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Listening to rhythms activates motor and premotor cortices

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ABSTRACT

We used functional magnetic resonance imaging (fMRI) to identify brain areas involved in auditory rhythm perception. Participants listened to three rhythm sequences that varied in temporal predictability. The most predictable sequence was an isochronous rhythm sequence of a single interval (ISO). The other two sequences had nine intervals with unequal durations. One of these had interval durations of integer ratios relative to the shortest interval (METRIC). The other had interval durations of non-integer ratios relative to the shortest interval (NON-METRIC), and was thus perceptually more complex than the other two. In addition, we presented unpredictable sequences with randomly distributed intervals (RAN). We tested two hypotheses. Firstly, that areas involved in motor timing control would also process the temporal predictability of sensory cues. Therefore, there was no active task included in the experiment that could influence the participant perception or induce motor preparation. We found that dorsal premotor cortex (PMD), SMA, preSMA, and lateral cerebellum were more active when participants listen to rhythm sequences compared to random sequences. The activity pattern in supplementary motor area (SMA) and preSMA suggested a modulation dependent on sequence predictability, strongly suggesting a role in temporal sensory prediction. Secondly, we hypothesized that the more complex the rhythm sequence, the more it would engage short-term memory processes of the prefrontal cortex. We found that the superior prefrontal cortex was more active when listening to METRIC and NON-METRIC compared to ISO. We argue that the complexity of rhythm sequences is an important factor in modulating activity in many of the rhythm areas. However, the difference in complexity of our stimuli should be regarded as continuous.

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1. Introduction

The ability to perceive the temporal regularities of stimuli is essential for a number of human behaviors, from the simple

prediction of moving object trajectories to language comprehension and music performance. In this paper we investigate the neural processing of very basic forms of temporal regularities. The participants listened to rhythm sequences which

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all had the same auditory tone, and differed only in their repeating structure of temporal intervals. Three rhythm sequences were presented with varying degrees of sequence complexities (Fig. 1). The simplest sequence was an isochronous sequence. The other two rhythm sequences had the same total duration, but they differed in the relative relationship between the intervals. Two important parameters that determine perceptual complexity of rhythm sequences are how well they can be segmented into sub-sequences by a regular beat, and the total complexity of the resulting sub-sequences (Shmulevich and Povel, 2000). As can be seen in Fig. 1 the METRIC sequence had a relatively low complexity: the intervals were of integer ratio to the shortest interval, and it could be segmented into four segments, each of 800 msec duration and two of which were identical. The NON-METRIC sequence, however, was more complex: the intervals were of non-integer ratios to the shortest interval, and it could only be divided into two asymmetrical 1600 msec segments.

It is reasonable to assume that the brain predicts the single interval of an isochronous rhythm sequence with less variability than more complex rhythm sequences. A higher variability for rhythmic sequence production than isochronous movements has been demonstrated in rhythmic finger-tapping tasks (MacDorman, 1962). It is also reasonable to assume that METRIC is perceived as more predictable than NON-METRIC. Metrical rhythms are reproduced with higher accuracy than non-metric rhythms (Essens and Povel, 1985; Sakai et al., 1999), and are identified early in development by infants (Bergeson, 2000, as cited in Trehub, 2001). Moreover,

when asked to tap rhythmically, humans spontaneously produce metric rhythms (Essens and Povel, 1985). Thus, by manipulating the predictability of the rhythm sequences we could study brain activity that varied with this factor. A rhythm sequence was presented repeatedly in a block. In addition, we presented sequences with intervals randomly distributed within a 29 sec long sequence (RAN).

Our first hypothesis was that motor and premotor cortices would be active when listening to rhythms. Perceiving a rhythm sequence involves predicting the sensory stimuli in time. Engel and colleagues (2001) have suggested that sensory prediction would rely on similar mechanisms to those of motor preparation, since both involve internally generated states of prediction. Several studies have suggested a common source of control for motor and sensory predictions. For example, patients with Parkinson's disease show timing deficits on both perceptual and motor tasks (Harrington et al. 1998). Parkinson's disease is associated with the loss of nigral dopaminergic cells projecting to putamen, which connect to supplementary motor areas (SMAs) (Alexander et al., 1990), as well as loss of neurons in preSMA (McDonald and Halliday, 2002). Also, people improve their motor timing ability by familiarizing themselves with the interval duration perceptually (Meegan et al., 2000), and a correlation is found between motor timing variability and acuity duration judgment of perceptual events (Keele et al., 1985). Thus, one would expect that areas such as the SMA, the preSMA, the dorsal premotor cortex (PMD) and the cerebellum would be active, since these areas have been observed active in motor preparation tasks

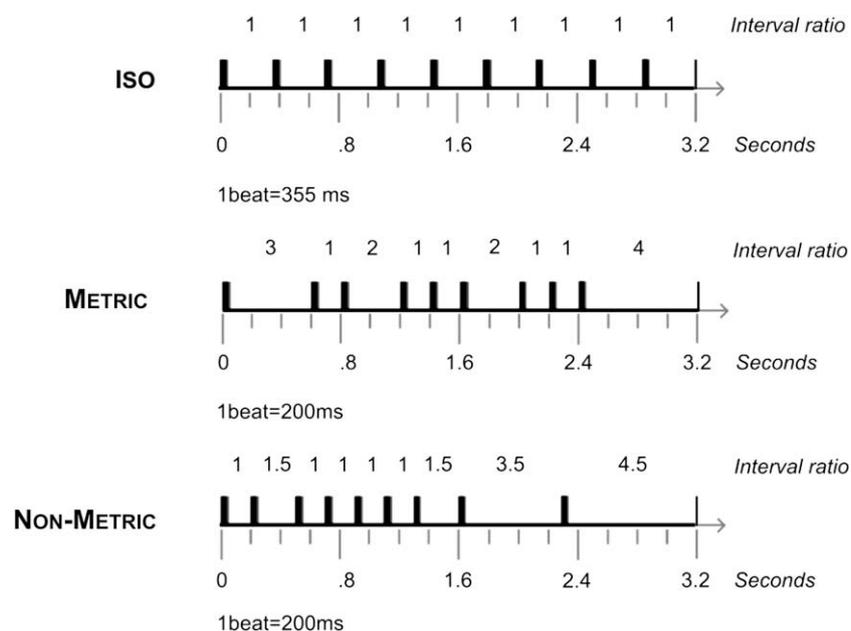


Fig. 1 – The three rhythms ISO, METRIC and NON-METRIC were each presented during blocks of 29 sec. In addition, unpredictable sequences of randomly distributed intervals were presented. Participants were listening without performing any additional task. The simplest sequence is the isochronous sequence (ISO), having a regular beat of one repeating interval. The other two rhythm sequences both have a total duration of 3200 msec but they differed in the relative relationship between the intervals. The METRIC sequence has a relatively low complexity: the intervals are of integer ratio to the shortest interval, and it can be segmented into four segments, each of 800 msec duration and two of which are identical. The NON-METRIC sequence, however, is more complex: the intervals are of non-integer ratios to the shortest interval, and it can only be divided into two asymmetrical 1600 msec segments.

(Deiber et al., 1996; Lau et al., 2004). In fact, previous studies on rhythm perception have suggested that premotor areas and the cerebellum are engaged. However, these studies involved active behavioural responses, and therefore, the role of the motor areas remains uncertain (Sakai et al., 1999; Schubotz et al., 2000; Rao et al., 2001; Coull et al., 2004). To test this hypothesis we compared listening to rhythm sequences with listening to sequences of randomly distributed intervals.

Our second hypothesis was that the more complex the rhythmic structure, the more it would rely on prefrontal processing. In the study by Sakai et al., 1999 it was shown that the dorsolateral prefrontal cortex (DLPC) was sensitive to the interval ratios during the memory delay period before the successful reproduction of rhythm sequences. However, since in that study participants were asked to reproduce the rhythm sequence, it is unclear if the prefrontal activation was due to the rhythm perception per se, or the action preparation. Nevertheless, prefrontal damage results in deficient top-down control of organizing the temporal order of events (Mangels et al., 1998; Miller and Cohen, 2001). Thus, the prefrontal cortex appears to play a critical role for the internal representation of temporal sequences. We compared brain activation when people listened to METRIC and NON-METRIC to that when they listen to ISO. We also compared METRIC to NON-METRIC.

2. Methods

2.1. Participants

Seventeen right-handed, healthy subjects (20–36 yrs, mean 23.6 yrs, 14 males), with no history of neurological disease, participated in the study. At the time of the experiment, only one participant played a musical instrument, at an amateur level. The protocol was approved by the ethical committee of the National Institute for Physiological Sciences, Okazaki, Japan, and all subjects gave their written informed consent for the study.

2.2. Experimental procedure

The participants were instructed to listen attentively to the temporal structure of the series of auditory stimuli that would be presented. They were asked to relax and to not make any movements during the scans. One hour before the scanning session, the participants were familiarized with the stimuli while they listened to each rhythm sequence and a random sequence for 20 sec each. The experimenter made sure that they understood the regularity of the rhythm sequences by asking after the presentation of each and every rhythm: “Did you hear a rhythm?” All subjects responded ‘yes’ for all three rhythm sequences, and recognized – correctly – that a random sequence lacked any regular structure. When the participants lay in the scanner, before the actual data collection begun, they were again presented with the stimuli to ensure they could hear them well and perceive the different rhythm sequences also in the scanner environment. The volume was adjusted separately for each individual.

During the functional magnetic resonance imaging (fMRI) experiment, the subjects were lying blindfolded in a supine position on the bed of the scanner. In order to control for any hand movements during the listening, electromyogram (EMG) (PowerLab, ADInstruments, Colorado Springs, CO, USA) was measured on all but one (due to technical failure) of the subject’s flexor and extensor muscles of the right and left arm. The EMG was displayed online; 3 min of EMG were recorded for each subject. In addition, two experimenters were carefully and closely observing the participants from different angles at all times during the scanning.

After the fMRI scanning the participants filled in a questionnaire where they answered questions about if they had associated the different rhythms to real-life events, if they had manage to stay alert, and if they had readily perceived the four different stimuli.

2.2.1. Stimuli

The same auditory tone was used in all conditions: a sampled (44 kHz sampling frequency) brief drumbeat of 55 msec duration. The stimuli sequences were created with the software Adobe Audition (Adobe Systems Incorporated) and were presented through headphones to the subject. Five conditions were included: in the isochronous rhythm sequence: ISO, all interval durations were 355 msec, this being the mean duration of the intervals in the other sequences. The metric rhythm sequence: METRIC, consisted of a sequence of nine temporal intervals of integer ratios, with interval durations 200, 400, 600, and 800 (all in msec). Notably all included durations were thus integer (2–4) multiples of the shortest interval (200 msec). As illustrated in Fig. 1A the sequence was 600, 200, 400, 200, 200, 400, 200, 200, 800 (all in msec). For the NON-METRIC sequence the durations 200, 300, 700, and 900 (all in msec) were used; the longer intervals of the sequence thus had non-integer ratios to the shortest interval. The sequence was 200, 300, 200, 200, 200, 200, 300, 700, 900, (all in msec). Both the METRIC and NON-METRIC rhythm sequences had a total duration of 3.2 sec. In a block, a single rhythm sequence was repeated 9 times (i.e., 28.8 sec). The fourth sequence RAN had the same interval durations as METRIC, but the order of the intervals was scrambled randomly within the total 28.8 sec period of the epoch. A random sequence was only presented once to each participant. A baseline condition, REST, where the participant rested passively without any sound stimuli was also included. Importantly, all the sequences contained the same number of sound elements. In addition, as illustrated in Fig. 1, the two complex rhythm sequences contained the same number of short, intermediate and long intervals.

2.2.2. Data acquisition

fMRI was conducted on a 3T scanner (Allegra, Siemens, Erlangen, Germany). A cushion was used to restrict head movements. At the beginning of each experiment a high-resolution, 3D gradient-echo T1-weighted anatomical image volume of the whole brain was collected ($1 \times 1 \times 1$ mm voxels). Functional imaging data was then recorded as gradient-echo, echo-planar (EPI) T2*-weighted images with blood oxygenation level dependent (BOLD) contrast (Ogawa et al., 1992). Image volumes of the whole brain were built up from contiguous oblique slices ($n = 48$). The following parameter

values were used for the fMRI scanning: echo time, 40 msec; field of view, 19.2 cm; matrix size, 64×64 ; pixel size 3×3 mm; flip angle, 90° ; slice thickness: 3 mm; repetition time (T_R), 3.0 sec; number of volumes per run: 127. Data was collected during three separate runs. All five conditions were presented in each run. To reduce possible time and order effects, three different task-orders were used for different runs. Each condition – the rhythm sequences or random sequences, as well as the rest condition, was presented in epochs of 28.8 sec for each sequence, followed by a second of silence between two consecutive conditions. In total, each condition was presented in seven epochs. We started each run by recording six “dummy” image volumes that were not stored, to allow for T1 equilibration effects.

2.2.3. Image processing

Functional MR data was pre-processed and analysed using the SPM2 software package (Wellcome Trust Centre for Neuroimaging, UK). The volumes were realigned to correct for head movements. Subsequently, the volumes were coregistered to each individual's T1-weighted image and normalized to the stereotactic coordinate system of Talarach and Tournoux (1998), using the standard brain template from 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 10 mm full width at half-maximum, and temporally with a Gaussian kernel of width 4 sec.

2.2.4. Statistical analysis

The fMRI data was modelled with a standard linear regression model, where we defined five conditions of interest that corresponded to the 29 sec epochs when the subjects perceived an auditory temporal sequence or rested. Five conditions of no interest were also modelled, corresponding to the 1 sec period of silence between the auditory conditions. To test our hypotheses, conjunction analyses were performed using SPMs of the minimum t-statistic, in order to identify regions of consistent activation in all contrasts of interest (Friston et al., 1999). We made sure that the contrasts were orthogonal, i.e., that different data points were used in the different contrasts of each subject. We also performed simple contrasts at a 2nd level random effect, between conditions of interest, and we report the t-values from individual contrasts as additional information in the table.

Firstly, we compared the activity during each of the three rhythm sequences versus the random sequences in a conjunction analysis ($[(ISO)-(RAN)]$ & $[(METRIC)-(RAN)]$ & $[(NON-METRIC)-(RAN)]$). This analysis highlighted brain activation reflecting the differences in temporal regularity between rhythmic and random sequences. Importantly, it should be noted that this comparison eliminates effects related to the differences in absolute timing between intervals, and differences between the numbers of different intervals in ISO and NON-METRIC compared to RAN. This is so because we matched the absolute interval durations, and the number of different intervals between METRIC and RAN. Since we were interested in areas involved in the prediction of the stimuli, we also compared $[(ISO)-(METRIC)]$ & $[(ISO)-(NON-METRIC)]$.

Secondly, we performed the conjunction analysis ($[(METRIC-ISO)]$ & $[(NON-METRIC-ISO)]$). This conjunction reflects

positive activations present when listening to complex rhythm sequences, in contrast to isochronous. To ensure that the resulting brain activation is not simply reflecting the fact that METRIC and NON-METRIC have several different intervals whereas ISO only has got one interval duration, but rather reflects the recognition of a complex rhythm sequence, we also contrasted METRIC–RAN to verify the data.

Finally, for completeness, we compared NON-METRIC to METRIC. NON-METRIC and METRIC had been carefully designed so that the interval durations were similar.

Since we hypothesized that prefrontal, motor and cerebellar areas would be active during rhythm perception we report and discuss peaks of activity that correspond to $p < .001$ (uncorrected for multiple comparisons), in clusters of at least five voxels of these regions. In addition, to thoroughly test if motor regions that are involved in sensorimotor predictions are also active in rhythm perception, we performed corrections for multiple comparisons in main regions of interest. For this, we used the small volume corrections (SVCs), where we searched for activation in spheres of 10 mm diameters, centred on peak coordinates taken from published (preSMA: Coull et al., 2004; PMD: Sakai et al., 1999, and cerebellum: Sakai et al., 1999) (Table 1A). For completeness, we report all activations in the whole brain that correspond to $p < .001$ (uncorrected) in clusters of at least five voxels. In the tables, the Z-value for the conjunction analysis, and the t-value for each single contrast, is reported. We do not report areas where all conditions were de-activated in relation to the resting condition.

Anatomical localizations were determined from a mean structural MRI of the 17 subjects. To localize cerebellar activations we used the atlas of Schmahmann et al. (1999).

In the bar diagrams (Fig. 2) we have plotted the fitted BOLD signal from volumes of interests (VOIs) of some relevant regions for each rhythm sequence in relation to RAN. The values correspond to the mean signal across the 17 subjects. A VOI was defined as having a diameter of 10 mm.

3. Results

3.1. Behaviour

EMG recordings showed no muscle activity in any of the conditions during the fMRI scanning. Since rhythm perception could evoke associations to rhythmic movements, we expected some people to spontaneously associate the rhythms to a previously experienced moving object or body part. For that reason, we asked the participants after the fMRI session what they thought about when they heard the rhythms using open-end questions. Seven of the 17 subjects associated the rhythmic stimuli with real-life events, reporting: falling rain (1 subject), someone walking (1 subject), sound of insects (2 subjects), sound of drums (1 subject) or heartbeat (2 subjects).

3.2. Brain imaging

3.2.1. Temporal prediction

When comparing the three rhythm sequences to the random sequences, we localize brain activation involved in rhythm

Table 1A – RHYTHM SEQ > RANDOM

Location	Side	X	Y	Z	Z-value	Single contrast t-values		
						ISO–RAN	METRIC–RAN	NM–RAN
<i>Frontal lobe</i>								
Middle frontal gyrus (lateral area 10)	L	–30	51	21	3.9	4.91	3.74	3.38
Superior frontal gyrus (area 9)	L	–24	54	9	3.7	2.97	3.29	1.75
Inferior front gyrus (area 45/46)	L	–21	42	45	3.3	1.67	2.95	2.61
Anterior bank Precentral sulcus*	L	–48	27	15	3.2	2.70	1.84	2.55
Superior frontal gyrus (preSMA)*	L	–39	9	48	3.3	1.89	2.14	3.18
Cingulate motor area (CMA)	M	–3	12	54	3.3	3.89	2.0	2.67
Superior frontal gyrus (SMA)*	L	–12	12	39	3.2	3.9	1.71	2.47
<i>Occipital lobe</i>								
Calcarine sulcus	R	–3	12	54	3.3	2.85	1.37	1.92
Parieto-occipital fissure	R	15	–78	3	3.9	1.72	4.25	1.85
Cuneus	R	18	–69	12	3.1	1.64	4.01	1.61
<i>Cerebellum</i>								
Lobule V*	R	18	–81	30	3.3	.7	2.25	4.38
Increased BOLD contrast signal of conjunction analyses performed over subjects. $p < .001$ uncorrected for multiple comparisons in clusters of at least five voxels. (1A) contrast: [(ISO)–(RAN)], [(METRIC)–(RAN)], [(NON-METRIC)–(RAN)]. (1B) Contrast: [(ISO)–(METRIC)], [(ISO)–(NON-METRIC)]. (1C) Contrast: [(METRIC)–(ISO)], [(NON-METRIC)–(ISO)].								

perception ([(ISO)–(RAN)] & [(METRIC)–(RAN)] & [(NON-METRIC)–(RAN)]). The result is tabulated in Table 1A and illustrated in Fig. 2A. Particularly interesting is the finding of the motor and premotor cortices. We found two clusters of activation on the medial wall in the superior frontal gyrus. The posterior cluster was located in the SMA ($y = -12$). The second cluster was located in preSMA ($y = 12$), assuming that the border between preSMA and SMA is located at approximately $y = 0$ (Picard and Strick, 1996). In the left anterior bank of the superior part of the precentral sulcus, i.e., the rostral part of the dorsal PMD (Picard and Strick, 2001), another active cluster was found. In addition, we found activation in the middle frontal gyrus (MFG), possibly corresponding to Brodmann area (BA) 10 in the left DLPC, and the left inferior frontal gyrus (IFG) pars triangularis [BA 45 (Amunts et al., 1999)].

When we compared ISO with METRIC and NON-METRIC (Table 1B; Fig. 2B), conspicuous activation was observed in lateral prefrontal areas, as well as in the preSMA, the cingulate motor area (CMA) and the right rostral PMD. In addition, increased activation of the bilateral insular lobe was observed with activation extending to the posterior superior temporal gyrus (STG) bilaterally. The peak coordinates of these temporal activations fall into the centre part of the cytoarchitectonically mapped TE10 (Morosan et al., 2001) which belongs to the primary auditory cortex.

3.2.2. Perception of rhythmic sequences of several elements
Neural activity related to the percept of a rhythm sequence of several elements, as opposed to a simple isochronous rhythm, is reported in Table 1C ([METRIC–ISO] & [NON-METRIC–ISO]). The resulting pattern of activation is illustrated in Fig. 2C,

where the bar diagrams show the percent signal change for each condition relative to the random condition. In line with our hypothesis, we observed prefrontal activations. The clusters of activations were located in the bilateral superior frontal gyrus and appear to correspond to BA 9. We also observed activity in the right superior temporal sulcus, and in the right occipital lobe in the transverse occipital gyrus, the inferior lingual gyrus, and the fusiform gyrus. To further highlight the brain areas associated with processing the sequential feature of a rhythm, we investigated the contrast METRIC–RAN. This contrast is matched in the number of different interval durations, and thus differs only in regularity. Here, the superior frontal areas, the right inferior lingual gyrus, and the transverse occipital gyrus remained active.

3.2.3. Perception of non-metric and metric rhythm sequences
Differences in the processing of the complex rhythm sequences were investigated by contrasting NON-METRIC–METRIC. We found a statistical trend for activation in the bilateral anterior cerebellum and right supramarginal gyrus $p < .002$ (uncorrected) (Table 1E, Fig. 2E). For completeness we also report the contrast METRIC–NON-METRIC in Table 1D and Fig. 2D.

4. Discussion

Unlike previous imaging studies on rhythm perception, we avoided confounds that could influence the subjects' percept and brain activity, by excluding tasks involving decision-making, response preparation, or learning. It was particularly relevant in the present study to exclude any form of motor

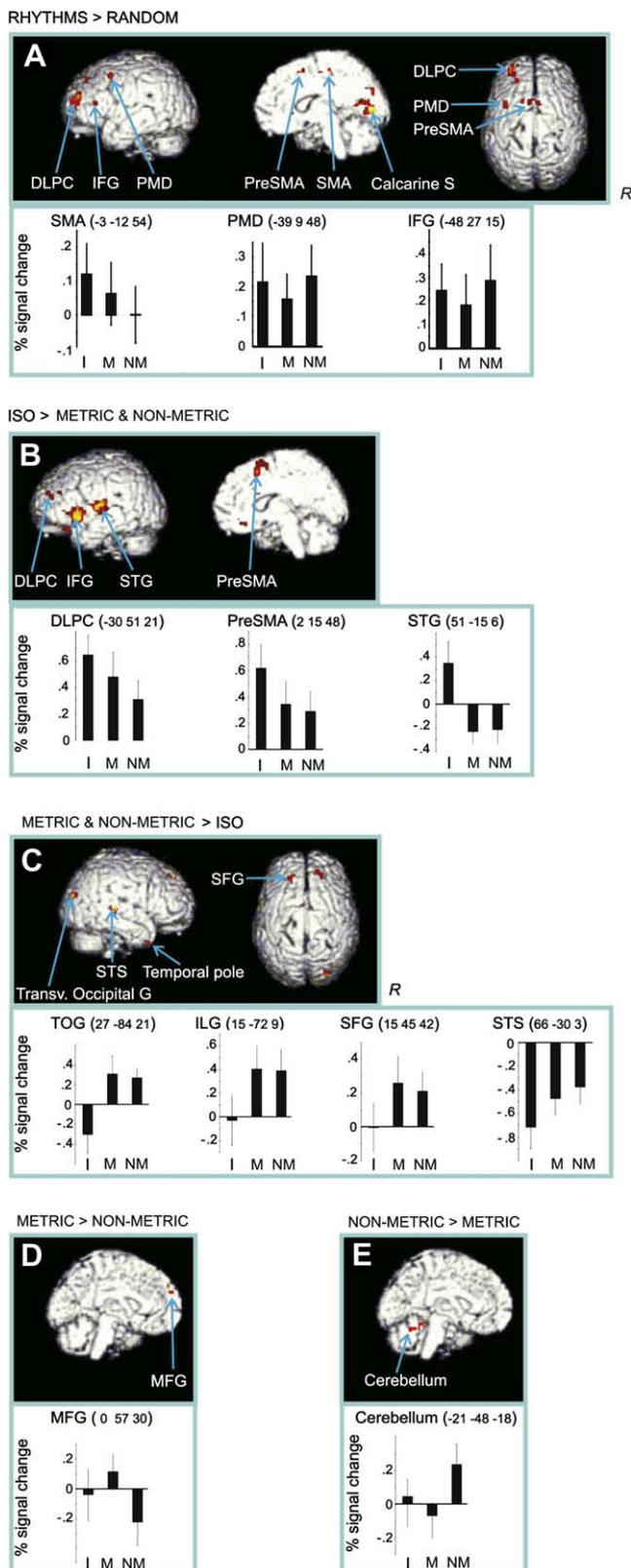


Fig. 2 – Brain activation patterns as shown by the analyses. The bar diagrams illustrate the percent BOLD-signal change for each rhythm relative to RAN. I: isochronous rhythm, M: metric rhythm, NM: non-metric rhythm. (2A and B) Brain areas involved in the perception of regular, in contrast to random temporal sequences, were the

response. There were two main findings: firstly, motor and premotor cortices, as well as cerebellum, were active when participants listened to rhythms. That these activations reflected stimuli prediction, was supported by the observation that several of these areas showed parametrical modulation as a function of stimuli predictability. Secondly, the rhythm sequences METRIC and NON-METRIC activated largely the same network as did ISO, with additional recruitment of superior prefrontal and visual areas.

That areas involved in motor preparation were also involved in rhythm perception suggests that the rhythm perception automatically engages prediction mechanisms that are used for the preparation of motor behaviors. From earlier studies it is known that the classical motor areas pre-SMA, SMA and PMD are important for temporal motor preparation. For example, in monkeys, cells in SMA and preSMA areas discharge in temporal preparation to motor elements in sequences (Shima and Tanji, 2000), and PMD processes sensorimotor prediction of external cues (Kurata et al., 2000). Similarly, preSMA and PMD activation increases during motor timing learning, i.e., the better you get at predicting the stimuli in time (Ramnani and Passingham, 2001). That the brain predicts forthcoming sensory events as well, and that this prediction activates motor areas, have been suggested in previous studies (although these included motor responses; Schubotz and von Cramon, 2002, 2004). One theoretical model to why this is so, would be that the brain engages in ‘motor simulation’ (Jeannerod, 2001), i.e., makes associations to goal-directed movement. This is a specialized form of sensory prediction. For example, motor areas become activated during observation (Rizzolatti et al., 1996) or listening (Kohler et al, 2002) to goal-directed actions. Motor simulation could be automatically triggered by rhythmic auditory stimuli since movements are innately strikingly rhythmic (Forsberg, 1985). Alternatively, which we would argue is the most parsimonious interpretation of the present results since the stimuli were not easily associated with real-life movements, the activation of premotor and motor cortices reflect temporal sensory prediction, i.e., ‘sensory preparation’. A shared neural substrate for temporal sensory prediction and motor timing would fit well with the documented correlations in performance between timing production and perception (see Section 1). Our finding suggests why humans spontaneously synchronize movements with auditory rhythmic stimuli (e.g., dancing) (Sameroff, 1967). An increased activation in motor cortex during listening would lower the threshold for executing a movement.

pre-supplementary and supplementary motor areas, the dorsal premotor area, and the dorsolateral area 10. (DLPC: dorsolateral prefrontal cortex; IFG: inferior frontal gyrus; PMD: dorsal premotor cortex; SMA: supplementary motor area; preSMA: pre-supplementary motor area). (2C) We found the superior prefrontal cortex, as well as occipital and temporal areas involved in the perception of rhythmic patterns of several interval durations. (SFG: superior frontal gyrus; TOG: transverse occipital gyrus; ILG: inferior lingual gyrus; STS: superior temporal sulcus). (2D and E) There was a difference between metric and non-metric rhythms in the cerebellum.

Table 1B – ISO > METRIC & NON-METRIC

Location	Side	X	Y	Z	Z-value	Single contrast t-values	
						ISO-METRIC	ISO-NM
<i>Frontal lobe</i>							
Middle frontal gyrus (area 10)	L	-36	48	24	3.4	3.37	3.42
	R	39	48	21	3.5	2.33	3.61
Middle frontal gyrus (area 46)	L	-33	33	24	3.3	1.91	3.42
Middle frontal gyrus pars triangularis (area 45/46)	L	-45	30	3	3.2	2.18	2.34
	R	42	33	12	3.4	4.31	2.02
Inferior frontal gyrus pars opercularis	R	60	3	15	3.3	3.30	1.96
Superior frontal sulcus	R	21	12	63	4.0	3.32	2.94
Superior frontal gyrus (PreSMA)	M	6	15	54	4.0	1.84	3.82
Cingulate gyrus	M	-3	12	24	3.4	2.74	2.18
	R	12	21	30	3.1	2.74	2.25
<i>Limbic lobe</i>							
Post orbital gyrus	L	-24	21	-24	4.3	2.42	2.08
Short insula gyrus	L	39	9	-3	6.2	4.55	5.34
Long insula gyrus	L	39	-27	15	4.4	3.41	2.68
Circular insula sulcus	R	-42	9	0	5.0	3.95	3.80
Long insula gyrus	R	-39	-18	3	5.7	5.01	3.37
<i>Temporal and parietal lobe</i>							
Superior temporal gyrus (TE10)	L	-51	-15	6	4.6	2.72	3.01
	R	51	-15	6	4.5	3.41	3.58
Supramarginal gyrus	L	-60	-36	24	3.2	2.20	3.82
<i>Cerebellum</i>							
Lobule VIIIB	L	-30	-48	-42	3.2	2.77	2.07

Increased BOLD contrast signal of conjunction analyses performed over subjects. $p < .001$ uncorrected for multiple comparisons in clusters of at least five voxels. (1A) contrast: ((ISO)-(RAN)), [(METRIC)-(RAN)], [(NON-METRIC)-(RAN))]. (1B) Contrast: ((ISO)-(METRIC), [(ISO)-(NON-METRIC)]). (1C) Contrast: ((METRIC)-(ISO), [(NON-METRIC)-(ISO)]).

Area 10 and the interconnected region preSMA (Bates and Goldman-Rakic, 1993), as well as SMA, displayed a BOLD-signal pattern that reflected the temporal prediction of the stimuli by showing greater activity for the predictable rhythm sequences and more, a sequence dependent activation decreasing with sequence complexity (Fig. 2A and B). Thus, the stronger lateral prefrontal and preSMA activity during

isochronous rhythm perception could reflect that more precise sensory predictions are being formed during this type of simple, externally triggered rhythm. Indeed, it is well known that the prefrontal cortex plays a vital role in anticipating events. Prefrontal activation is observed in omission of auditory predictable stimuli (Raj et al., 1997), and in deviations from predictable musical contours (Trainor et al., 2002).

Table 1C – METRIC & NON-METRIC > ISO

Location	Side	X	Y	Z	Z-value	Single contrast t-values	
						METRIC-ISO	NM-ISO
<i>Frontal lobe</i>							
Superior frontal gyrus (area 9)	L	-18	45	42	3.2	2.58	2.06
	R	15	45	48	3.3	2.64	3.79
<i>Temporal lobe</i>							
Superior temporal sulcus	R	66	-30	3	3.7	2.02	3.04
Temporal pole	R	48	12	-39	3.5	2.86	3.18
<i>Occipital lobe</i>							
Transverse occipital gyrus	R	27	-84	21	3.9	3.50	3.58
Inferior lingual gyrus	R	15	-72	-9	3.3	3.20	2.74
Fusiform gyrus	R	33	-63	-6	3.3	3.03	3.07

Increased BOLD contrast signal of conjunction analyses performed over subjects. $p < .001$ uncorrected for multiple comparisons in clusters of at least five voxels. (1A) contrast: ((ISO)-(RAN)), [(METRIC)-(RAN)], [(NON-METRIC)-(RAN))]. (1B) Contrast: ((ISO)-(METRIC), [(ISO)-(NON-METRIC)]). (1C) Contrast: ((METRIC)-(ISO), [(NON-METRIC)-(ISO)]).

Table 1D – METRIC > NON-METRIC

Location	Side	X	Y	Z	t-Value
<i>Frontal lobe</i>					
Middle frontal gyrus	M	0	57	30	3.3
Increased BOLD contrast signal of second level subtraction contrasts between METRIC and NON-METRIC. $p < .002$ uncorrected for multiple comparisons in clusters of at least five voxels. The x, y and z give the Talaraich coordinates of the activity peak.					

Also, area 10 is more active during the anticipation to sensory stimuli than to the exposure of the stimuli itself (Carlsson et al., 2000), and in a similar area of the Macaque's brain, cell ensembles increase their firing in proportion to the predictability of reward outcome, as indicated by cues signalling various degrees of probability (Quintana and Fuster, 1999). This suggests that complexity is an important factor in modulating activity in many of the rhythm areas. It also suggests that the difference in complexity of our stimuli should be regarded as continuous, rather than a difference in category of rhythms.

Like the frontal motor cortices, right lateral cerebellum (lobule V) was responsive to rhythm sequences. Lateral cerebellum is reciprocally connected to premotor areas and SMA (Dum and Strick 2003). Cerebellum is regarded important for timing both in motor, sensory and cognitive domains (Ivry, 1996). Cerebellar patients have deficits in discriminating between temporal intervals, regardless of experimental instructions (Mangels et al., 1998), as well as deficits in motor timing (Ivry et al., 1988). Its importance for fine motoric interval timing has been demonstrated in several neuroimaging studies (e.g., Penhune et al., 1998; Ramnani and Passingham, 2001). However, the lateral cerebellum and the preSMA/SMA may not perform the same operation during rhythm perception, since these regions showed differences in their responses. Specifically, lateral cerebellum showed stronger activity during NON-METRIC rhythm perception compared to METRIC (Table 1E and Fig. 2E), and no such difference was observed in the pre/SMA. Since we matched METRIC and NON-METRIC in other aspects, we suggest that lateral cerebellum plays a role in timing functions required for processing highly complex intervals. Our result could either reflect that neuronal computations in cerebellum are critically needed for the estimation of temporal intervals with a non-integer ratio (Sakai

Table 1E – NON-METRIC > METRIC

Location	Side	X	Y	Z	t-Value
<i>Parietal lobe</i>					
Supramarginal gyrus	R	63	-15	21	3.3
<i>Cerebellum</i>					
Lobule V	L	-21	-48	-18	3.3
Lobule V	R	21	-48	-21	3.3
Increased BOLD contrast signal of second level subtraction contrasts between METRIC and NON-METRIC. $p < .002$ uncorrected for multiple comparisons in clusters of at least five voxels. The x, y and z give the Talaraich coordinates of the activity peak. * $p < .05$ corrected for multiple comparison (see Section 2).					

et al., 1999) or reflect an 'error-detection response' (Tesche and Karhu, 2000) in that the participants fail to establish a proper metric representation. In favor of the latter, cerebellum is put forward as a key structure for detection of the mismatch (error) between the predicted sensory signals and the actual sensory feedback (Wolpert and Miall, 1996; Blakemore et al., 1998). When asked to tap rhythmically, humans spontaneously produce metric rhythms (Essens and Povel, 1985). Thus, cerebellar networks may automatically predict metric interval ratios even when perceiving a non-metric rhythm sequence. Our results suggest a twofold role of lateral cerebellum: First, it supports the SMA and preSMA in the basic timing prediction of regular sensory stimuli. Second, it is involved in the processing of non-metric rhythm sequences.

Only a few additional areas are recruited when listening to the two complex rhythm sequences compared to the isochronous. The increased activation in the superior prefrontal area 9 in METRIC and NON-METRIC, in contrast to ISO (Table 1C, Fig. 2C), suggests this to be locus for the memory representation of complex rhythm sequences. The dorsal prefrontal cortex (incl. area 9) plays a role in the comparison of consecutive non-spatial stimuli within working memory (Petrides, 1995). During music perception and imagery of musical tunes, bilateral middle prefrontal cortex is active, with the suggested role of retrieving information from music semantic memory (Zatorre et al., 1996; Halpern and Zatorre, 1999). Given the established role of the prefrontal cortex in top-down control (Fuster, 2001; Miller and Cohen, 2001), the result supports models stipulating that the brain contains a higher-order representation of the complex rhythm sequence (Mangels et al., 1998; Lalonde and Hannequin 1999). The right superior temporal sulcus and occipital areas appear to assist this memory mechanism because they as well, showed stronger activity when listening to the rhythms with longer sequence. Area 9 has anatomical connections with the temporal and occipital areas in the primate's brain (Macko et al., 1982; Poremba et al., 2003). Likewise, connections between the superior temporal cortex and occipital areas have been demonstrated (Catani et al., 2003). The right temporal sulcus processes sound pattern memory (Samson and Zatorre, 1994; Colombo et al., 1989). Similar to the present finding, Zatorre et al. (1994) found right temporal lobe activation in concert with occipital activation (area 19) in a purely auditory task, when subjects were listening to pitch sequences. Possibly, this may be a consequence of the intrinsic amodal character of a rhythm sequence. Its structure can be specified regardless stimulus modality.

We found increased activity in the Heschl's gyrus in both hemispheres (Table 1B, Fig. 2B). Heschl's gyrus is associated with processing perceptual details of auditory stimuli, rather than the meaning of it (Binder et al., 2000; Wong et al., 2008). We observed high activation for ISO and RAN. Once the auditory stimuli create a meaning, activation in higher-order areas are increased. For example, musicians activate the inferior prefrontal cortex, an area involved in language processing, when tapping the main meter as opposed to the counter meter (Vuust et al., 2006). Organizing sounds into meaningful patterns puts load on working memory and, therefore, interaction with frontal lobes areas are often observed when people listen to music (Zatorre et al., 2002). The less activation of the

Heschl's gyri for METRIC and NON-METRIC, could be because of a compensatory enhanced activation in the prefrontal cortex. A recent finger-tapping study showed that the more pronounced metric structure in the rhythm sequence, the stronger was the interaction between the Heschl's gyrus and the superior prefrontal gyrus (Chen et al., 2006).

In conclusion, a principal finding of the present study is that the perception of auditory rhythms is associated with activity in areas outside the classical auditory system of the temporal lobe. These include both areas that appear to be primarily involved in stimulus prediction – such as the lateral and mesial premotor areas, as well as regions specifically involved in analyzing the temporal structure of the stimulus sequence. The latter group includes superior prefrontal, occipital, temporal, and cerebellar areas. Hence, the complexity of rhythm sequences is an important factor in modulating the brain activity in many of the rhythm areas. However, the differences in complexity of our stimuli should be regarded as continuous. A natural next step would be to compare perception of rhythms presented in different modalities to more fully investigate how general this pattern of brain activation is for rhythm perception. Of particular interest is the activation of the areas previously observed in motor timing tasks, indicating that the brain uses a common mechanism for timing perception and production. This provides important information on how the brain represents time in that it supports models of a common network of brain areas processing temporal information (Treisman, 1963; Keele et al., 1985) and contradicts models advocating modality specific and task-specific timing networks.

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