-SMA, extending from the rostral pre-SMA to the SMA/pre-SMA border, the right IFG, right inferior part of the precentral sulcus (PMV and area 44), the right anterior part of the STG, the left posterior part of the STG and the right insula (Fig. 4A, Table 2). ORDINAL – TEMPORAL, by contrast, revealed activations in the bilateral PMD, the left CMA, the frontal operculum, the right subcentral gyrus and the bilateral postcentral and SPG. Subcortically, activations were seen bilaterally in the putamen, the right caudate nucleus, the left thalamus and in the cerebellum. In the cerebellum, peaks were seen both in vermal lobule V and bilaterally in lobules VI and VIIIA-B in the hemispheres (Fig. 4B, Table 2).

#### The combined sequence–interaction analysis

To investigate the possibility that some brain regions would show an activity increase specifically related to combining a long ordinal and a long temporal structure, the interaction term in the factorial design was examined using the contrast [(COMBINED – ORDINAL) – (TEMPORAL – EVEN ONE KEY)]. This contrast reveals areas that showed significantly stronger activity when the subjects performed COMBINED than the sum of the activities observed when they executed ORDINAL and TEMPORAL. Only subcortical regions were found to be active. One significant peak of activity was found in lobule III of the anterior vermis. The corresponding cluster had a second subthreshold peak in the superior colliculi with a Z-value of 3.97, and was significant on the cluster-level ( $P < 0.004$ , corrected; Fig. 5).

A second activation was observed in the right paravermal cerebellar hemisphere. However, in this second cerebellar peak, no significant difference in activity was found between COMBINED and ORDINAL. Thus, the activity in this cerebellar subregion cannot be unambiguously linked to performing combined spatiotemporal sequence. Rather, this interaction effect seems to reflect the relative low activity in TEMPORAL. By contrast, the activity of the cluster in the anterior vermis and superior colliculus corresponding to the significant interaction effect also showed the highest activity with no deactivations in the other sequence conditions, suggesting that this region is particularly involved in the integration of temporal and ordinal structures (Fig. 5).

No cortical regions were found to be specifically involved in combining a temporal and ordinal sequential structure ( $P < 0.05$  after correction for multiple comparisons). Similarly, the brain activity in a COMBINED – REST contrast (data not shown) consisted essentially of the set of cortical regions activated in TEMPORAL – REST and ORDINAL – REST. These results suggest that, at a cortical level, the combined task activated the temporal and ordinal networks without any super-additive increases in the degree of activation in these networks and without any additional areas being recruited.

## Discussion

Subjects performed overlearned spatiotemporal sequences of key-presses from memory. All tasks were correctly performed and were matched in terms of motor output. Furthermore, no changes in accuracy were found during the scanning, indicating that no significant

learning took place during the experiment. The isochronous tasks showed a somewhat lower temporal variability than the two conditions with a long sequential temporal structure, COMBINED and TEMPORAL. This is an expected finding: temporal variability in rhythm production tasks has earlier been shown to increase with the complexity of the rhythmic pattern (MacDorman, 1962; Summers *et al.*, 1986). However, when investigating the interaction term in the factorial model (see below) no cortical regions were found to be significantly more active in the COMBINED task, which showed the highest temporal variability. We therefore conclude that the observed differences in brain activity between conditions essentially reflect differences in the load on neural control systems for ordinal and temporal sequence performance, and not processing of timekeeping error.

#### Dissociating areas involved in temporal and ordinal sequential control

A central finding of the study is the dissociation between brain regions preferentially controlling the temporal and ordinal structure of the sequences. The pre-SMA, the bilateral STG, the right IFG (pars opercularis) and the right inferior part of the precentral sulcus were activated both in the main effect contrast for long temporal structure and when directly contrasting TEMPORAL with ORDINAL, suggesting that these regions are key structures for the control of the rhythmical aspect of the sequences. Another set of brain regions, including the bilateral PMD, the central operculum, the right subcentral gyrus, the bilateral postcentral and superior parietal gyri, as well as large regions of the cerebellum and the basal ganglia, were activated in both the main effect contrast for long ordinal structure and when contrasting ORDINAL and TEMPORAL, suggesting specific involvement in ordinal sequential control. In addition, some brain regions showed significant activity increases related to the control of both temporal and ordinal sequences, e.g. the SMA, the left inferior part of the precentral sulcus and parts of the cerebellum. Only the medial cerebellum and the superior colliculi showed an activity increase specifically related to combining a temporal and an ordinal structure (Fig. 6).

#### Neural control of temporal sequential structure

Increased cortical activity specifically related to rhythmic sequences was found in the bilateral STG, the right IFG and the right inferior part of precentral sulcus. Activity in these regions has been observed during subvocal rehearsal of words (Paulesu *et al.*, 1993), and when the subject perform self-paced finger tapping, following a period of tapping synchronized to an auditory metronome (Rao *et al.*, 1997; Ullén *et al.*, 2003). In the present study, the temporal structure of the sequences was presented auditorily during training. It has been suggested that STG and IFG interact during silent rehearsal of auditory representations, which could be used to trigger movements at appropriate points in time using an auditory-motor loop (Zatorre *et al.*, 1996; Rao *et al.*, 1997). Indeed, a role for the anterior right STG in the reproduction of auditory temporal patterns has been demonstrated in patients with parts of their temporal lobes removed (Penhune *et al.*, 1999). Likewise, activation of the right IFG and the right inferior part of the precentral sulcus have previously been shown to be active in tasks requiring explicit timing, e.g. encoding of temporal sequences (Schubotz & von Cramon, 2001), selective attention to temporal as opposed to ordinal properties of visual stimuli (Coull & Nobre, 1998) and in bimanual temporal coordination (Ullén *et al.*, 2003). Thus it is plausible that these areas support the timing of rhythmical movement sequences.

Activity in the rostral part of the SMA proper ( $y = 3$ ), at the pre-SMA border, was found during all sequential conditions, as expected

from a large number of studies demonstrating involvement of the mesial area 6 in sequence production (Roland *et al.*, 1980; Halsband *et al.*, 1993; Sadato *et al.*, 1996; Catalan *et al.*, 1998; Shima & Tanji, 1998; Hikosaka *et al.*, 2000; Shima & Tanji, 2000). Our data suggest a particular role of the pre-SMA in the control of rhythmical structures. Pre-SMA activation has earlier been reported during learning (Ramnani & Passingham, 2001), perceptual encoding (Schubotz & von Cramon, 2001) and reproduction (Penhune *et al.*, 1998) of temporal sequences. This is in accord with the notion that pre-SMA is involved in more abstract, effector-independent aspects of motor control (Picard & Strick, 2001). Possibly, pre-SMA acts together with STG/IFG to retrieve auditory-motor associations formed during the training to guide precise timing of the movements. Shima & Tanji (2000) recorded neuronal responses in the SMA and pre-SMA of the monkey during sequential movements. Interestingly, whereas sequence-related activity was found in both regions, rank-order-selective cells, i.e. cells that were active during a particular temporal interval of a sequence regardless of its ordinal structure, were found predominantly in the pre-SMA. This suggests that the pre-SMA may be involved in temporal sequence control in both monkey and humans (Shima & Tanji, 2000; Tanji, 2001).

#### *The basal ganglia, the cerebellum and timing*

In the main effect contrast for long temporal structure, subcortical activity was found in the left cerebellar hemisphere, the vermis and the right globus pallidus. Surprisingly, however, no activity in the basal ganglia or the cerebellum was seen when directly contrasting TEMPORAL with ORDINAL.

All conditions used in the present study require the explicit timing of motor responses. The control conditions and ORDINAL use a simple isochronous pulse, whereas TEMPORAL and COMBINED require the generation of a sequence of different temporal intervals. It is important to note therefore that neural activity relating to basic timekeeping functions common to all tasks may thus not be revealed by contrasting the different conditions. With regard to the production of organized sequences of temporal intervals, our data do not support a specific role for the basal ganglia. Similarly, other investigators found no striatal activation when rhythmic sequence production was contrasted with passive listening to a temporal sequence (Sakai *et al.*, 1999), a randomly timed motor sequence (Ramnani & Passingham, 2001; Sakai *et al.*, 2002) or an isochronous tapping task (Penhune & Doyon, 2002). By contrast, the basal ganglia have been observed to be active in isochronous tapping tasks (Lejeune *et al.*, 1997; Rao *et al.*, 1997) and patients with pallidal dysfunction show deficits in timing behaviour (for a review, see, e.g. Harrington & Haaland, 1999). Structures in the basal ganglia may thus not primarily be involved in the control of temporal sequences, but rather in basic timekeeping and in ordinal sequential control, a notion also supported by Dreher & Grafman (2002).

The importance of the cerebellum for explicit timing has been demonstrated in a large number of investigations. These include both neuroimaging studies showing cerebellar activation during perceptual and motor timing tasks (Ivry, 1996, 1997; Rao *et al.*, 1997; Penhune *et al.*, 1998; Jäncke *et al.*, 2000; Ramnani & Passingham, 2001; Rao *et al.*, 2001; Schubotz & von Cramon, 2001; Penhune & Doyon, 2002; Ullén *et al.*, 2003) and demonstrations of decreased temporal accuracy following cerebellar lesions (Ivry *et al.*, 1988; Ivry & Keele, 1989) or transient disruption of cerebellar activity with transcranial magnetic stimulation (Théoret *et al.*, 2001). The posterior lateral cerebellar activation in the present study is consistent with the view that lateral cerebellum is particularly important for central timing functions (Ivry *et al.*, 1988), although several studies have also demonstrated an

involvement of medial cerebellum in timing (e.g. Rao *et al.*, 2001; Théoret *et al.*, 2001; Ullén *et al.*, 2003).

We found no indication that the cerebellum should play a specific role for the programming of sequences of temporal intervals, as when contrasting TEMPORAL with ORDINAL. This is in line with suggestions that cerebellum may play a more general role for sensorimotor processing in a variety of tasks that require timing and anticipation of events (Ivry, 2000; Rao *et al.*, 2001; Ivry *et al.*, 2002). Presumably, the lack of cerebellar activity in the present study was also related to the fact that the sequences were overlearned. Ramnani & Passingham (2001) and Penhune & Doyon (2002) demonstrated cerebellar activity during early stages of learning of temporal sequences; in later stages the cerebellar activity decreased (Penhune & Doyon, 2002). Cerebellar patients show impaired learning of temporal sequences (Shin & Ivry, 2003).

#### *Neural control of ordinal sequence structure*

The brain activity pattern of the main effect for long ordinal sequence is consistent with earlier imaging studies showing that performance of long sequences, when contrasted with shorter, activates the SMA (Orgogozo & Larsen, 1979; Roland *et al.*, 1980; Gordon *et al.*, 1998), the PMD, the posterior parietal cortex (Deiber *et al.*, 1991; Sadato *et al.*, 1996; Catalan *et al.*, 1998), the thalamus (Sadato *et al.*, 1996; Boecker *et al.*, 1998), the basal ganglia (Boecker *et al.*, 1998) and the cerebellum (Sadato *et al.*, 1996).

However, a new and important finding here is the dissociation of regions predominantly involved in ordinal as opposed to temporal sequence control. The PMD, the postcentral and subcentral gyri, the SPG, the IPG, the basal ganglia and the cerebellum showed significantly higher involvement in ordinal than rhythmic control, as demonstrated in the direct ORDINAL – TEMPORAL contrast.

In the present study, the sequences consisted of spatially targeted key-presses with a particular serial order. During training these were presented orally to the subject as a sequence of numbers. In principle, neural activity seen in the conditions with long ordinal structure could therefore reflect both processing of the ordinal structure of the sequence, represented abstractly as a series of labels for the different keys, and movement implementation, i.e. the execution of a spatial movement trajectory to each target location. The PMD and the posterior parietal cortex are anatomically connected and form neural circuits involved in sensorimotor transformations during actions towards extrapersonal objects (Jeannerod *et al.*, 1995; Wise *et al.*, 1997). The posterior parietal cortex represents the spatial trajectories of arm and hand movements as well as the location of spatial targets (Andersen *et al.*, 1997; Cohen & Andersen, 2002; Gottlieb, 2002). Interestingly, a recent fMRI study found that both cognitive and motor sequences activate common areas in bilateral inferior parietal lobules and lateral premotor cortex, suggesting the ordinal information in these areas to be represented in an abstract way (Koechlin *et al.*, 2002). The activity seen in these regions could thus reflect a more abstract, superordinate ordinal control of the sequence of keys.

#### *A possible role for cerebellum and the superior colliculi in combining temporal and ordinal structures*

When the combined sequence is performed, temporal and ordinal sequential information must be integrated. Our results suggest that this integration is achieved essentially through two mechanisms. At the cortical level, COMBINED engages the same networks that control the temporal and ordinal structures performed in isolation (i.e. TEMPORAL and ORDINAL). No cortical areas showed significant increases in synaptic activity, above the sum of activities associated with TEMPORAL and ORDINAL, in COMBINED. The neural control

of combined sequences appears to involve coordinated activity of the networks that process temporal and ordinal sequential information.

Subcortically the vermis and the superior colliculi of the mesencephalon showed particularly strong activity during COMBINED, suggesting that these are important for the integration of temporal and ordinal sequential information during sequence performance (Fig. 5). Lesion of the anterior vermis has been observed to result in minor deterioration of visuospatial ability (Schmahmann & Sherman, 1998). The superior colliculus is known to be involved in multimodal integration of visual and auditory signals and, notably, collicular neurons show superadditive activity increases when visual and auditory signals converge closely in time (Calvert *et al.*, 2000, 2001; Bushara *et al.*, 2003). The activation maps associated with ORDINAL and TEMPORAL suggest that ordinal information may partly be represented visuo-spatially, i.e. in the posterior parietal lobes, whereas temporal control uses auditory representations in the superior temporal lobes. Multimodal integration in subcortical structures may thus support the coordinated execution of combined sequences.

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## Abbreviations

BOLD, blood oxygenation level-dependent; CMA, cingulate motor area; fMRI, functional magnetic resonance imaging; IPS, intraparietal sulcus; PMD, dorsal premotor cortices; SMA, supplementary motor area; SPG, superior parietal gyri; SPMs, statistical parametric maps; STG, superior temporal gyri.

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