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Cerebellar Contributions to Motor Timing: A PET Study of Auditory and Visual Rhythm Reproduction

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Abstract

■ The perception and production of temporal patterns, or rhythms, is important for both music and speech. However, the way in which the human brain achieves accurate timing of perceptual input and motor output is as yet little understood. Central control of both motor timing and perceptual timing across modalities has been linked to both the cerebellum and the basal ganglia (BG). The present study was designed to test the hypothesized central control of temporal processing and to examine the roles of the cerebellum, BG, and sensory association areas. In this positron emission tomography (PET) activation paradigm, subjects reproduced rhythms of increasing temporal complexity that were presented separately in the auditory and visual modalities. The results provide support for a supramodal contribution of the lateral cerebellar cortex and cerebellar vermis to the production of a timed motor response, particularly when it is complex and/or novel. The results also give partial support to the involvement of BG structures in motor timing, although this may be more directly related to implementation of the motor response than to timing per se. Finally, sensory association areas and the ventrolateral frontal cortex were found to be involved in modality-specific encoding and retrieval of the temporal stimuli. Taken together, these results point to the participation of a number of neural structures in the production of a timed motor response from an external stimulus. The role of the cerebellum in timing is conceptualized not as a clock or counter but simply as the structure that provides the necessary circuitry for the sensory system to extract temporal information and for the motor system to learn to produce a precisely timed response. ■

INTRODUCTION

Speech and music rely on the perception and production of temporal patterns, or rhythms, as a vital part of their power to communicate. However, the way in which the human brain achieves accurate timing of perceptual input and motor output is as yet little understood. In this experiment, we used the reproduction of rhythmic sequences to examine the neural bases of temporal processing. The mechanisms underlying the encoding of temporal information from sensory stimuli are poorly defined in comparison with the large body of data that exists regarding encoding of other aspects of sensory information. Temporal perception in humans has been examined most commonly in the auditory modality, and deficits have been observed in patients with lesions in the auditory and association cortices of the temporal lobe (Milner, 1962; Peretz, 1990; Robin, Tranel, & Damasio, 1990). Control of motor timing has been linked to a number of motor structures, including the BG (O'Boyle, Freeman, & Cody, 1996; Rao et al., 1997), cerebellum (Ivry & Keele, 1989), and supplementary motor area (SMA) (Halsband, Ito, Tanji, & Freund, 1993). In an influential series of experiments, Ivry et al., (Ivry, 1993; Ivry & Keele, 1989; Ivry, Keele, & Diener, 1988) argued for central control of both perceptual and motor timing functions, mediated by the cerebellum. However, a number of studies have indicated that the BG may be involved in perceptual timing as well (Artieda, Pastor, Lacruz, & Obeso, 1992; Rammsayer, 1993). In the present study, we were interested in testing the hypothesized central control of temporal processing and in examining the roles of the cerebellum, BG, and sensory association areas. To do this we designed a PET experiment in which subjects reproduced rhythms of increasing temporal complexity that were presented in both the auditory and visual modalities. If timing is a central process, we predicted that the patterns of activation should be very similar for the two modalities. Further, we predicted that the cerebellum and/or BG would be preferentially involved in the more complex conditions for which temporal processing would be most important.

The neuropsychological literature on rhythm perception can be divided into two categories: (1) studies that examine the basic parameters of auditory timing, such as duration perception, gap-detection, and perception of temporal order, and (2) studies that use more complex, musical stimuli. Both types of temporal perception have

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been linked to the fine-grained temporal perception thought to be required for human speech, with the hypothesis that the left hemisphere would be dominant (Gordon, 1978; Robinson & Solomon, 1974). Support for this hypothesis has been inconsistent, whether from studies of basic parameters or specifically of musical stimuli. Data from studies of basic parameters have linked these functions to the auditory cortices of the temporal lobe (Efron, Yund, & Nichols, 1985; Milner, 1962; Sherwin & Efron, 1980) but have demonstrated no consistent lateralization to either the left or right hemisphere. The few studies that have examined visual temporal perception show equally inconsistent results for patients with left- or right-hemisphere damage (Efron, 1963; Swisher & Hirsh, 1972; Van Allen, Benton, & Gordon, 1966). Data from studies using more complex, musical stimuli have shown no greater agreement. Prior, Kinsella, and Giese (1990) and Peretz (1990) found left-hemisphere-damaged patients to be impaired in rhythm discrimination, whereas Kester et al., (1991) and Shapiro, Grossman, and Gardner (1981) found either right-hemisphere- or right- and left-hemisphere-damaged patients to be impaired. An important problem for the hypothesis linking left-hemisphere specialization for speech perception to temporal perception for rhythmic stimuli is that the relevant timeframes are quite different. The temporal information important for speech perception is usually in the tens-of-milliseconds range (Phillips, 1993), far briefer than a typical rhythmic pattern, which is in the hundreds-of-milliseconds range (Fraisse, 1974). Finally, interpretation of all of these results is often made difficult by the use of patient groups that have large or poorly described lesions.

More recently, investigators have examined the role of neural structures traditionally associated with motor control in the control of both perceptual and motor timing. Most of these studies use a simple tapping task in which subjects produce a series of isochronous (equal interval) finger taps, first in synchrony with a pacing stimulus and then continuing on their own. These sequences are clearly much simpler than a typical rhythmic pattern, but this paradigm has generated a number of important hypotheses. Ivry and colleagues have proposed a central role for the cerebellum in temporal processing based on a series of experiments in patients and normal controls. These studies make use of the simple tapping task, and analysis of performance is based on Wing and Kristofferson's (1973) two-process model of timed motor response that takes the total variance of the responses and divides it into two components, one attributable to motor implementation and the other to motor timing. In normal subjects, the timing component of variance was found to be similar across motor effectors, and this variance was correlated with subjects' performance on perceptual timing tasks (Keele, Pokorny, Corcos, & Ivry, 1985). This lead to the hypothesis of a central timing mechanism in the human brain. Then, in a series of experiments with patients, this function was linked to the cerebellum. First, patients with cerebellar damage showed increased variability in the timing component of the finger-tapping task, as well as showing decrements in discrimination of auditory intervals (Ivry & Keele, 1989). Similarly, cerebellar patients showed increased variability in discriminating the velocity of moving visual targets (Ivry & Diener, 1991). The presence of perceptual timing deficits is supported by Nichelli, Alway, and Grafman (1996), who found that patients with cerebellar atrophy had increased thresholds for auditory duration discrimination. In a second experiment, Ivry et al., (1988) reported evidence that patients with damage to the lateral cerebellar hemispheres show increased variability in the timing component of the tapping task in comparison to patients with damage to central cerebellar regions, who showed increased variability on the motor implementation component of the task. This finding was given some support by a recent PET study comparing motor and perceptual timing (Jueptner et al., 1995). Taken together, these results point to cerebellar involvement in motor timing and in perceptual timing across modalities.

Other investigators have produced evidence for the possible involvement of the BG in both motor and perceptual timing. A recent functional magnetic resonance imaging (fMRI) study showed evidence of BG involvement in the continuation portion of the simple tapping task (Rao et al., 1997). O'Boyle et al., (1996) found that patients with Parkinson's disease showed specific decrements in the timing component of the finger-tapping task. Conversely, in the same study that showed cerebellar patients to be impaired on this task, Ivry and Keele (1989) found no changes in either the timing or motor implementation in a group of Parkinson's patients. Artieda et al., (1992) found that such patients showed decrements in temporal discrimination thresholds for auditory, visual, and somatosensory stimuli. Finally, Rammsayer (1993) administered haloperidol, a dopamine antagonist active in the BG, to normal subjects and found decrements in their performance for discrimination of brief auditory intervals (50 to 98 msec).

The data reviewed above indicate the possible participation of at least three different neural systems in some aspect of perceptual or motor timing. The association cortices of the temporal lobe are implicated in auditory temporal perception, and the cerebellum and/or BG may be important for both perceptual and motor timing. Although data regarding the cerebellum and BG point to a supramodal mechanism controlling motor and perceptual timing across modalities, data from studies in auditory temporal perception suggest the involvement of sensory-specific regions. The present experiment was designed to test the hypothesized central control of temporal processing and to examine the contributions of each of these candidate regions to this function. An advantage of PET activation studies over brain lesion

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studies is that, for a given task, the involvement of multiple brain areas can be assessed rather than that of the lesioned area alone. This makes PET studies well suited to examining the contributions of different brain structures to what may be a distributed function.

The Present Experiment

The task in the present experiment was based on previous studies in which normal subjects perceived and reproduced short auditory and visual rhythms (Glenberg & Jona, 1991). Three sets of rhythmic sequences were created for each modality at increasing levels of temporal complexity, along with a perceptual baseline. The four conditions were: (1) perception of isochronous sequences (BASE), (2) perception and reproduction of isochronous sequences (ISO), (3) perception and reproduction of a repeated sequence (REP), and (4) perception and reproduction of a series of novel sequences (NOV). Figure 1 illustrates the stimulus sequences as well as the mode of response. The sequences were all six elements long and were composed of short and long elements separated by a constant interstimulus interval (ISI). In the auditory conditions the elements were tones, and in the visual conditions the elements were white squares that appeared sequentially at the same location in the center of a computer monitor. In the BASE and ISO conditions, the sequences were composed of either all short or all long elements (see Figure 1, top panel). In the REP and NOV conditions, sequences were composed of both short and long elements, and were constructed to be equally complex (see Figure 1, middle panel). In all conditions, each sequence was followed by a pause. In the active conditions (ISO, REP, and NOV), subjects were asked to reproduce the sequences during the pause by tapping on a single key of the computer keyboard, "as if you were tapping on a piano."

Data were analyzed using a paired-image subtraction technique (Raichle, Martin, Herscovitch, Mintun, & Markham, 1983) designed to allow the examination of differences in cerebral blood flow (CBF) among the various task conditions. In each subtraction, the appropriate modality-specific baseline was compared to the active condition. Reproduction of the sequences at the lowest level (ISO − BASE) was expected to reveal CBF changes related to production of a simple timed motor response, excluding those related to perceptual input. In this subtraction, very similar regions of activation were predicted for the auditory and visual conditions in accordance with the hypothesized supramodal control of timing. The second subtraction (REP − ISO) was expected to reveal CBF differences in the cerebellum and/or BG related to production of a complex timed motor response, without involving a significant working memory load. In the third subtraction (NOV − REP), reproduction of a series of novel sequences was de-

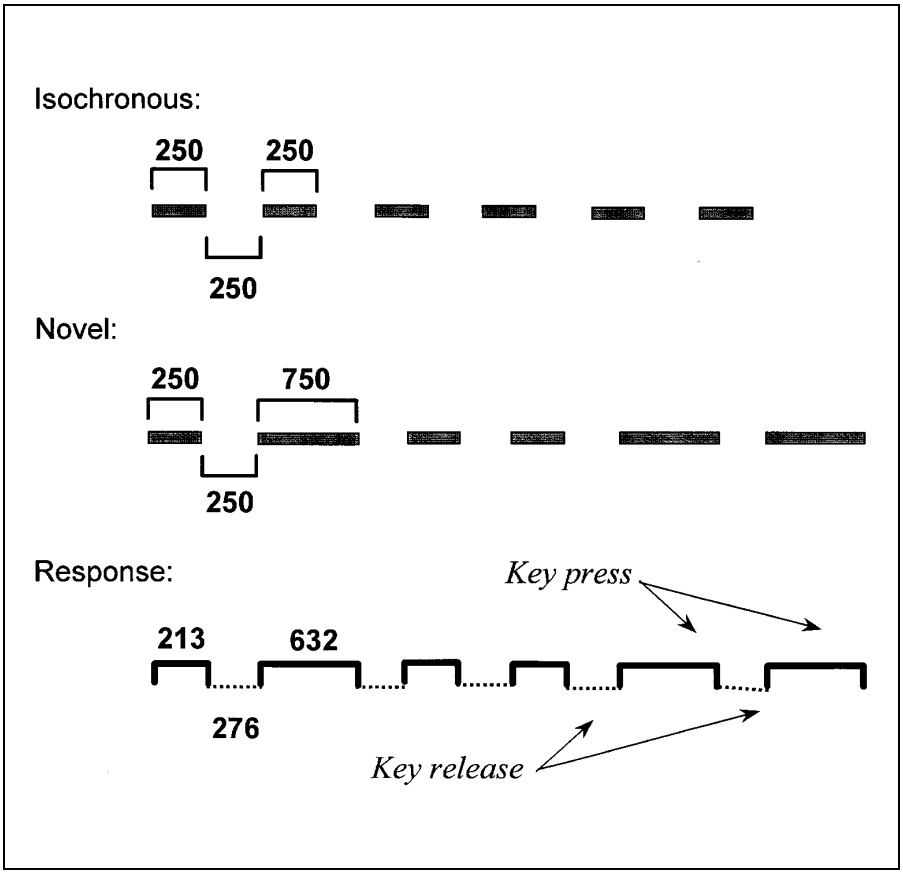

Figure 1. The top panel illustrates the temporal structure of the short isochronous sequences. The middle panel gives one example of the type of sequence used in the REP and NOV conditions. The bottom panel illustrates the keypress and keyrelease response performed by the subjects. All durations are measured in milliseconds.

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signed to place greater demands on neural timing mechanisms. Additional changes in the cerebellum and/or BG were predicted, as well as changes in regions related to modality-specific temporal working-memory processes.

RESULTS

Behavioral results

Subjects' keypress responses in the ISO condition were averaged across trials to generate an average short and long response for each subject. Paired *t* tests for the average and *SD*s of all responses across modalities showed that only the average long responses differed, with the auditory longer than the visual (Auditory: Avg. short = 218 ± 36 msec, Avg. long = 632 ± 94 msec; Visual: Avg. short = 235 ± 37 msec, Avg. long = 532 ± 84 msec; $t(11) = 4.3$, $p < 0.001$). For the REP and NOV conditions, each subject's performance was scored by using their average short and long responses from the ISO condition ± 2 *SD* as the upper and lower limits for correct response. Performance in the REP and NOV conditions was scored as percent correct at each of the six positions in the sequence (see Figure 2). In the REP condition, analysis of variance (ANOVA) revealed a significant interaction of position and modality ($F(5, 55) = 4.95$; $p < 0.001$), largely as a result of two subjects who tended to lengthen their short responses in both modalities. These

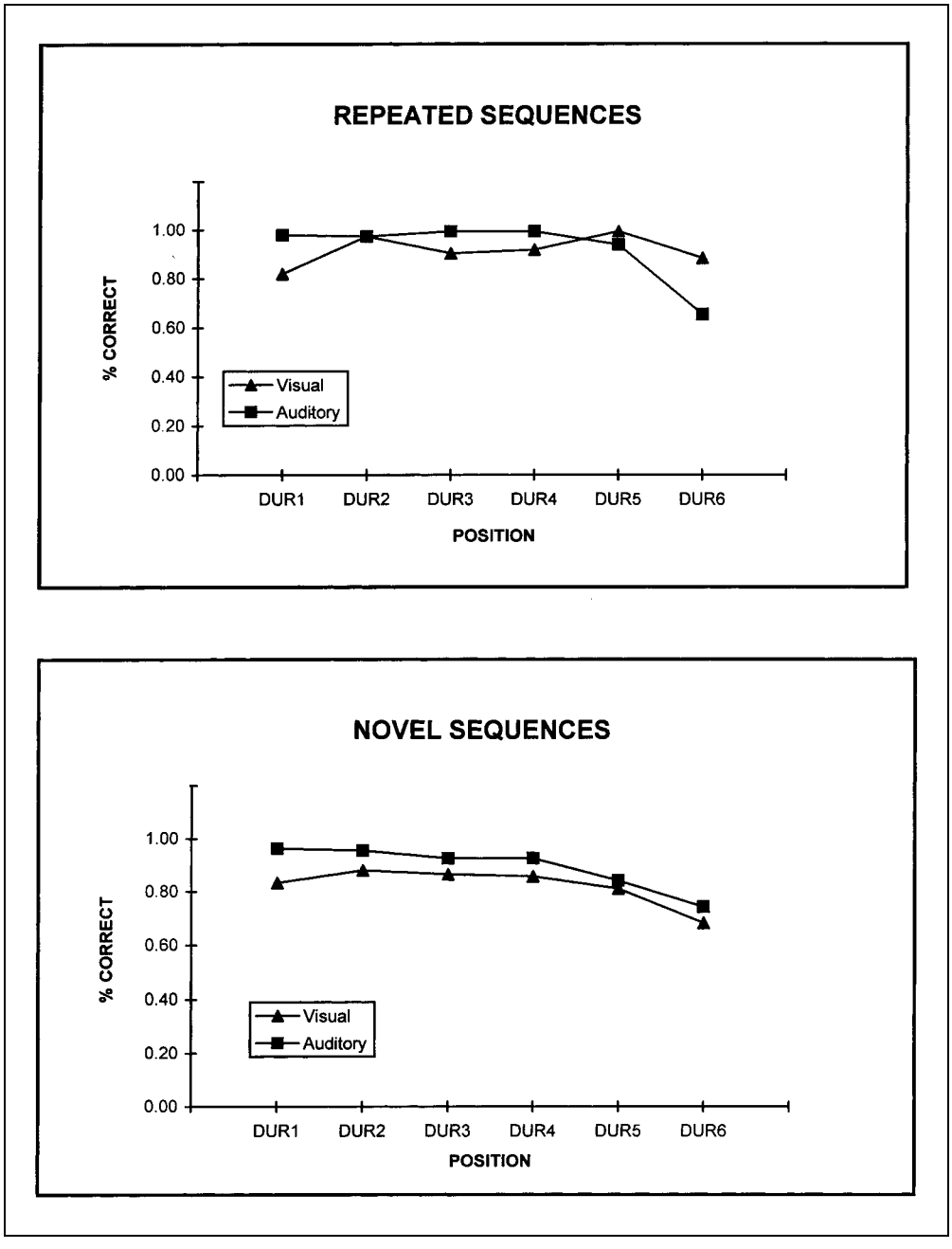

Figure 2. The top graph shows the average percent correct for all subjects across each serial position for the sequences in the REP conditions. The bottom graph illustrates the same information for subjects' performance in the NOV conditions.

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responses were clearly distinguishable as short in comparison with their long responses but fell outside of the ±2-*SD* cutoff. In the NOV condition, ANOVA revealed an effect of position but no difference in the pattern of performance between modalities ($F(5, 50) = 14.68$; $p < 0.0001$; $F(1, 10) = 4.04$; $p < 0.72$. Note that behavioral data for only 11 subjects were included in this analysis due to technical problems). Because no consistent differences in performance were observed between the two modalities, any modality-specific differences in CBF can be related to the modality of sensory input rather than to a global difference in task difficulty.

PET results

ISO − BASE

This subtraction was designed to reveal CBF changes specifically related to production of a simple timed motor response, while excluding those related to perceptual input. Although common regions of activation were observed for the two modalities in motor output areas, distinct, modality-specific regions of activation were also observed. Most importantly, in the visual condition there was activation of the left lateral cerebellar cortex, contralateral to the hand performing the motor response and in the cerebellar region proposed by Ivry et al., (1988) to be preferentially involved in timing. Modality-specific patterns of activation were observed for both conditions in the frontal and temporal lobes. Overall, in this experiment, regions of decreased CBF did not yield consistent patterns of results and will not be discussed, although locations of negative peaks are reported for all subtractions.

For both modalities, the ISO − BASE subtraction (see Figure 3 and Table 1) revealed CBF increases in the contralateral primary motor (M1) and primary sensory (S1) areas, regions directly related to motor output and somatosensory feedback. Activations were also seen in left globus pallidus (GP), the primary output nucleus of the basal ganglia system. Cerebellar peaks were localized using an on-line, MRI-based stereotaxic atlas (Schmahmann et al., 1996). An additional increase common to both modalities was observed in the ipsilateral anterior lobe of the cerebellum in paravermal lobules V/VI, a region identified through anatomy and physiology as the anterior somatomotor hand region of the cerebellum (Snider, 1950; Woolsley, 1952). This region has also been found to be active in other PET studies using tasks involving movements of the hand or fingers (Grafton, Woods, & Mazziotta, 1993; Sadato et al., 1996). Together, these cortical and subcortical areas form part of well-known neural pathways subserving voluntary motor response. CBF increases unique to the auditory modality were observed in the right superior temporal gyrus in the region of the planum temporale (PT), in the right parietal lobe (area 40) and in left frontal polar cortex (area 10). CBF increases unique to the visual modality were observed in two regions of right ventrolateral frontal cortex (areas 47/11 and 44/45), in the right superior temporal sulcus (STS), in left anterior insular cortex, and in left lateral cerebellar cortex (Crus Ia). Thus, contrary to our prediction, the lateral cerebellar cortex was active in the simple timed motor task but only for the visual condition.

REP − ISO

This subtraction was designed to reveal changes in CBF related to motor timing, excluding changes related to basic motor response. However, very few regions of CBF increase or decrease were observed for either modality (see Table 2). An additional region of cerebellar activation was observed in the left paravermal region for the visual condition only. The fact that so little additional activation was observed in this subtraction may be related to the stage of learning of the sequences the subjects had attained in both conditions. In PET activation studies of motor skill learning, Jenkins, Brooks, Nixon, Frackowiak, and Passingham (1994) have observed decreasing cerebellar activation with learning, and Doyon, Owen Petrides, Sziklas, and Evans (1996) have shown that the cerebellum is involved in the acquisition of a motor sequence, but not in its performance during the final, overlearned phase. It may be that because learning was at a similar stage for both the ISO and the REP conditions, no differential cerebellar involvement was observed for the auditory condition.

NOV − REP

This subtraction was designed to reveal changes in CBF related to reproduction of a series of complex temporal sequences, excluding changes related to production of a familiar timed motor response. Because the sequences in the NOV and REP tasks were of similar rhythmic complexity, and contained the same number of elements and because the same number of sequences were performed during the period of the scan, the observed changes should be related to the timing demands of the task rather than to changes in the rate or complexity of motor output.

In this subtraction, the only areas of activation common to both modalities were found in the anterior and posterior cerebellar vermis and bilaterally in the lateral cerebellar hemispheres (see Figure 3, panel C and Table 3). The increases in the vermis were within millimeters of each other in the two modalities, and the increases in the lateral cortices were all within Crus I of the posterior lobe (see Table 3). These results are broadly consistent with the cerebellar timing hypothesis, confirming that both the lateral and the vermal regions of the cerebellum are important for the production of a timed motor response.

For the visual condition, modality-specific increases in

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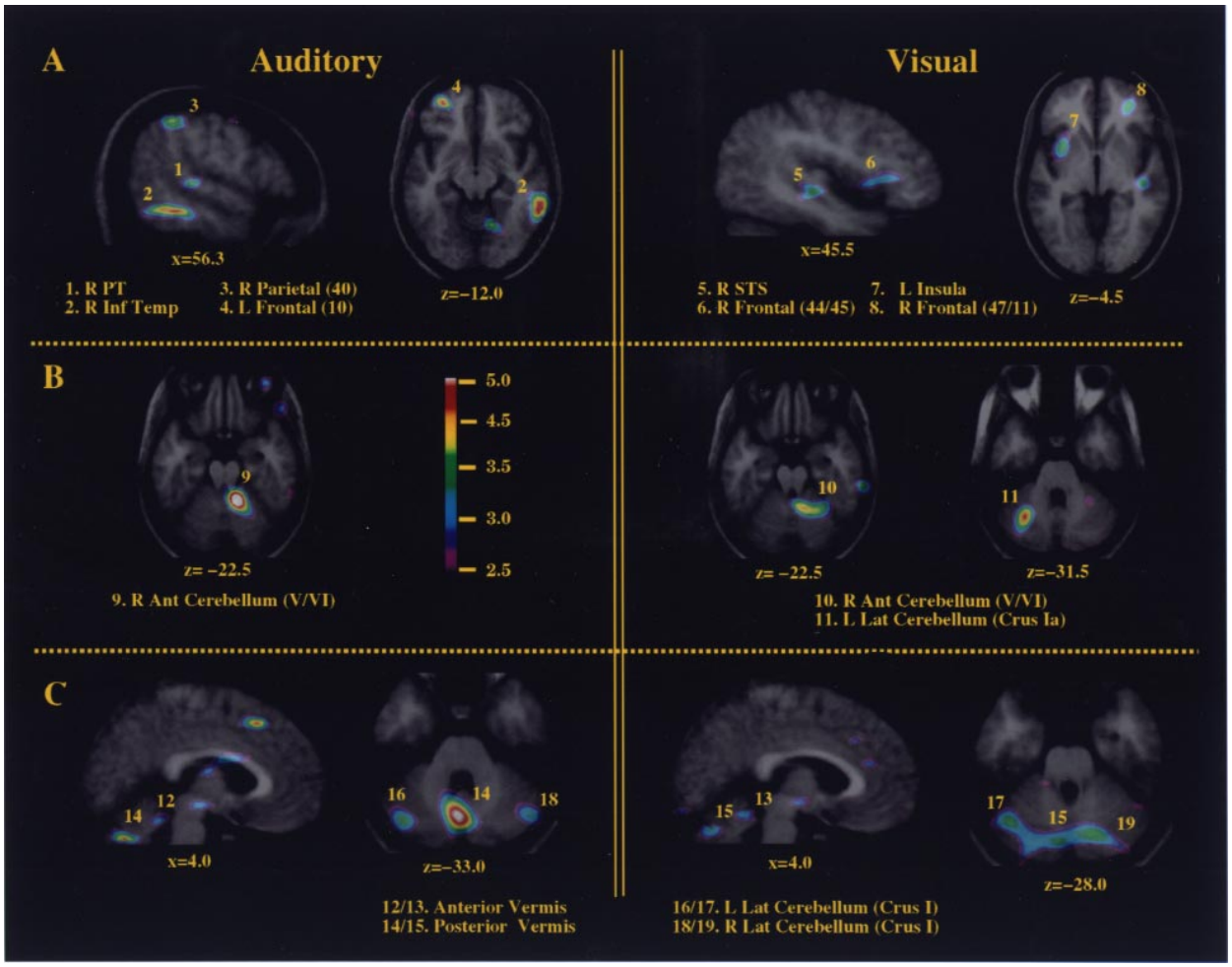

Figure 3. *Z*-statistic maps of significant ($z \geq 3.5$) CBF increases are presented in representative slices overlaid on the averaged MRI for all 12 subjects. All slice levels are given in the standardized stereotaxic space of Talairach and Tournoux (1988). Numbered activations are identified in bold in Tables 1, 2, and 3. Data for the auditory modality are presented on the left and the visual modality on the right. Panel A illustrates significant modality-specific CBF increases found in the ISO − BASE subtractions in sagittal (left) and horizontal (right) slices. Panel B illustrates significant CBF increases in the cerebellum for the same subtractions (horizontal slices). Panel C illustrates the four common sites of CBF increase in the cerebellum found in the NOV − REP subtractions in sagittal (left) and horizontal (right) slices.

CBF were again observed in the ventrolateral frontal cortex, in the same region (area 47/11) observed in the ISO − BASE subtraction, perhaps indicating increased demands on working memory retrieval mechanisms. Increased CBF was also observed in the right insular cortex, the anterior cingulate, and VA/VL nucleus of the thalamus. In the auditory condition, CBF increases were observed in the SMA and red nucleus and bilaterally in the putamen.

DISCUSSION

The results of this experiment reveal a supramodal contribution of the lateral cerebellar cortex and cerebellar vermis to the production of a timed motor response, particularly when it is complex and/or novel. These results are generally consistent with the findings of Ivry and Keele (1989), and Ivry, Keele, and Diener (1988), showing involvement of both of these regions in timed motor response. However, the pattern of cerebellar activation across conditions supports its role in motor learning as well. These results are less consistent with regard to the involvement of BG structures in motor timing, perhaps indicating that their role is more directly related to implementation of the motor response than to timing per se. Finally, these data show clear, modality-specific participation of frontal- and temporal-lobe structures in the auditory and visual conditions.

In the ISO − BASE subtractions, activations in the right PT for the auditory condition and in the multimodal STS for the visual condition may represent modality-specific encoding in short-term memory. Single-unit recordings

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Table 1. Changes in CBF Observed for ISO–BASE Subtractions

Location	Auditory				Visual			
	X	*Y*	*Z*	*t* Value	*X*	*Y*	*Z*	*t* Value
Positive Changes								
Motor/Sensory								
L M1/S1	−38.9	−22.9	61.5	4.4	−50.9	−22.9	42.0	4.9
L MI/S1	−46.9	−16.0	42.0	3.9	–	–	–	–
SMA	−2.7	2.9	54.0	4.5	–	–	–	–
Globus Pallidus	−12.1	1.2	−7.5	4.5	−22.8	−7.4	7.5	3.4
L Red nucleus	–	–	–	–	−8.0	−22.9	−18.0	4.3
Cerebellum								
R paravermis (V/VI)	16.1	−59.0	−15.0	4.6	12.1	−48.7	−22.5	5.5
L Lateral (Crus la)	–	–	–	–	−29.5	−60.7	−31.5	4.7
Modality Specific								
R Planum Temporale	50.9	−29.8	4.5	4.4	–	–	–	–
R Inferior temporal gyrus (20)	60.3	−40.1	−13.5	4.7	–	–	–	–
L Frontal (10)	−30.8	54.5	−10.5	4.5	–	–	–	–
R Parietal (40)	52.3	−43.5	48.0	4.2	–	–	–	–
L Parietal (behind S1)	−44.2	−31.5	46.5	4.0	–	–	–	–
R Superior temporal sulcus	–	–	–	–	45.6	−22.9	−6.0	3.8
R Ventolateral frontal (47/11)	–	–	–	–	30.8	42.5	−3.0	4.0
R Ventrolateral frontal (44/45)	–	–	–	–	45.6	18.4	3.0	3.6
L Insula	–	–	–	–	−33.5	8.1	−4.5	4.0
	–	–	–	–	−38.9	8.1	3.0	3.5
Negative Changes								
L ventromedial temporal cortex	−40.2	−34.9	−24.0	5.6	−44.2	−55.6	−12.0	4.0
Anterior cingulate	1.3	−51.1	4.5	4.4	1.3	44.2	−10.5	4.2
Precuneus	5.4	−50.4	37.5	3.9	−1.3	−47.0	37.5	4.0
L ventrolateral frontal (47)	−33.5	−20.1	−16.5	5.1	–	–	–	–
Posterior cingulate	2.7	−36.6	45.0	4.6	–	–	–	–
L precuneus	−12.1	−53.8	52.5	3.5	–	–	–	–
R hippocampal gyrus	24.1	−24.6	−25.5	3.7	–	–	–	–
L Temporo-parietal (39)	−49.6	−64.2	15.0	3.6	–	–	–	–
L ventromedial temporal cortex	–	–	–	–	−33.5	−26.3	−25.5	4.7
L 19	–	–	–	–	−41.5	−71.0	−6.0	4.6
R 19	–	–	–	–	40.2	−71.0	22.5	4.6
R 19	–	–	–	–	37.5	−67.5	7.5	4.2
L 18	–	–	–	–	−21.4	−84.5	−12.0	4.1
L 18	–	–	–	–	−16.1	−90.0	0.0	4.0
R 18	–	–	–	–	29.5	−88.2	−9.0	3.6
R 18/19	–	–	–	–	21.4	−77.9	3.0	4.3
L middle frontal (8)	–	–	–	–	−29.5	27.0	49.5	3.6

in nonhuman primates have shown that cells in higher-order auditory and visual areas are active during short-term memory tasks (Colombo, D'Amato, Rodman, & Gross, 1990; Miller, Li, & Desimone, 1991). These activations are also consistent with the patient studies reviewed above that point to temporal-lobe involvement in temporal perception (cf. Milner, 1962; Robin et al., 1990; Swisher & Hirsh, 1972; Van Allen et al., 1966). Activation in the right PT is also consistent with other neuroimaging studies showing activation of auditory cortical areas when subjects are actively retaining or imagining auditory tonal sequences (Rao et al., 1997; Zatorre, Halpern, Perry, Meyer, & Evans, 1996). These data contrast with previous studies suggesting left-hemisphere specialization for rhythm processing (Peretz, 1990; Peretz & Kolinsky, 1993; Prior et al., 1990). Activation of the STS and the insula in the visual task could reflect cross-modal coding or recoding of the visual stimuli in the auditory modality. Both regions are considered to be regions of multimodal cortex receiving inputs from both auditory

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Table 2. Changes in CBF Observed for REP − Subtractions

Location	Auditory				Visual			
	X	*Y*	*Z*	*t* Value	*X*	*Y*	*Z*	*t* Value
Positive Changes								
L 18/19	−21.4	−74.5	1.5	4.0	–	–	–	–
L ventromedial temporal cortex	−32.2	−41.8	−22.5	3.6	–	–	–	–
R 17/18	–	–	–	–	24.1	−91.7	−6.0	4.3
L paravermis (VI)	–	–	–	–	−12.1	−64.2	−18.0	4.3
L M1/S1	–	–	–	–	−38.9	−17.7	57.0	3.8
Negative Changes								
Sub-callosal/gyrus rectus	−4.0	30.4	−12.0	4.8	–	–	–	–
L anterior-medial thalamus	−6.7	−7.4	9.0	4.0	–	–	–	–
L posterior parietal (40)	−41.0	−62.0	48.0	3.5	–	–	–	–
R Occipito-temporal (21)	–	–	–	–	52.3	−53.0	10.5	3.9

and visual association areas (Mesulam & Mufson, 1985; Petrides & Iversen, 1978; Seltzer & Pandya, 1978).

Regions of the inferior frontal cortex were also differentially activated in the two modalities, possibly representing specific working memory retrieval mechanisms. According to Petrides' (1994, 1995) multi-stage model of working memory, the ventrolateral frontal cortex is involved in active retrieval of sensory information held in short-term memory. He further hypothesizes that sensory information is held in short-term memory in modality-specific association areas or in multimodal regions of the posterior temporal and parietal cortex. Data from the ISO − BASE subtraction in the visual condition are consistent with this model in showing activation of right ventrolateral frontal area 47/11 together with multimodal association areas in the STS and insula. The additional right ventrolateral frontal activation in the visual condition for the NOV − REP subtraction may represent increased demands on frontal retrieval mechanisms. Data from the auditory condition are less clear, with activation in right auditory association cortex (PT) and in left frontal polar cortex (area 10). The specific role of the frontal polar cortex is not known, but it may participate in the frontal-lobe working memory system. Finally, differential activation of inferior frontal regions in the left and right hemispheres for the two conditions may be the result of different retrieval strategies.

The additional left cerebellar activations in the ISO − BASE and REP − ISO subtractions for the visual condition may reflect specific demands placed on the timing system by the visual task. At the neurophysiological level, variability of the afferent latency of visual stimuli has been estimated to be 10 times greater than that of auditory stimuli (Divenyi & Danner, 1977; Zacks, 1973). Further, when tapping in synchrony with isochronous sequences, subjects show greater variability for visual than for auditory stimuli (Kolers & Brewster, 1985). Greater variability in afferent latency may require additional, compensatory processing by the putative cerebellar timing mechanism in order to achieve accurate reproduction of the visual sequences. Although no significant differences in performance were observed between the two modalities, on subjective report, 10 of 12 of the subjects indicated that the visual condition was more difficult to perform. For this reason, the additional left lateral cerebellar activations observed in the visual conditions could be considered in the light of the effortfulness of performance. It is also possible that in the ISO − BASE subtraction, the left cerebellar activation in the visual condition might be related to the other modality-specific activations; both the ventrolateral frontal cortex and the STS are connected to cerebellum through the basis pontis (Schmahmann & Pandya, 1991, 1997). Thus the additional cerebellar activation observed in this condition probably reflects differential cerebellar involvement in production of the motor response from the visual stimulus rather than strictly visual processing.

Data from this study are less clear with regard to the role of the BG in timed motor response. Theories of BG function have hypothesized that these structures are important for movement sequencing (Graybiel, 1995) and/or selection of motor response (Marsden & Obeso, 1994; Mink & Thach, 1993). Such functions would appear to be integral to the performance of all of our experimental tasks. In the ISO − BASE subtraction, the left GP was active for both modalities, consistent with a role in simple timed motor output and consistent with fMRI data showing BG involvement in the continuation portion of the simple tapping task (Rao et al., 1997). Conversely, no activity was observed in the BG for the REP-ISO subtractions, and in the NOV − REP subtractions, the putamen was active only in the auditory condition. Perhaps because the same basic sequencing and response selection functions are required to perform each

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Table 3. Changes in CBF Observed for NOV − REP Subtractions

Location	Auditory				Visual			
	X	*Y*	*Z*	*t* Value	*X*	*Y*	*Z*	*t* Value
Positive Changes								
Cerebellum								
Anterior vermis - III/IV	8.0	48.7	−21.0	3.5	1.3	−50.4	−15.0	3.6
Posterior vermis - VIIIa/VIIb	−1.3	−69.3	−33.0	5.2	−8.0	−77.9	−28.5	3.8
R lateral - Crus Ia	18.8	−74.5	−27.0	3.5	21.4	−74.5	−27.0	4.5
L lateral - Crus Ia	–	–	–	–	−28.1	−77.9	−24.0	3.7
R lateral - Crus Ip	45.6	−65.9	−31.5	3.5	–	–	–	–
L lateral - Crus Ip	−37.5	−67.6	−30.0	4.3	−38.9	−62.4	−31.5	4.5
L lateral - Crus Ip	–	–	–	–	−22.8	−77.9	−28.5	3.5
Motor								
SMA	4.0	21.8	46.5	4.6	–	–	–	–
Anterior cingulate	–	–	–	–	−1.3	25.3	33.0	3.6
Basal ganglia								
L Putamen	−22.8	15.0	−1.5	4.2	–	–	–	–
R Putamen	26.8	16.7	−7.5	3.8	–	–	–	–
Brainstem								
Red Nucleus	−1.3	−19.4	−9.0	3.8	–	–	–	–
L Thalamus (VA/VL)	–	–	–	–	−18.8	−10.8	6.0	3.7
Other								
R Ventrolateral frontal (47/11)	–	–	–	–	17.4	28.7	−19.5	4.1
R Ventrolateral frontal (47/11)	–	–	–	–	21.4	44.2	−16.5	3.6
R Anterior insula	–	–	–	–	36.2	20.1	1.5	5.1
Negative Changes								
L ventromedial temporal cortex	−37.0	−47.0	−18.0	3.6	−44.0	−40.0	−21.0	4.0
L ventromedial temporal cortex	−48.0	−22.0	−25.0	3.5	−49.0	−31.0	−27.0	4.7
L ventromedial temporal cortex	–	–	–	–	−53.0	−41.0	−14.0	4.2
L Planum temporale	−49.0	−26.0	15.0	4.3	–	–	–	–
L Superior-temporal sulcus	−60.0	−24.0	−7.5	3.7	–	–	–	–
Precuneus	–	–	–	–	−4.0	−55.0	36.0	4.3
L S1	–	–	–	–	−40.0	−22.0	55.5	3.6

of the tasks, subtracting them from each other obscures underlying BG activity. This possibility is partially supported by activations in the putamen or GP in both modalities when the REP − BASE and NOV − ISO subtractions were performed, although these activations were not consistent across modalities. The interpretation that the BG are simply involved in sequencing and response selection does not, however, address data showing deficits in perceptual timing following either temporary or permanent impairment of the BG in humans (Artieda et al., 1992; Rammsayer, 1993). In a recent review, Ivry (1996) has incorporated a role for the BG into his theory of timing, suggesting that it may be involved in some aspect of timing not tapped by current tasks. The design of this experiment does not allow us to assess the purely perceptual component of timing or to distinguish response selection or motor sequencing from timing per se. Future studies directly contrasting these parameters for the same stimuli could shed further light on the differential roles of the BG and the cerebellum.

Although the results of this experiment can be interpreted as supporting cerebellar involvement in motor timing, they should also be examined in terms of other proposed domains of cerebellar function: motor learning, error detection, and sensory integration. Numerous studies in both animals and humans have linked the cerebellum to motor learning for both simple and complex movements (see Glickstein & Yeo, 1990; Thach, Goodkin, & Keating, 1992, for reviews). Thach (1996) and Thach et al. (1992) in particular have hypothesized that the basic function of the cerebellum is in the learning of motor "synergies," aggregations of simple movements that make up more complex behaviors. PET activation studies in humans have shown activation of the cerebellum during the early phases of motor skill learning

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(Doyon et al., 1996), with progressively less activation as learning proceeds (Grafton, Woods, & Tyszka, 1994; Jenkins et al., 1994; Van Mier, Perlmutter, Raichle, & Petersen, 1996). Viewed in this context, the results of this experiment are quite consistent with the hypothesized cerebellar role in motor skill learning. The strongest cerebellar activations in this experiment were observed in the NOV − REP subtractions, where reproduction of a well-learned sequence was subtracted from reproduction of novel sequences. In the NOV condition, reproduction of each sequence can be considered as the first trial of learning, and the observed increases in cerebellar activation could be related to the earliest phase of learning. Conversely, in the REP − ISO subtractions differential activation of the cerebellum was observed only in the visual condition. In the REP condition, the sequences were temporally complex, were learned over two to three trials (Avg. aud = 2.3; Avg. vis = 2.5) and then practiced to a criterion of six correct repetitions. In the ISO condition, the sequences were temporally simple and easily acquired and were practiced for six to eight trials prior to scanning. Because the sequences in the REP condition were more temporally complex than those in the ISO condition, if the primary contribution of the cerebellum is to motor timing, the REP − ISO subtraction should have shown strong cerebellar activation in both modalities. However, consistent with the learning hypothesis, additional cerebellar activation was observed only in the visual condition, presumably because subjects had similar amounts of practice on each task. The additional lateral cerebellar activation in the visual condition for both this subtraction and the ISO − BASE subtraction could then be interpreted as resulting from the relative unfamiliarity of making a motor response from the visual stimuli. Thus after similar amounts of practice, the cerebellum may still be required to make the motor response in the visual, but not the auditory, condition.

An alternative role for the cerebellum in motor learning has been described as that of a comparator or error detector. According to this theory, sensory feedback from a current movement allows the cerebellum to compare ongoing performance to an internal model and then to make corrections in force, trajectory, etc. In an fMRI study of skill acquisition in a visuomotor association task, Flament, Ellermann, Kim, Ugurbil, and Ebner (1996) showed that cerebellar activation was greatest during a random association condition in which no learning could occur but where many movement errors were made and corrected. Although this concept seems most relevant to acquisition of a motor skill that is detectably correct or incorrect on every trial, reproduction of the timed sequences in this experiment could be viewed as requiring on-line correction to compensate for slight deviations in production of durations or ISIs.

Based on studies of cerebellar connectivity, Bower (1995) and Bower and Kassel (1990) have argued that the primary function of the cerebellum is "coordinating the acquisition of sensory data," which then allows optimization of motor response. Consistent with this idea, a recent fMRI study showed greater activation in the cerebellar dentate nucleus when subjects performed tactile discrimination tasks compared to a simple motor task or somatosensory stimulation (Gao, Parsons, Bower, Xiong, & Fox, 1996). However, cerebellar involvement in sensory integration need not be antithetical to its involvement in timing functions or motor learning. Bower (1996) has recently argued that the lateral cerebellar cortex is relatively more important for sensory integration; part of this sensory integration might involve extraction of temporal parameters. This hypothesis would be consistent with Ivry et al.'s (1998) findings that patients with lateral cerebellar lesions are specifically impaired in motor timing and in temporal perception. Bower (1996) has also argued that the posterior cerebellar vermis may coordinate proprioceptive input from muscle stretch receptors that would then be used to optimize motor control. This could also be consistent with Ivry et al.'s (1988) findings that patients with central cerebellar lesions are more impaired on the motor implementation component of a tapping task. Further, Smith (1996) has hypothesized that cerebellar involvement in the production of complex movements may be based on its ability to regulate time-varying joint stiffness. Both coordination of proprioceptive information and precise control of joint stiffness would be necessary to accurately produce the timed motor responses required in the present experiment. Further, both of these functions would be vitally related to learning of motor synergies required to make a precisely timed response. Viewed in this way, the timing function of the cerebellum might be reconceptualized as an emergent property of sensory integration and motor learning. The cerebellum may act not as a clock or counter but simply as the structure that provides the necessary circuitry for the sensory system to extract temporal information and for the motor system to learn to produce the timed response.

CONCLUSION

The results provide support for a supramodal contribution of the lateral cerebellar cortex and cerebellar vermis to the production of a timed motor response, particularly when it is complex and/or novel. Examined in the light of several theories of cerebellar function, this experiment suggests that this structure may contribute in two ways: first, in computing the temporal parameters of incoming sensory stimuli and outgoing movements, and second, in learning novel, temporally precise motor responses. The role of the BG is less clear from this study, and consistent with other researchers (Graybiel, 1995; Marsden & Obeso, 1994; Mink & Thach, 1993), we hypothesize that it contributes most directly to the selec-

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tion and sequencing of motor responses. In addition, this experiment revealed that different regions of the sensory association cortex and ventrolateral frontal cortex were involved in encoding and retrieval of the auditory and visual temporal patterns. Taken together, these results point to the participation of a number of neural structures in the production of a timed motor response from an external stimulus. Future experiments directly comparing perceptual and motor timing which differentiated between response selection and response timing would provide explicit tests of these hypothesized functions.

METHODS

Subjects

The subjects in this study were 12 (6 male and 6 female) young right-handed normal volunteers (Avg. = 22.4 years; range = 20–30 years) selected to have a minimum of musical training or experience (Avg. = 2.6 years; range = 0–4 years). Subjects were drawn from the McGill University and Montreal area population, were paid for their participation, and gave informed consent. The experimental protocol was approved by the Ethics Committee of the Montreal Neurological Institute.

Stimuli and Task Conditions

The stimulus sequences constructed for each of the four conditions, BASE, ISO, REP, and NOV, are illustrated in Figure 1. All sequences were six elements long and were made up of short (250 msec) and long elements (750 msec) with a constant ISI (250 msec). The auditory elements were 3000-Hz tones with 0.05-msec rise and fall delivered binaurally over Eartone 3A insert earphones at 75 dB SPL (A). The visual elements were 2.5-cm white squares that appeared sequentially at the same location in the center of an NEC monitor positioned approximately 54 cm from the subject's eyes. Stimulus delivery and response collection were controlled by MAPLE software (Bregman, Achim, & Ahad, 1992) running on a 486/50 IBM-compatible computer. In the BASE and ISO conditions, the sequences were isochronous. In the REP and NOV conditions, sequences were complex and composed of both short and long elements. These sequences were constructed to be of equal difficulty: Each one had no more than three repeated elements and contained three transitions from short to long. These rules produce sequences that are temporally regular but do not conform to a simple musical beat pattern (i.e., they result in syncopated rhythms). In all conditions, each sequence was followed by a 6.5-sec pause, and in the active conditions (ISO, REP, and NOV), subjects were asked to reproduce the sequences during the pause by tapping with the index finger of the right hand on a single key of the computer keyboard.

Procedure

In each scanning session the four task conditions were performed in a fixed order: BASE, ISO, REP, and NOV, but the modality performed first was counterbalanced across subjects. In the auditory conditions, subjects kept their eyes closed. In the BASE conditions, subjects were simply instructed to pay close attention to the stimuli and made no response. Before beginning each of the ISO conditions, subjects were trained in the keypress response. They were instructed to imitate the sequences by matching the duration and order of the elements "as if you were tapping on a piano key." No auditory or visual feedback was given. Practice was given on three trials of the all-short and all-long sequences to be certain that the keypress was correctly used to imitate the durations, and that short and long keypresses were readily distinguishable. In all of the active conditions, the keypress and keyrelease durations were recorded by the computer (see Figure 1, bottom panel). During the ISO scans, subjects perceived and reproduced a pseudorandom series of all-short and all-long sequences. In the REP conditions, subjects were taught a single sequence (different in each modality) between scans by trial and error to a criterion of six consecutive correct reproductions. During the scans, they repeatedly perceived the same sequence and reproduced it. Before beginning each NOV condition, subjects were given practice with feedback on six sample novel sequences that were similar to those used during the actual scan. During the scans, subjects reproduced a series of novel sequences presented in random order. No feedback was given during the scan. In the BASE and ISO conditions, there were 10 sequences in total, with 5 or 6 occurring in the 60-sec scan. In the REP and NOV conditions, 12 sequences were presented, with 5 or 6 occurring during the period of the scan. The number of sequences perceived and reproduced, the number of finger movements, and the total stimulus energy in each modality was very similar (although not identical) across all task conditions.

Scan Acquisition and Analysis

PET scans were obtained with a Scanditronix PC-2048B 15-slice tomograph (intrinsic resolution = $5 \times 5 \times 6$ mm). The distribution of CBF was measured during a 60-sec scan using the O^{15}-labeled water-bolus method (Raichle et al., 1983). Magnetic resonance imaging (MRI) scans were obtained with a Philips Gyroscan ACS (1.5T), which produced 160 contiguous 1-mm sagittal slices (TR = 19 msec; TE = 10 msec; flip angle = 30°). CBF volumes were normalized to correct for differences in global CBF, coregistered with each individual's MRI scan (Woods,

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Mazziotta, & Cherry, 1993) and both were transformed into the standardized stereotaxic space of Talairach and Tournoux (1988) by means of an automatic feature-matching algorithm (Collins, Neelin, Peters, & Evans, 1994). The transformed CBF volumes were reconstructed with a 12-mm Hanning filter, averaged across subjects for each scanning condition, and differences in CBF between conditions of interest were assessed by paired-image subtraction. Subtraction of one condition from another resulted in a difference volume, which was then converted to a *t*-statistic map by dividing the mean CBF difference at each voxel by the mean standard deviation of normalized CBF across all voxels (Worsley, Evans, Marrett, & Neelin, 1992). *T*-statistic peaks were identified by an automatic algorithm with a threshold for significant peaks set at $z \geq \pm 3.5$. The transformed MRI scans were also averaged across subjects and merged with the *t*-statistic maps in order to examine the anatomical location of significant *t*-statistic peaks and to compare these locations with the Talairach atlas. Significant positive and negative peaks and their locations are reported in Tables 1, 2, and 3.

Because the Talairach atlas contains little information regarding the cerebellum, peaks in this region were localized using an on-line, MRI-based stereotaxic atlas of the cerebellar sulci developed at the Brain Imaging Centre at the Montreal Neurological Institute (Schmahmann et al., 1996). Probabilistic MRI-based maps of gray-matter volumes of the cingulate gyrus and PT were used to assist in localizing activations in these regions (Paus et al., 1996) and (Westbury, Zatorre, & Evans, 1996). Such maps allow the location of peaks to be assessed in comparison with a sample of normal subjects rather than with a single subject as in the Talairach atlas.

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