Neural Control of Rhythmic Sequences

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ABSTRACT: We investigated if the temporal structure of movement sequences can be represented and learned independently of their ordinal structure, and whether some brain regions are particularly important for temporal sequence performance. Using a learning transfer design, we found evidence for independent temporal representations: Learning a spatiotemporal sequence facilitated learning its temporal and ordinal structure alone; learning a temporal and an ordinal structure facilitated learning of a sequence where the two were coupled. Second, learning of temporal structures was found during reproduction of sequential stimuli with random ordinal structure, suggesting independent mechanisms for temporal learning. We then used functional magnetic resonance imaging to investigate the neural control of sequences during well-learned performance. The temporal and ordinal structures of the sequences were varied in a 2 × 2 factorial design. A dissociation was found between brain regions involved in ordinal and temporal control, the latter mainly involving the presupplementary motor area, the inferior frontal gyrus and precentral sulcus, and the superior temporal gyri. Finally, in a second fMRI experiment, well-learned temporal sequences were performed with the left or right index fingers, or using rhythmic speech. The overlap in brain activity during performance with the different effectors included a similar set of brain regions as that found in the first fMRI experiment: the supplementary motor area (SMA), the superior temporal gyrus, and the inferior frontal cortex. We thus suggest that this set of regions is important for abstract, movement-independent, temporal sequence control. This organization may be important for increased flexibility in voluntarily timed motor tasks.

KEYWORDS: fMRI; music; timing; supplementary motor area; superior temporal gyrus; Broca's area

INTRODUCTION

An influential view in motor control theory has been that movement sequences are controlled by generalized motor programs, where the temporal structure (relative timing) is invariant, once the sequence is well learned.[1] This theory received support from findings of a fixed relative timing at different speeds and over long periods of time for such skills as typing and handwriting.[2–6]

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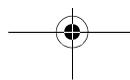
More recent studies have examined temporal sequence learning using the serial reaction time paradigm.[7–9] These results have been less clear-cut, which may reflect certain disadvantages of this paradigm for the study of temporal learning.[10] Lee[8] thus found indications of an independent representation of temporal structures, when studying spatial sequences of hand movements, with a temporal structure of alternating long and short time intervals. Phase-shifting this temporal structure in relation to the ordinal structure gave small deficits in performance. However, Shin and Ivry[9] suggested that temporal and ordinal learning, rather, may be integrated processes. In that study, temporal sequence learning was found only when a temporal sequence was coupled to a particular ordinal sequence.

In an attempt to resolve this question, we performed two behavioral experiments to directly investigate the representation and learning of temporal sequential structures.[10] First (experiment 1), we used a learning transfer paradigm to test whether independent representations of the temporal and ordinal structure of movement sequences can indeed be formed. Second (experiment 2), we investigated whether independent processes for learning of temporal and ordinal information exist. These experiments gave support for the existence of independent mechanisms for both learning and representation of temporal structures.

We therefore 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 (experiment 3).[11] Several earlier studies have investigated learning, encoding, and performance of temporal sequences.[12–18] New in this study was to ask the same subjects to perform well-learned sequences, the ordinal and temporal structures of which were varied independently, so that increases in activity specifically related to temporal processing could be revealed. Finally (experiment 4), we used fMRI to investigate which brain regions are involved in effector-independent aspects of temporal sequence control. The participants performed a well-learned temporal sequence, using tapping movements with the left or right index finger, or silent rhythmic speech (imagery) on the syllable *pa*. Sequence performance was contrasted with rest for each effector, and a conjunction analysis of these contrasts was employed to reveal overlap in activity.

METHODS

Participants

In all four experiments, the participants were right-handed[19] nonmusicians. No subject participated in more than one experiment. The experimental procedures were approved by the Ethical Committee of the Karolinska Institutet. The number of subjects in the different experiments were as follows: experiment 1, $n = 24$ (12 males); experiment 2, $n = 12$ (6 males); experiment 3, $n = 7$ (5 males); and experiment 4, $n = 7$ (4 males).

Experimental Procedures and Analysis

Experiment 1

A detailed description of the procedures in experiments 1 and 2 has been presented elsewhere.[10] The tasks consisted of rhythmic sequences of key presses, per-

formed with the right index finger on the numerical keypad of a personal computer. All subjects learned three different sequences: *Combined* had an ordinal structure of nine key presses and a corresponding temporal structure of eight temporal intervals, with durations of 375, 750, or 1125 milliseconds. *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 temporal structure of one element, that is, a regular rhythm. In addition, fourteen of the subjects learned a control sequence, *Control*, that had the same length of the temporal and ordinal structure as Combined.

Each sequence was learned in a single continuous session. The session started with one audiovisual presentation of the sequence. The subject tried to reproduce the sequence on the keyboard. If the response contained an ordinal or temporal error (relative error > 30%), the sequence was presented again. If the sequence had been produced without any errors, temporal or ordinal, the participant was instructed to reproduce the sequence again, without a new sequence presentation. The learning session was terminated when the subject had successfully performed twelve success-ful productions in a row.

To quantify transfer effects, subjects were divided into two groups, with 12 subjects in each group. Group I started by learning Combined, and thereafter learned Temporal and Ordinal; group II started by learning Temporal and Ordinal, and there-after learned Combined. Of the fourteen subjects that learned the sequence Control, 7 learned it before the experimental sequences, and 7 afterwards. Learning transfer was estimated by between-group comparisons of the total number of failed repro-ductions before a particular sequence was learned (Mann-Whitney U Test). Within-subject correlations of the duration of the same temporal interval, as performed in the Temporal and Combined tasks, were analyzed by calculating the Pearson product-moment correlation coefficient.

Experiment 2

Sequence presentation and data collection were performed as in experiment 1, but here all sequences consisted of seven key presses separated by six temporal intervals. Three different tasks were included in the experiment. For each task, the participant performed a session of 50 trials without a break. Each trial consisted of one sequence presentation followed by a reproduction. No feedback was provided. The only in-struction to the subject before each session was to repeat both the temporal pattern and the key sequence as accurately as possible in each trial. In the first task, *Fix Tem-poral*, the sequences in all 50 trials of the session had a constant temporal structure (750–375–375–1125–375–750; all in ms), while the ordinal structure was varied randomly. *Fix Ordinal*, had a constant ordinal structure (left–right–center–right–left–center–left) but varying temporal structure. *Random*, the third task, had both varying temporal and varying ordinal structure.

The median number of correct key presses and correct temporal intervals were calculated for each trial in the different tasks, using data from all subjects. Correla-tions between trial number and number of correct responses were analyzed by calculating the Pearson product-moment correlation coefficient. To evaluate if sub-jects had explicit awareness of the structure of the different sequences, subjects filled out a brief questionnaire after each session, where they were asked if they noticed any pattern in the sequences and, if so, what pattern. This information was used to
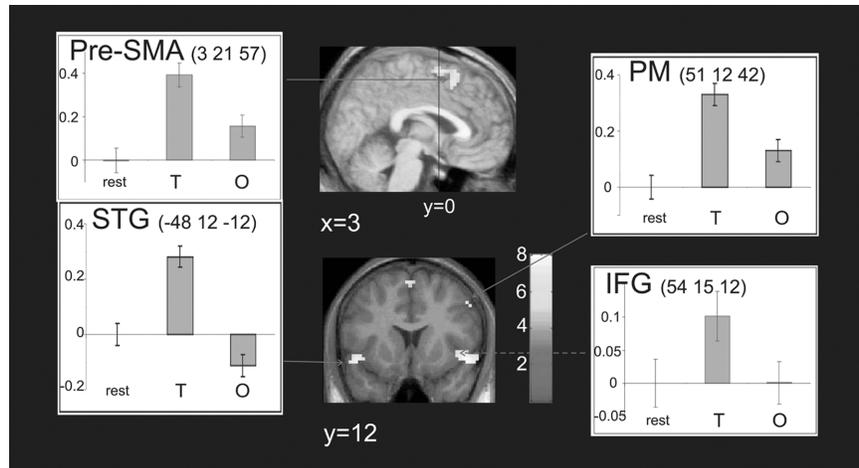
FIGURE 1. Direct comparisons between long temporal structure (*left*) and long ordinal structure (*right*). Activity maps of brain regions with significantly increased BOLD contrast signals ($P < .05$ corrected) are shown. Activated brain regions included the pre-SMA ($x = 3$), the bilateral superior temporal gyri (STG) ($y = 12$), the inferior frontal gyrus pars opercularis (IFG) ($y = 12$), and the right inferior part of the precentral sulcus (PM) ($y = 12$). The *bars* illustrate the adjusted relative hemodynamic response for each task in one local peak voxel (C = *Combined*, T = *Temporal*, O = *Ordinal*, E1 = *Even One Key*, E2 = *Even Two Keys*). The color scale (*online version only*) shows Z values. (Modified from Bengtsson *et al.*[11] Reproduced with kind permission of Blackwell Publishing.)

investigate if learning took place in those subjects that reported that they detected no regularities in the stimuli.

Experiment 3

A full description of this experiment is given elsewhere.[11] As in experiment 1, the tasks consisted of rhythmic sequences, where the length of the temporal and ordinal structures were varied to allow analysis with a 2×2 factorial model. The ordinal structure of a sequence had either eight or one element. The temporal structure of a sequence also had either eight or one element (durations of 375, 750, 1125, or 1500; all in ms), that is, an isochronous pulse with the period 750 milliseconds. The tasks are illustrated schematically in FIGURE 1. Combined, Temporal, and Ordinal correspond to the tasks with the same names in experiment 1. Two control sequences were used: *Even One Key* consisted of a regular pulse performed on the middle key, and *Even Two Keys* had a isochronous rhythm performed on the two outer keys, alternatingly, and was included to control for lateral wrist movements in Ordinal and Combined. A rest condition (*Rest*) was also included, where the subject was completely relaxed. All tasks were practicsed for about one hour in one training session one or two days before the fMRI experiment and for 30 min immediately before the scanning. In the experiment the tasks were performed in epochs lasting 40 seconds. During the first 8 s of each epoch, the subjects were given a verbal instruction, followed by five beats of an auditory metronome at 80 beats per minute providing the correct

tempo. We analyzed the brain scans obtained during the 32-s periods when the metronome was turned off and the subjects repetitively generated the movement sequences.

fMRI was conducted on a 1.5 T scanner (Signa Horizon Echospeed, General Electric Medical Systems, Milwaukee, WI, USA). Functional imaging data was then recorded as gradient-echo echo-planar (EPI) T2∗–weighted images with blood oxygenation level–dependent (BOLD) contrast.[20–22] The fMRI data was analyzed using the SPM-99 software package (Wellcome Department of Imaging Neuroscience, London, UK), using a standard linear regression model, with six conditions of interest corresponding to the periods when the subjects performed the tasks. 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, pooling data from all subjects in a fixed-effects group analysis. Reported activations were significant at $P < .05$, after correction for multiple comparisons, on the basis of a test of peak height.[23]

Here we will discuss brain regions active in the main effect contrast for the long temporal structure, as well as regions that showed a significantly higher activity during performance of long temporal structures than during performance of long ordinal structures, as revealed by the contrast Temporal–Ordinal.

Experiment 4

A full description of this study will be given elsewhere.[24] Six experimental conditions and one baseline rest condition were used. Here we will discuss results pertaining to three experimental conditions, *SeqRight*, *SeqLeft*, and *SeqSpeech*, where the subjects performed a rhythmic sequence of six temporal intervals, with the right index finger, the left index finger, and using rhythmic speech, respectively. The rhythmic sequence had the temporal pattern 375–375–750–1125–375–1500 (all in ms). Task training was performed as in experiment 3. During the MR scans, the tasks were performed repetitively in epochs of 40 seconds. fMRI data was processed using the SPM-99 software package, as described for experiment 3. The focus of the experiment was to investigate brain regions involved in effector-independent control of motor timing. For this purpose, we used conjunction analyses,[25] which can be interpreted as logical AND-operations, giving only those activations that are significant in all individual contrasts of the conjunction. Here we will discuss the results of the conjunction between the three contrasts, SeqRight–Rest, SeqLeft–Rest, and SeqSpeech–Rest.

RESULTS

Experiment 1

Strong transfer effects were seen on all tasks. Learning of Combined in group II, which before that had learned Temporal and Ordinal, was significantly quicker ($M = 4.5$ trials; $P = .0003$) than in group I ($M = 12.5$ trials). Likewise, a quicker learning of both Temporal ($M = 1$ trial; $P = .015$) and Ordinal ($M = 2$ trials; $P = .0002$) was seen in group I subjects than in group II subjects ($M = 12$ and 13 trials, respectively). Learning of Control was significantly faster ($M = 3$ trials;

P = .01) in participants that trained this task at the beginning of the experiment, than in the group that trained at the end (M = 16 trials). The transfer effects were thus specific to the experimental sequences and not due to an increase in general ability to learn this type of task.

Further evidence for independent representations of temporal structures were found when comparing the relative errors in the temporal pattern produced in Temporal and Combined. Pooling data from all subjects, high positive within-subject correlations were found for the duration of all individual temporal intervals of the sequence during performance of Temporal and Combined (r values: .65–.86; P < .001).

Experiment 2

In the three conditions Fix Temporal, Fix Ordinal, and Random, learning—as indexed by a significant correlation between trial number and number of correct responses—was observed only in two cases: for number of correct temporal intervals in Fix Temporal (P < .00001; r = .73) and for number of correct key presses in Fix Ordinal (P < .01; r = .35). The weaker correlation in the latter case is due to the fact that the ordinal structure of the sequence was learned very rapidly, so that the learning curve reached an early plateau, and the relationship with trial number was curvilinear. Independent mechanisms for learning of temporal and ordinal information thus appear to exist. Interestingly, learning of temporal information (P < .00001; r = .65) was also seen in a subgroup of subjects (n = 9) that reported having detected no regularities in the stimuli of Fix Temporal, suggesting that temporal sequences can be learned implicitly.

Experiment 3

The main effect contrast for long temporal structure revealed a large cluster of active voxels located in the presupplementary motor area and the supplementary motor area (SMA). Activity was also seen in the bilateral superior temporal gyri (STG), extending into the bilateral insula and the right inferior frontal gyrus (IFG). Bilateral activity in the inferior part of the precentral sulcus was also seen (PMV/BA 44). 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.

A similar pattern of activity was seen in the contrast Temporal–Ordinal (Fig. 1). Activations were seen in the pre-SMA, extending from the rostral pre-SMA to the SMA/pre-SMA border; the right IFG; the right inferior part of the precentral sulcus (PMV/BA 44); the right anterior part of the STG; the left posterior part of the STG; and the right insula.

Experiment 4

The conjunction analysis among SeqRight–Rest, SeqLeft–Rest, and SeqSpeech–Rest revealed a similar set of brain regions to that found in experiment 3. On the medial wall of the frontal lobe, activations were seen in the left SMA, extending into the caudal cingulate motor area and rostrally to the SMA/preSMA border. Further, activity was seen in the left IFG and in the left anterior STG, as well as the posterior
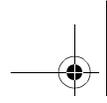
left STG, close to the temporoparietal junction. Subcortical activations included the left lobule V/VI of the vermis and lobule VI of the cerebellar hemispheres.

DISCUSSION

A main conclusion from these studies is that the processing of temporal sequences in voluntarily timed motor tasks is largely independent from the processing of ordinal information. Temporal sequences can be learned and represented independently, and performing well-learned rhythmic sequences predominantly involves a set of brain regions, different from those controlling ordinal structures. These brain regions appear to be involved in rhythm production independently of both the effector and the ordinal structure of the movements, suggesting that they represent rhythmic patterns in a more abstract, movement-independent manner. We propose that this organization gives larger flexibility and faster learning of alternative behavioral strategies to reach a certain goal. A detailed discussion of the results is given elsewhere.[10,11,24] We will here add some comments on the findings in relationship to recent studies.

Garraux and coworkers[26] manipulated ordinal and temporal structure in a sequence reproduction task. In the temporal condition, participants were asked to produce random temporal intervals in the range 1.3–3.3 seconds. In this study timing-related increases in brain activity were found only in the right putamen. Interestingly, this suggests different neural mechanisms for the voluntary production of specific temporal patterns[11,16,27] and production of sequences of random durations.

The supplementary motor area and the adjacent nonprimary motor areas on the medial wall are active in a large variety of tasks that involve voluntary timing,[28] including the sequential tasks discussed here. The specific contributions of the different areas for temporal sequence production are not well understood, however. Recent work suggests that the pre-SMA may be of particular importance for such superordinate functions as initiation of repetitive rhythm performance[29] and metric organization of temporal sequences.[30]

In studies of self-paced rhythm production, the movement rate is often established by the use of a metronome, which is switched off after a while. Recent studies have shown that the neural activity during the self-paced phase is dependent both on the modality of the metronome[31,32] and on the coordination between movements and metronome beats[33] in the initial phase, before the metronome is turned off. The activity in auditory association as seen in the present experiments could therefore reflect either that the temporal sequences were presented in the auditory modality during training or that an auditory metronome was used to set the movement rate during scanning. Further experiments will be needed to elucidate this question.

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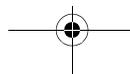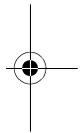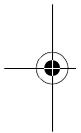
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