

Cerebro-cerebellar Interactions Underlying Temporal Information Processing

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Abstract

■ The neural basis of temporal information processing remains unclear, but it is proposed that the cerebellum plays an important role through its internal clock or feed-forward computation functions. In this study, fMRI was used to investigate the brain networks engaged in perceptual and motor aspects of subsecond temporal processing without accompanying coprocessing of spatial information. Direct comparison between perceptual and motor aspects of time processing was made with a categorical-design analysis. The right lateral cerebellum (lobule VI) was active during a time discrimination task, whereas the left cerebellar lobule VI was activated during a timed movement generation task. These findings were consistent with the idea that the cerebellum con-

tributed to subsecond time processing in both perceptual and motor aspects. The feed-forward computational theory of the cerebellum predicted increased cerebro-cerebellar interactions during time information processing. In fact, a psychophysiological interaction analysis identified the supplementary motor and dorsal premotor areas, which had a significant functional connectivity with the right cerebellar region during a time discrimination task and with the left lateral cerebellum during a timed movement generation task. The involvement of cerebro-cerebellar interactions may provide supportive evidence that temporal information processing relies on the simulation of timing information through feed-forward computation in the cerebellum. ■

INTRODUCTION

Where and how is temporal information processed in the brain? Before answering this question, the timescale of interest should first be defined. The neural underpinnings for subsecond (tens to hundreds milliseconds), “interval” (seconds to hours), and circadian timing (hours to days) seem to differ (Buhusi & Meck, 2005). Of these timescales, the neural mechanisms of subsecond time processing, despite being fundamental to many important forms of cognitive, linguistic, and motor behaviors, are most poorly understood.

The cerebellum (Mangels, Ivry, & Shimizu, 1998; Nichelli, Alway, & Grafman, 1996; Ivry, Keele, & Diener, 1988) and the BG (Rammsayer & Classen, 1997; O’Boyle, Freeman, & Cody, 1996; Rammsayer, 1993; Artieda, Pastor, Lacruz, & Obeso, 1992; Pastor, Jahanshahi, Artieda, & Obeso, 1992) are the strongest candidates for subsecond and seconds-to-hours timings. Ivry (1996) has suggested that the cerebellum and the BG are preferentially involved in subsecond timing and seconds-to-hours timing, respectively. Nevertheless, how the cerebellum contributes to subsecond-range time processing remains controversial. Previously, the centralized “internal clock” model was predominant (Treisman, 1963). More recently, it has been suggested

that feed-forward timing prediction underlies time processing in the cerebellum (Mauk & Buonomano, 2004).

Subsecond time processing has at least two major roles in the generation and guidance of behavior: motor timing, which contributes to production of timed movements, and perceptual timing, which analyzes the temporal structure of incoming stimuli. To assist in the generation of accurately timed movement, the cerebellum may predict the time point at which the sensory outcome of movement should be perceived. During this process, the cerebellum is considered to compute virtual timing information that can be compared with timing of sensory inputs resulting from actual movement (Miall, Weir, Wolpert, & Stein, 1993; Kawato & Gomi, 1992; Ito, 1970).

Feed-forward computation may also serve perceptual processing of temporal information. Schubotz (2007) suggests that perceptual timing could be achieved through feed-forward mechanisms subserved by the lateral premotor cortex. Another possibility is that the cerebellum might serve feed-forward computation. If this is the case, it would be important to ask if the cerebellum exercises the timing function alone or in collaboration with other areas. Considering its homogenous microcircuitry and uniform computational function (Doya, 1999; Voogd & Glickstein, 1998), the cerebellum probably achieves various cognitive and motor functions through the cerebro-cerebellar interactions (Allen & Tsukahara, 1974). An updated model proposes that temporal information processing may be

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mediated by a “controller” that sends an output command to an “emulator” for feed-forward prediction (Grush, 2004). Moreover, this theory suggests that temporal information processing for both motor and sensory behaviors might be achieved by the same set of the controller and the emulator. Although the neural correlates of the controllers and emulators are not established yet, it is suggested that the cerebellum and the cerebral cortical areas might serve as the emulators and the controllers, respectively.

Recently, O’Reilly, Mesulam, and Nobre (2008) showed that the cerebro-cerebellar interactions were involved in the prediction of spatiotemporal events by using a functional connectivity analysis. This landmark study indicated that the lateral premotor–parietal cortical areas might serve as the controllers of spatiotemporal events. Another strong candidate for the presumptive cerebral time controller is the SMA, which is implicated in both motor and perceptual timing (Jantzen, Oullier, Marshall, Steinberg, & Kelso, 2007; Jahanshahi, Jones, Dirnberger, & Frith, 2006; Bengtsson, Ehrsson, Forssberg, & Ullen, 2005; Coull, Vidal, Nazarian, & Macar, 2004; Ferrandez et al., 2003; Lewis & Miall, 2003; Kawashima et al., 2000; Rao et al., 1997) as well as temporal organization of movements (Shima & Tanji, 1998). In a recent monkey neurophysiology study, it was clearly demonstrated that temporal information in the range of seconds was coded by neurons in the anterior section of the SMA (pre-SMA; Mita, Mushiake, Shima, Matsuzaka, & Tanji, 2009). Based on these lines of evidence, we built a hypothetical model in which the SMA served as a time controller and the cerebellum as an emulator (Figure 1). This model is consistent with a concept that common neural networks should serve both motor

and sensory timing processes (Rubia & Smith, 2004). In this study, we hypothesized the SMA to be the central time controller because the timing paradigm did not involve coprocessing of spatial information. It is repeatedly shown that the lateral premotor and SMA are important for spatial and nonspatial information processes, respectively (Tanaka, Honda, & Sadato, 2005).

The present fMRI study investigated brain activity during subsecond time processing, which is thought to have neural mechanisms unique to this timescale (Mauk & Buonomano, 2004). A 2×2 factorial design was used to incorporate both motor and sensory timing tasks. Ample evidence indicates that the cerebellum plays an important role in both motor and sensory timing processing. In the present experiment, we also assumed that the cerebellum might serve as an emulator interacting with cerebral time controllers, presumably the SMA (see Figure 1). The possible cerebral time controllers were explored with a functional connectivity analysis using timing-specific cerebellar activity as a seed.

METHODS

Subjects and Imaging Procedure

Fourteen healthy subjects (4 women, 10 men; age range = 24–31 years) gave written informed consent to participate. All subjects were right-handed on the Edinburgh Handedness Inventory (mean laterality quotient = 94.9; range = 79–100; Oldfield, 1971). Procedures were approved by the institutional review board. Functional images were acquired using a 3-T whole body scanner equipped with an

Figure 1. A hypothetical schema representing control mechanisms for temporal information processing applicable to both motor and sensory timing. It is assumed that the SMA serves as a time controller, which sends a signal of temporal information to the controlled object as well as to the emulator in the cerebellum. In motor timing tasks, temporal information is sent from the controller to the sensorimotor system and also to the emulator in the cerebellum. The emulator predicts the temporal consequence of the movement. Temporal error between the actual and the predicted temporal consequences could be used to re-calibrate motor commands (feedback error learning). The “measurement inverse” calculates what control signal will be required to correct the error. In the sensory timing tasks, the temporal information is sent from the controller to the emulator, and the predicted timing is compared with the real timing of the incoming stimulus from the sensory system.

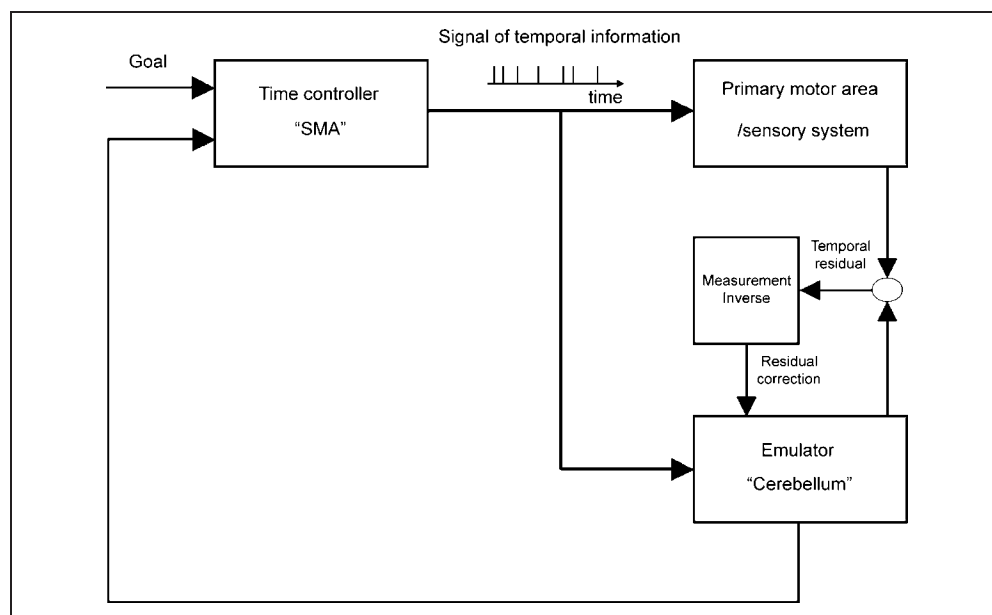
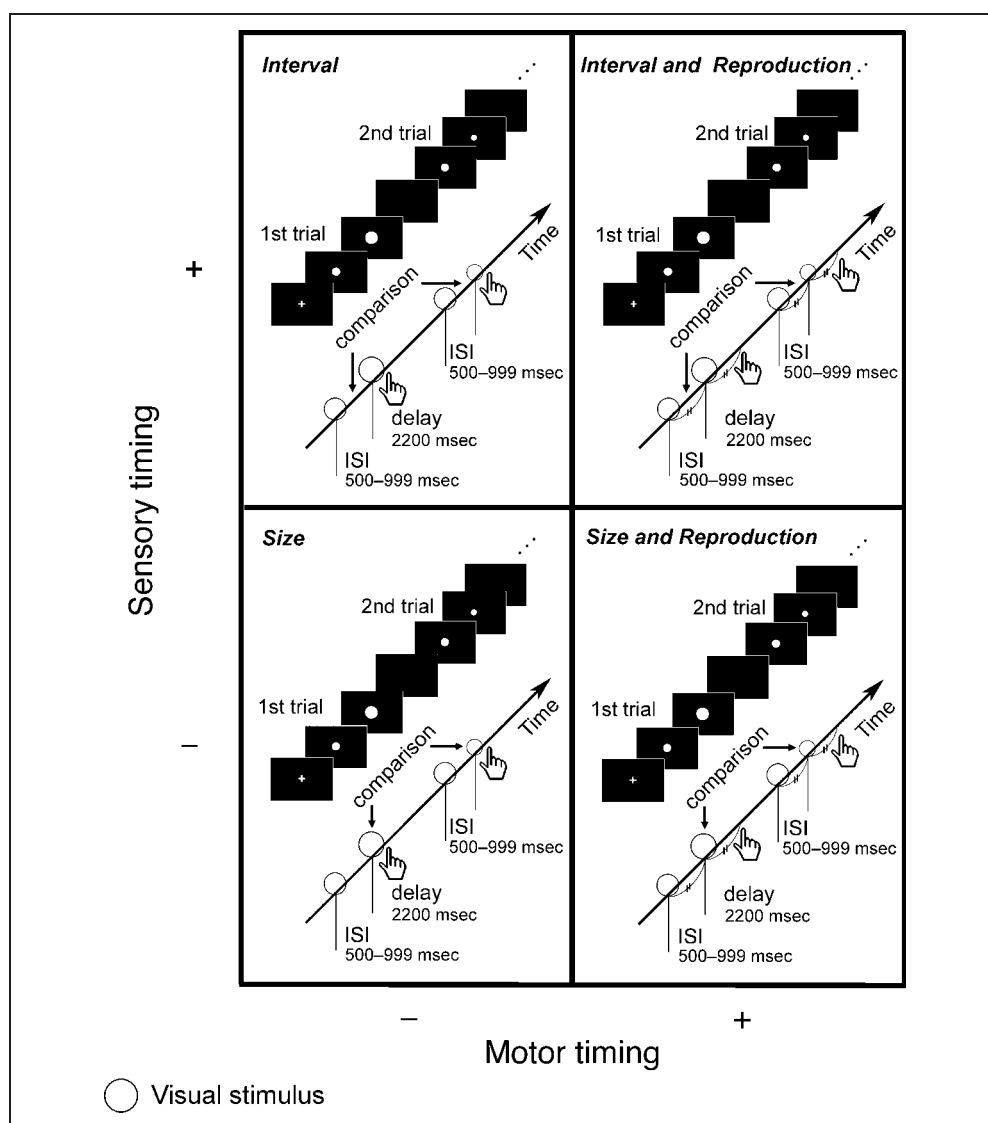


Figure 2. Schematic overview of the activation tasks. In the size condition, subjects indicated whether the diameter of the second circle of each stimulus pair was smaller or larger than that of a previous pair. In the interval condition, subjects indicated whether the interval of the paired stimuli was shorter or longer than that of the previous pair. In the size and reproduction condition, subjects reproduced the interval of the paired stimuli to report the result of size discrimination. In the interval and reproduction condition, subjects reproduced the interval of the paired stimuli to indicate the result of interval discrimination.



8-channel phased array head-coil (Siemens Trio, Erlangen, Germany) as a series of T2*-weighted, gradient-echo, EPI volumes (repetition time = 2.75 sec, echo time = 30 msec, flip angle = 90°, 64 × 64 matrix, 44 slices, field of view = 192 mm, thickness = 3 mm). The first two scans were not saved to allow for T1 equilibrium effects. In addition, high-resolution T1-weighted anatomical images were acquired for each subject (3D-MPRAGE-sequence, repetition time = 2000 msec, echo time = 4.38 msec, flip angle = 8°, 240 × 256 matrix, 208 slices, field of view = 225 × 240 mm, thickness = 1 mm).

Stimulation and Behavioral Task

Visual stimuli were rear projected onto an opaque screen attached to the head coil from a digital light processing projector (resolution = 800 × 600 pixels). The visual stimuli were displayed in white at the center of view against a black uniform background. Subjects were placed in a supine position on the scanner bed with their head sup-

ported and partially stabilized by foam pads and looked at the screen through a mirror attached to the head coil. Response buttons were placed under the index and the middle finger of the right hand.

Each subject underwent two imaging runs. The condition order was pseudorandomized so that the same condition was not repeated in succession. Each imaging run lasted for 805 sec (293 images) and contained four repetitions of the four main experimental tasks and a sensorimotor control task in a block design. The experimental tasks were size, interval, size and reproduction, and interval and reproduction (Figure 2). Each imaging run (805 sec) started with a rest period for 5 sec and included 20 cycles of the alternating task and rest period (40 sec in total). A task period started with an instruction stimulus presented for 2 sec (e.g., “interval discrimination and timed response”), followed by a 5-sec delay period. Then, the subjects consecutively underwent eight task trials for a period of 22 sec. During a low-level baseline (11 sec), the subjects fixated onto a crosshair. Essentially, the same

visual stimuli were used for all the four experimental conditions; hence, the task condition was differentiated only by the instruction stimulus.

For all the trials, two filled circles (each for 50 msec) were serially presented. The trials were separated by a constant intertrial delay period of 2200 msec. In the control condition, the diameter of the circles was always 30 pixels (ca. 2.1° visual angle), and the ISI between the two circle presentations was fixed at 750 msec. The subjects were asked to press a button under the index finger as soon as possible after the appearance of the second circle. In the four experimental conditions, the diameter of the first circle was fixed at 30 pixels, but that of the second circle was varied trial by trial. The diameter of the second circle in each trial was increased or reduced by more than 20% of that in the preceding trial, within the range of 20–40 pixels (ca. 1.4 – 2.8° visual angle). In a similar manner, the ISI in each trial was increased or reduced by more than 25% of that in the previous trial, within the range of 500–999 msec. In the size condition, the task was to focus on the diameter of the second circle in each trial and to judge whether it was smaller or larger than that in the previous trial. As the size of the first circle was always the same, the subjects were expected to encode the size of the second circle relative to that of the first circle. In the size trial, therefore, they encoded the size information of the second circle (perhaps, as a ratio of the second circle size relative to the first circle size) in a trial, maintained it until the next trial, and then compared the two sets of size information over the successive trials. In the interval condition, subjects judged whether the ISI in the current trial was shorter or longer than that in the previous trial. Thus, they needed to encode ISI information in a trial, maintain it until the next trial, and compare the two sets of ISI over the successive trials. For the behavioral responses in these two conditions, the subjects pressed a button with the index or middle finger, indicating smaller (shorter) or larger (longer) as soon as possible after the second circle appearance (i.e., choice RT [CRT]). In the size and reproduction and interval and reproduction conditions, a timed delay response (TDR) was required instead of CRT. In the size and reproduction condition, therefore, the subjects not only discriminated the circle size but also encoded the ISI in a given trial. The subjects reported their judgment about size discrimination by a button press at the time point when they estimated that elapsed time (from presentation of the second circle) matched the ISI of the trial. That is, the participants were asked to make a delayed response in which latency was equal to the ISI in a given trial (TDR-type response). In the interval and reproduction condition, the subjects performed the discrimination of ISI and reported their judgment about temporal discrimination by using a TDR-type response. In all the four experimental conditions, subjects were required to make judgment about information (size or ISI) in a trial always in reference to the information in

the previous trial. Therefore, subjects were free to press any button after the second circle presentation in the first trial of the blocks as a reference was not available yet. The subjects were extensively pretrained outside the scanner to be familiarized with the behavioral tasks.

Image Processing and Data Analysis

Imaging data were analyzed using statistical parametric mapping software (SPM5, <http://www.fil.ion.ucl.ac.uk/spm>) implemented in MATLAB (Mathworks, Sherborn, MA). The functional volumes were spatially realigned to the first scan of the first run and were spatially normalized to the EPI template in the Montreal Neurological Institute space. Spatial smoothing was applied to the normalized functional volumes using a Gaussian kernel of 10-mm FWHM.

We used a two-staged procedure for obtaining population-level statistical inference by assuming that the subjects were randomly sampled from the population. At the first level, the time series data from each subject were analyzed separately with a general linear model. Regressors were created by convolving the canonical hemodynamic response function and its first time derivative with a boxcar function modeling the task effects. Low-frequency drifts were removed by applying a high-pass filter (cutoff = $1/512$ Hz). Correction for serial correlations was omitted as a second-level analysis was used in the present study. Global scaling was applied to the functional data to normalize activity across subjects and different scanning days. For each subject, the size of task effects was estimated by using linear contrasts of interest after the model fitting. The summary images of the effect size were then subjected to the second-level analysis using a one-sample *t* test.

We first tested condition-specific effects by contrasting each activation condition to the control condition. We next examined the main effects of the motor timing (TDR versus CRT) and the sensory timing (ISI vs. size discrimination) modeled in a 2×2 factorial design. The main effect of the motor timing was defined as [(Interval and Reproduction + Size and Reproduction) – (Interval + Size)], and that of the sensory timing was defined as [(Interval and Reproduction + Interval) – (Size and Reproduction + Size)]. The effects of [(Interval and Reproduction – Interval) – (Size and Reproduction – Size)] and [(Size and Reproduction – Size) – (Interval and Reproduction – Interval)] were tested to confirm any interaction effects produced by the combination of the task components. Activities were considered to be significant if they passed a false discovery rate (FDR) threshold of $p < .05$ corrected for whole brain voxels. We also reported activations at a threshold of $p < .001$, uncorrected, and at an extension level >30 voxels as nonnegligible effects. The cerebellar atlas was used for anatomical localization and nomenclature (Schmahmann et al., 1999).

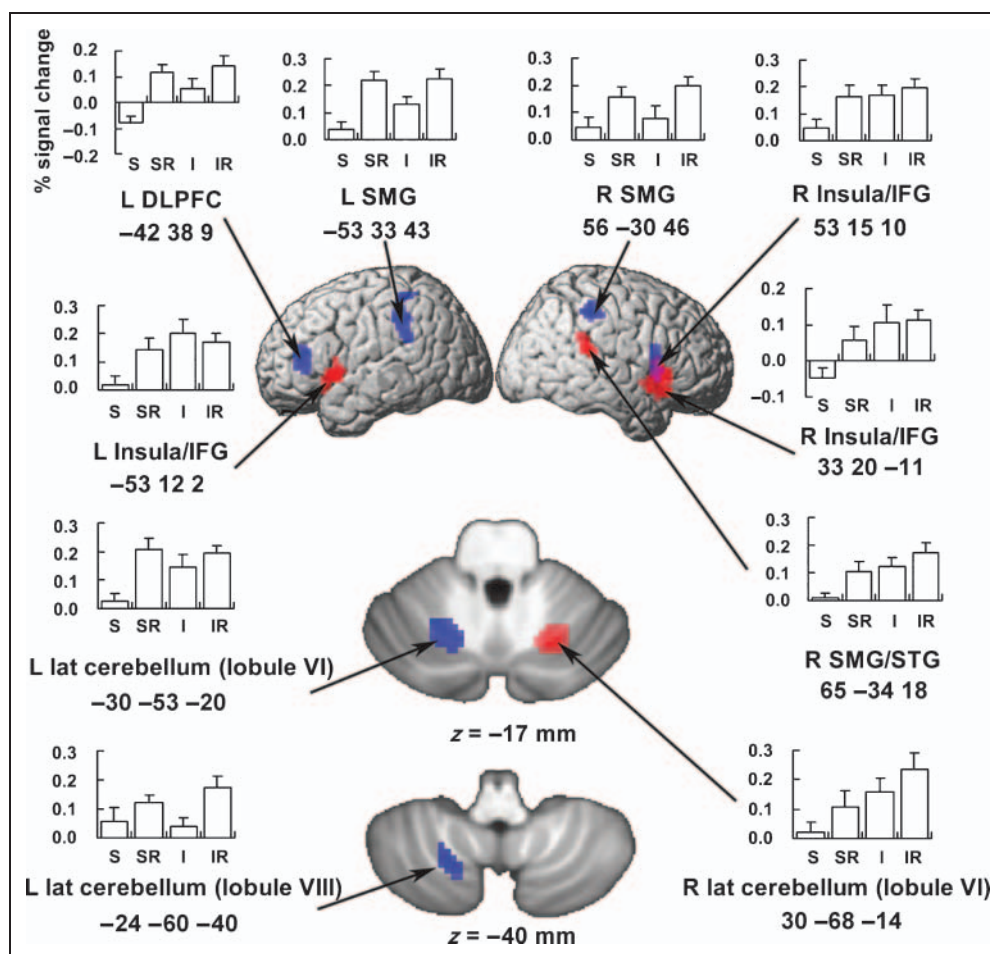
To test whether cerebellar time modules are functionally coupled with cerebral areas during the timing tasks, a psychophysiological interaction (PPI) analysis was conducted.

This analysis tests to what extent neuronal responses in each voxel can be explained by the interaction between influences from a given brain area (seed) and cognitive processing (Friston et al., 1997). For this analysis, we used an inclusion mask to limit the search volume to the whole cerebrum. In the PPI analysis for the sensory timing, the significantly activated cerebellar cluster from the main effect of the sensory timing was defined as a VOI for the PPI seed. Three regressors were used for creating a new general linear model in the PPI analysis. The regressors represented the psychological factor (interval and reproduction and interval vs. size and reproduction and size), the time course of the right cerebellar VOI (physiological factor), and the interaction between the two (PPI). The PPI regressor was built as follows. Original neuronal activity was estimated by hemodynamic deconvolution of the signal time course of the cerebellar VOI. The product of the estimated neuronal activity and the psychological factor was reconvolved with the canonical hemodynamic response function. The PPI analysis was carried out for each subject, and the effect size images were subjected to a second-level analysis. In essence, the PPI for the sensory timing tested whether there are any brain regions that showed increased functional connectivity with the right cerebellum during ISI judgment as compared with that

during size judgment (see Results). Similar procedures were applied to the left lateral cerebellum (VI; Table 2), which was significantly activated in the main effect of the motor timing. The PPI for the motor timing tested the functional connectivity between the left lateral cerebellum and other brain regions during the TDR tasks (interval and reproduction and size and reproduction) relative to that during the CRT tasks (interval and size).

The PPI effects were first tested separately for the motor timing and sensory timing in the whole cerebrum at a threshold of $p < .05$ (FDR corrected). A liberal threshold of uncorrected $p < .001$ was used to report a non-negligible trend for activation. In this analysis, we were especially interested in testing the hypothesis about the “cerebral time controllers” shared by both motor and sensory timing functions (see Figure 1). We hypothesized that if the same cerebral time controller sent commands to the motor and sensory timing emulators in the cerebellum, then the time controllers should be detected as a shared region by two independent PPI analyses using motor timing-specific and sensory timing-specific cerebellar activities, if any, as seeds. In practice, as we were able to identify the right cerebellar activity specific to sensory timing and the left cerebellar activity specific to motor timing (see Figure 3), we searched an overlap of two

Figure 3. Areas demonstrating main effects for motor timing and sensory timing. Activation maps during motor timing and sensory timing are colored in blue and red, respectively, and are superimposed on a surface-rendered brain viewed from the left, right (top), and on the axial slices of cerebellum templates (middle, bottom). The bar graphs show the mean \pm SEM percent signal change for the four conditions averaged across the cluster and subjects. DLPFC = dorsolateral prefrontal cortex; IFG = inferior frontal gyrus; SMG = supramarginal gyrus; STG = superior temporal gyrus; L = left; R = right; lat = lateral; S = size; SR = size and reproduction; I = interval; IR = interval and reproduction.



PPI analyses by setting seed ROIs in these cerebellar activities.

Finally, a small volume correction (SVC) was applied to each PPI analysis on the basis of the hypothesis that the SMA is the best candidate for a time controller without accompanying spatial information processing. There is evidence that the SMA is implicated in both motor and perceptual timing (Jantzen et al., 2007; Jahanshahi et al., 2006; Bengtsson et al., 2005; Coull et al., 2004; Ferrandez et al., 2003; Lewis & Miall, 2003; Kawashima et al., 2000; Rao et al., 1997) as well as temporal organization of motor sequences (Shima & Tanji, 1998) and auditory/phonological information (Chein & Fiez, 2001). Moreover, bidirectional anatomical pathways between this region and the lateral cerebellum have been reported (Sakai, Inase, & Tanji, 1999; Jurgens, 1984). A 15-mm radius spherical VOI was set up to cover the SMA by using the center coordinate of $x = -3$ mm, $y = -9$ mm, and $z = 56$ mm from a previous imaging study reporting SMA activity during an internal timing task (Rao et al., 1997). Considering that the BG are implicated in timing processing and they have anatomical connection with the dentate nucleus of the cerebellum (Hoshi, Tremblay, Feger, Carras, & Strick, 2005), the BG and the lateral cerebellum could be functionally connected during the present timing tasks. Therefore, the BG were also tested with the SVC method in the PPI analyses. The VOIs for the BG were defined anatomically and included the caudate nuclei, the putamen, and the globus pallidus bilaterally. Significance of the SVC-corrected PPI analysis was determined at a threshold of $p < .05$ FDR corrected for multiple comparison limited within the search volume.

RESULTS

Behavioral Data

Discrimination accuracy was very high in all of the four activation conditions (96.7%, 93.5%, 93.6%, and 94.7% for size, size and reproduction, interval, and interval and reproduction, respectively). A repeated measures ANOVA showed no significant difference in the discrimination accuracy across these four conditions, $F(3, 39) = 2.75$, $p > .05$. Response times were 433 ± 74 and 490 ± 115 msec (mean \pm SD) for size and interval, respectively. A two-tailed paired t test showed that the response time was significantly longer in the interval than that in the Size, $t(13) = 3.72$, $p < .01$, indicating that the interval task may have been more challenging than the size task. Precision of the TDR was first assessed by a correlation analysis between the TDR latency and the target ISI. The result indicated significant correlation in both the size and reproduction ($r = 0.43$, $p < .05$) and interval and reproduction ($r = 0.70$, $p < .05$). Secondly, absolute error of the TDR latency from the target ISI was calculated. Absolute errors were 27.35 ± 64.56 and 39.69 ± 61.42 msec (mean \pm SD) for size and reproduction and interval and reproduction, respectively. There was no significant difference in the

absolute error between these two conditions (a two-tailed paired t test), $t(13) = 1.46$, $p > .05$. The ratios of the TDR latency to the target ISI were 1.07 ± 0.09 and 1.07 ± 0.08 (mean \pm SD) for the size and reproduction and the interval and reproduction, respectively. The ratio did not differ significantly between these two conditions (a two-tailed paired t test), $t(13) = 0.07$, $p > .05$. These analyses suggest that performance of our subjects for generating TDR was comparably precise between the size and reproduction and the interval and reproduction conditions.

Brain Activity

Activated brain regions were first identified in each task condition relative to the sensorimotor control condition. The four task conditions induced a similar pattern of activation in the bilateral cortical and subcortical regions, which consisted of the dorsolateral prefrontal cortex (DLPFC), the medial frontal regions including both the pre-SMA and the SMA, the lateral premotor area, the inferior and superior parietal lobules, the anterior insula, the BG (caudate nucleus), the cerebellar vermis, and the lateral cerebellum (Table 1).

No interaction effects were found when the effects of the type of comparison (size or ISI) and the response (CRT or TDR) on fMRI activity were analyzed on the basis of the categorical design. This analysis indicates that the dual performance of motor and sensory timing tasks (interval and reproduction task) induced no additional activation compared with that elicited by the size and reproduction task. No interactions also suggested that divided attention to two stimulus properties (both size and ISI) in the size and reproduction task added no extra activation to that produced by the interval and reproduction task. The analysis of the main task effects revealed neural components associated with the motor timing component (TDR > CRT) or the sensory timing component (ISI comparison > size comparison; Figure 3, Table 2). Motor timing-related brain activity was found in the right insula/inferior frontal gyrus (IFG), the bilateral supramarginal gyrus (SMG), the left DLPFC, and the left lateral cerebellum (lobule VI and VIIIA). Sensory timing-related brain activity was observed in regions including the bilateral insula/IFG, the right SMG/superior temporal gyrus (STG), and the right lateral cerebellum (lobule VI). It may seem that the right lateral cerebellum could be involved in motor timing as well (see the graph in the Figure 3). However, the main effects of the motor timing were not significant in the right lateral cerebellum ($t = 1.74$, FDR-corrected $p = .46$). Although we had a hypothesis about the role of the SMA as a “cerebral time controller,” the categorical analysis unexpectedly failed to show the SMA activity for either motor timing or sensory timing. In fact, the SMA was commonly and highly activated in all the experimental conditions relative to the sensorimotor control condition. The failure to find SMA activity in the categorical analysis was primarily ascribed to substantially high SMA activity in the size only condition

Table 1. Areas Activated during Each of the Four Conditions Relative to the Sensorimotor Control

	<i>S > C</i>			<i>t</i>	<i>SR > C</i>			<i>t</i>	<i>I > C</i>			<i>t</i>	<i>IR > C</i>			<i>t</i>
<i>Cerebellum</i>																
Declive (lobule VI)																
L	-21	-60	-27	4.19	-27	-59	-20	4.95	-21	-60	-27	6.53	-45	-51	-28	8.37
R	45	-59	-22	4.39	27	-54	30	7.18	36	-57	-25	8.96	30	-54	-25	6.84
Pyramis (lobule VIIIA)																
L	-27	-66	-40	5.68	-27	-66	-42	6.46	-24	-69	-39	7.05	-24	-66	-40	7.05
R	18	-72	-42	5.07	21	-69	-39	7.94	18	-69	-46	5.47				
Vermis																
B	-6	-74	-24	7.97	-6	-77	-21	7.31	-3	-74	-24	10.36	-3	-60	-30	8.84
<i>Basal Ganglia</i>																
Caudate																
L	-12	-2	14	6.25	-18	-2	14	7.34	-15	1	11	11.52	-15	1	14	7.36
R	12	-5	17	4.30	21	1	17	4.15	21	1	17	9.30	18	4	14	6.79
<i>Talamus</i>																
L					-15	-9	0	6.93	-12	-3	3	9.60	-9	-15	1	7.64
R					15	-3	-6	7.86	15	-3	0	5.43	9	-14	3	8.37
<i>Frontal</i>																
Insula/IFG																
L	-33	20	-1	6.83	-33	20	-1	10.07	-33	20	-4	17.5	-30	20	2	11.47
R	30	23	2	7.82	33	23	2	7.37	30	23	2	10.67	30	21	4	13.56
SMA																
B	-3	11	49	9.04	-3	14	49	9.95	0	11	49	14.18	0	8	49	12.09
Dorsal premotor																
L	-24	-3	55	10.11	-24	-3	50	8.36	-24	-6	50	10.54	-24	-6	50	13.65
R	36	-3	47	7.81	30	-3	58		33	-3	50	9.49	30	-6	47	12.56
Ventral premotor																
L	-33	1	25	10.95	-39	7	22	11.13	-48	12	13	9.40	-42	7	22	9.34
R	45	10	30	8.87	45	10	30	8.04	48	10	22	10.21	48	10	22	9.30
DLPFC																
L	-33	41	9	6.15	-45	44	6	7.53	-39	33	23	8.89	-45	44	3	8.37
R	48	33	23	4.45	45	30	21	5.30	45	33	23	7.12	42	33	23	5.81
<i>Parietal</i>																
Intraparietal sulcus and adjacent areas																
L	-30	-44	44	10.3	-33	-44	46	10.73	-24	-48	38	12.92	-33	-50	49	10.91
R	42	-36	43	9.81	42	-39	43	10.81	42	-36	40	11.31	42	-36	40	9.82

Table 1. (continued)

	<i>S > C</i>		<i>t</i>	<i>SR > C</i>		<i>t</i>	<i>I > C</i>		<i>t</i>	<i>IR > C</i>		<i>t</i>				
<i>Temporal</i>																
Inferior temporal gyrus																
L	-45	-59	-5	3.92	-50	-47	-3	4.42	-42	-56	-5	3.16	-39	-58	3	4.21
R	48	-41	-8	3.88	50	-50	-13	3.51					50	-50	-10	3.22

IFG = inferior frontal gyrus; DLPFC = dorsolateral prefrontal cortex; IPS = intraparietal sulcus; ITG = inferior temporal gyrus; L = left; R = right; B = bilateral; C = Control; S = size; SR = size and reproduction; I = interval; IR = interval and reproduction.

and not to the lack of the SMA activity in the interval, size and reproduction, or interval and reproduction. The substantial SMA activity in the size condition could reflect implicit processing of the temporal structure of the stimuli because the ISI was variable in the size condition whereas it was fixed in the sensorimotor control condition. However, it may also be claimed that the SMA activity in the size condition reflected response selection not required for the control condition. To rule out this possibility, we tested activity during the interval and reproduction condition relative to the activity during the size only condition because the task load for response selection was the same between these conditions, but that for time processing most remarkably differed among the possible contrasts. In this analysis, significant activation was found in the SMA (Figure 4A), which was very close to the SMA region reported as the specific area for temporal processing in the previous literature (Rao et al., 1997). The finding of the SMA activity in the contrast between the interval and reproduction and the size conditions was consistent with

the hypothesis that the cerebral time controller may subserve both motor and sensory timing processes.

Because response time was longer in the interval than the size, different patterns of brain activation in these two conditions could partly reflect differences in general task demands. To test this possibility, a correlation analysis was performed between the changes of MRI signal (interval > size) and the corresponding difference in response times. No significant relationship was found between the response times and the MRI signals in the right lateral cerebellum or in any other region showing main effects of sensory timing (maximum r^2 value was .15 in the left IFG, $p > .05$). This analysis indicated that the observed main effects of sensory timing did not arise from differences in general task demands. Moreover, although it may be argued that the size and reproduction and the interval and reproduction could be regarded as a dual task and thus should be more challenging than the size and interval conditions, the production of response as soon and accurately as possible (CRT) is also mentally demanding. Although

Table 2. Areas Showing Main Effects for Motor Timing and Sensory Timing

<i>Location</i>	<i>Hemisphere</i>	<i>Coordinates</i>			<i>t</i>
<i>Main Effect for Motor Timing</i>					
DLPFC (46)	L	-42	38	9	5.45*
Insula/IFG (44)	R	53	15	10	5.58*
SMG (40)	L	-53	33	43	5.39*
SMG (40)	R	56	-30	46	6.85
Cerebellar declive (lobule VI)	L	-30	-53	-20	7.40
Cerebellar pyramis (lobule VIIIA)	L	-24	-60	-40	7.65
<i>Main Effect for Sensory Timing</i>					
Insula/IFG (44)	L	-53	12	2	7.42
Insula/IFG (47)	R	33	20	-11	9.03
SMG/STG (42)	R	65	-34	18	5.45*
Cerebellar declive (lobule VI)	R	30	-68	-14	7.10

Significant at an FDR threshold of $p < .05$ corrected for multiple comparisons (* $p < .001$, uncorrected).

DLPFC = dorsolateral prefrontal cortex; IFG = inferior frontal gyrus; SMG = supramarginal gyrus; STG = superior temporal gyrus; L = left; R = right; lat = lateral.

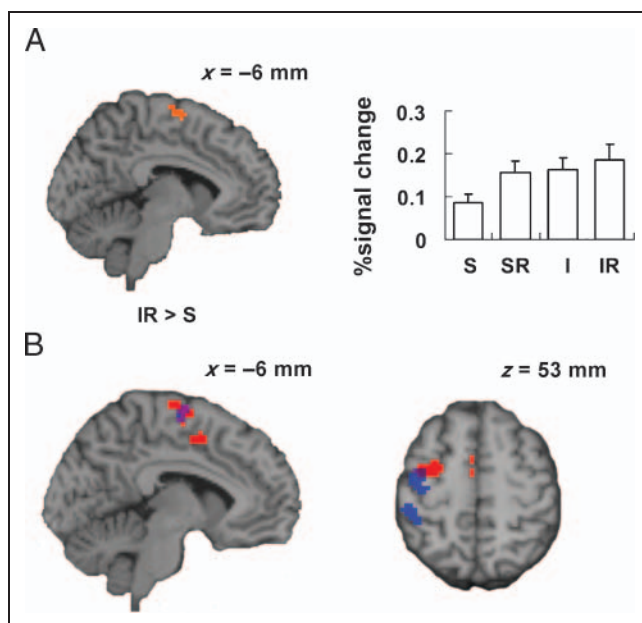


Figure 4. (A) The SMA region activated during the interval and reproduction condition relative to the size condition. Significant activity was seen in the SMA ($x, y, z = -3, -3, 58$) at FDR-corrected $p < .05$. The bar graph shows the mean \pm SEM percent signal change for the four conditions averaged across the cluster and subjects. S = size; SR = size and reproduction; I = interval; IR = interval and reproduction. (B) Cortical areas commonly activated in the two PPI analyses. Areas showing the PPI effects of motor timing and sensory timing are colored in blue and red, respectively, and are overlaid onto a sagittal slice ($x = -6$) and an axial slice ($z = 53$). The overlapping areas for the two PPI effects were colored in purple.

response times cannot be assessed to test the effects of task difficulty on motor timing-related activity, no significant differences in accuracy across the four conditions and accurate production of TDR responses suggest that motor timing-related activity indeed reflected motor timing components.

Cerebro-cerebellar Interactions

From the results of the categorical analysis, the right lateral cerebellum was specifically activated during sensory timing tasks whereas the left lateral cerebellum was during motor timing tasks. These findings supported the roles of the cerebellum for both sensory timing and motor timing. However, it was still unclear that these timing functions were achieved by the cerebellum alone or through the cerebro-cerebellar interaction. We assumed that the cerebral time controllers might be shared by sensory and motor timing processes according to our hypothetical model (see Figure 1). In the present study, such general purpose time controller should be identified within the cortical regions interacting with the right lateral cerebellum specifically during the time discrimination tasks and with the left lateral cerebellum specifically during the timed motor response tasks.

First, a PPI analysis was performed to find any distal cerebral regions connected functionally with the right lateral cerebellum (seed region) more strongly during the two ISI discrimination tasks than during the two size discrimination tasks. A PPI analysis was also performed by using the left lateral cerebellum (VI) as a seed region associated with the motor timing component. In either PPI analysis, significant activity was not identified in the whole cerebellum at an FDR-corrected threshold of $p < .05$. A non-negligible trend was shown in frontal-parietal regions in addition to the SMA at a threshold of uncorrected $p < .001$ (Table 3). The PPI effects for motor timing were observed only in the left cerebral hemisphere at the selected threshold. However, the motor timing PPI were essentially bilateral in the cerebral cortex. In fact, the right SMA and frontal-parietal regions showed PPI effects for motor timing at a threshold of $p < .01$ (uncorrected).

Secondly, we investigated the areas commonly activated across the two PPI analyses. The overlapping areas for the two PPI analyses were identified only in the SMA and the PMd (Figure 4B). The joint probabilities across the two independent PPI analyses thresholded at uncorrected $p < .001$ in these areas would correspond to uncorrected $p < 10^{-6}$ and t score of more than 8.1, which was highly unlikely to occur by chance and cleared the formal threshold of $p < .05$ (FDR corrected).

Finally, we aimed at associating the SMA region detected by the PPI analysis with an SMA region that was previously implicated for timing functions. The SVC method was used to corroborate the significance of the functional connectivity between the lateral cerebellum and the SMA. The area in the SMA was significantly coupled with the cerebellar timing modules in each of the SVC-corrected PPI analysis

Table 3. Cortical Areas Showing the Effects of PPIs

Location	Hemisphere	Coordinates			t
<i>PPI Effect for Motor Timing</i>					
PMd (6)	L	-42	-12	56	4.38
SMG (40)	L	-42	-35	57	4.22
SMA (6)	L	-6	-6	61	4.17
<i>PPI Effect for Sensory Timing</i>					
SMA (6)	L	-3	5	47	4.59
PMd (6)	L	-27	0	55	4.34
DLPFC (9)	R	48	16	24	4.31
SMG (40)	R	45	-56	50	4.25
SMA (6)	R	3	0	61	4.20
IFG (44)	L	-53	6	8	3.99

Significant at a threshold of $p < .001$, uncorrected. PMd = dorsal premotor area; SMG = supramarginal gyrus; DLPFC = dorsolateral prefrontal cortex; IFG = inferior frontal gyrus; L = left; R = right.

for sensory timing ($x, y, z = -6, 0, 61; t = 6.10; p_{\text{FDR}} < .05$) and motor timing ($x, y, z = -3, -6, 58; t = 4.52; p_{\text{FDR}} < .05$). This analysis confirmed that the SMA detected with the PPI analysis was consistent with the SMA region implicated for temporal processing in the previous literature (Rao et al., 1997). Note that the medial frontal activities shown by the PPI analysis are located around the border between the pre-SMA and the SMA, but we call this activity SMA for consistency with the previous study (Rao et al., 1997). We also checked a functional connectivity between the cerebellum and the BG with the SVC method. However, significant coupling was not observed within the search volume.

DISCUSSION

Many neuroimaging studies have already reported the involvement of distributed brain regions, including the cerebellum, in temporal information processing tasks with timescales that range from several hundred milliseconds to minutes (e.g., Livesey, Wall, & Smith, 2007; Stevens, Kiehl, Pearson, & Calhoun, 2006; Tregellas, Davalos, & Rojas, 2006; Xu, Liu, Ashe, & Bushara, 2006; Jantzen, Steinberg, & Kelso, 2005; Mathiak, Hertrich, Grodd, & Ackermann, 2004; Lewis & Miall, 2003; Rao, Mayer, & Harrington, 2001; Penhune, Zattore, & Evans, 1998). The present study supports the role for the cerebellum in processing subsecond temporal information. Very recently, O'Reilly et al. (2008) have suggested that the cerebellum may predict the timing of perceptual events through cerebro-cerebellar interactions on the basis of a forward model. This study adopted a time prediction task over a range of 800–1700 msec, whereas the present study only used subsecond-range timing. Moreover, they used tasks involving both space and time. We believe that time processing should be substantially different when involving spatial information and when not. When time information is processed in conjunction with spatial information, the combination of the stimuli might be perceived as motion. The temporal tasks in the present study did not essentially require spatial information processing, thereby providing the first evidence of cerebro-cerebellar interaction for subsecond time processing without accompanying spatial information processing.

In the present study, both motor and sensory timing effects were found in the insula, IFG, and SMG/STG. It has been suggested that temporal information is processed as internal auditory/phonological representations for both motor and sensory timing tasks (Jahanshahi et al., 2006; Ferrandez et al., 2003; Lewis & Miall, 2003; Kawashima et al., 2000; Rao et al., 1997). Phonological working memory (Baddeley, 1992) is composed of a phonological store, localized in the left SMG, and an articulatory control process, located in the left IFG (Paulesu, Frith, & Frackowiak, 1993). In addition, the IFG and the STG in the right hemisphere are suggested to form a specific network for rehearsing nonlinguistic auditory rhythms (Riecker, Wildgruber, Dogil, Grodd, & Ackermann, 2002). The coactivation of

the IFG and SMG/STG in the present tasks, all of which only used visual stimuli, supports the view that linguistic or nonlinguistic auditory representations are widely involved in time processing. In other words, these regions could be engaged in the encoding and the maintenance phases of temporal information processing. Little attention has thus far been paid to the role of the insula in temporal information processing, despite previously observed insular activations in various timing tasks (Livesey et al., 2007; Stevens et al., 2006; Tregellas et al., 2006; Jantzen et al., 2005; Pouthas et al., 2005; Lewis & Miall, 2003; Nenadic et al., 2003; Rao et al., 2001; Penhune et al., 1998). The insula is associated with various sensorimotor functions, including auditory/phonological information processing (Bamiou, Musiek, & Luxon, 2003) and visual–auditory interactions (Bushara et al., 2003). The possible interactions between the external visual stimuli and the internal timing representations could account for the insular activity in the present timing task.

The BG and the cerebellum have been considered critical for timekeeping over the range of subseconds to several seconds. In the present study, the BG, specifically the caudate nucleus, were active only in comparison with the low-level sensorimotor control task whereas the lateral cerebellar activity was detected in both motor and sensory timing tasks after nontemporal cognitive components were controlled for. This finding is consistent with the proposal that the cerebellum may be more specifically involved in the processing of subsecond temporal information than the BG (Ivry, 1996). Nevertheless, an important question as to how the cerebellum processes subsecond temporal information remains to be addressed. A recent proposal is that feed-forward computation may explain cerebellar activation as well as impaired performance after lateral cerebellar damage in subsecond timing tasks (Mauk & Buonomano, 2004). Such a function may be achieved by the network involving a cerebral controller and a cerebellar feed-forward emulator (Grush, 2004). Notably, the functional connectivity analyses revealed interaction between the cerebellum and the cerebral cortex such as the SMA and the PMd during both the motor and sensory timing tasks. This demonstration of such functional coupling supports the presence of functionally significant interactions between the cerebellum and the cerebral cortex.

The cerebellum may help perform the present motor timing task possibly as a feed-forward emulator by predicting a desired time point at which the button should be pressed. In this framework, movement might be planned so as to minimize the error between the predicted and the actual movement timings. Of note, the cerebellar activation associated with motor timing was found in the left superior cerebellar hemisphere (lobule VI). Magnetic stimulation applied over the left lateral cerebellum disrupts motor reproduction of subsecond-range (400–600 msec) but not second-range (1,600–2,400 msec) intervals (Koch et al., 2006). It is thus likely that the left lateral cerebellum is specifically involved in subsecond motor timing.

In contrast to the left lateral cerebellar activity during the motor timing tasks, the right lateral cerebellum was activated during the sensory timing tasks. Recently, the right lateral cerebellum was implicated in perceptual timing of subsecond intervals in repetitive transcranial magnetic stimulation studies (Fierro et al., 2007; Lee et al., 2007). However, the role of the cerebellum in sensory timing has not yet been established. The region of the lateral cerebellum involved in the present sensory timing tasks was close to the cerebellar activation observed during comparison of predicted motor outcome with information from sensory inputs (Blakemore, Frith, & Wolpert, 2001). Blakemore et al. (2001) introduced various subsecond-range delays (0–300 msec) between the movement of a robotic arm controlled by the subjects and tactile stimulus feedback. As the delay increased, the tactile stimulus was perceived to be more tickling, and greater activation of the right lateral cerebellum (lobule VI) was observed. These findings are taken as the evidence that the cerebellum is involved in feed-forward computational processes that help the brain interpret the meaning of sensory signals. Can we consider a similar processing mechanism for the discrimination of the subsecond intervals? In fact, activation of the right lateral cerebellum (crus I close to lobule VI shown here) has been reported in another fMRI study of temporal discrimination, which used nonverbal auditory stimuli with short subsecond intervals (30–140 msec; Mathiak et al., 2004). A feed-forward prediction mechanism can detect the temporal discrepancy between the intervals simulated internally and those given externally. For the present task, an emulator possibly in the cerebellum might reproduce or simulate representations of the previously encoded ISI, and the reproduced timing information could be compared with the actual timing of the current ISI. The sign of the error between the simulated timing and the actual timing of the current stimuli is sufficient information for completing the present time discrimination task.

In the present study, the SMA and the PMd were functionally connected with the lateral cerebellum during both sensory and motor timing tasks. More robust functional connectivity was found in the SMA than that in the PMd, and the location of the SMA was consistent with that in the direct comparison (Figure 4A) and that in the previous literature (Rao et al., 1997). It should be noted that PPI reflects a functional association rather than a direct anatomical connection. Anatomically, the cerebellum should be cross-connected with the cerebrum. However, the motor timing PPI was predominantly observed in the left cerebral hemisphere, although the left lateral cerebellar VOI was used as a seed. We should note that the PPI results were observed bilaterally at a liberal threshold. A similar phenomenon was previously reported (O'Reilly et al., 2008). Interhemispheric connections might explain this discrepancy.

Both the SMA and the PMd were reported to be activated during cognitive operation tasks involving phonological-

articulatory and visuospatial information (Hanakawa et al., 2002). However, Tanaka et al. (2005) recently showed that the SMA and the PMd played more critical roles in verbal and spatial information processing, respectively. It is tempting to assume that the SMA primarily processes temporal information in the phonological-articulatory form. This interpretation is supported by the coactivation of the IFG and SMG/STG as discussed above. Very recently, O'Reilly et al. (2008) showed that the functional connectivity was enhanced between the cerebellum and the frontal-parietal regions including the PMd during a temporal-spatial prediction task. Peculiarly, however, the interaction of the SMA with the cerebellum was not reported in their study. Our paradigm was designed to reduce elements of explicit spatial processing coexisting with temporal processing to identify the areas specific to temporal processing. The differences between O'Reilly's and our findings can be explained by whether coprocessing of spatial information was required or not. Therefore, we propose that the SMA is the cortical time controller interacting with the cerebellum when temporal information is processed independent of spatial information processing. However, note that this idea is strongly dependent on the hypothesis that there should be the time controllers in the cerebral cortex and the feed-forward emulators in the cerebellum.

The finding of the SMA-cerebellar interaction is consistent with the evidence that the SMA sends efferents to the basis pontis (Jurgens, 1984), which in turn projects to the lateral cerebellum, and receives transthalamic afferent input from the dentate nucleus, the primary output nucleus of the lateral cerebellum (Sakai et al., 1999). Recently, Akkal, Dum, and Strick (2007) have also reported that the SMA is the target of projections from the dentate nucleus. It is well established that the SMA is involved in the temporal organization of multiple movements. For instance, a human patient study has shown that the SMA is crucial in generating sequences that follow specific rhythms (Halsband, Ito, Tanji, & Freund, 1993) and particularly if the rhythms must be rehearsed from memory. Moreover, the SMA is thought to play an important role in the organization of auditory/phonological information, possibly serving as a verbal working memory system (Schumacher et al., 1996) with particular importance in articulatory rehearsal (Chein & Fiez, 2001). We propose a hypothesis that the SMA may extract temporal information from auditorily/phonologically recorded environmental stimuli and thus serve as the cerebral controller, which could feed control commands to the lateral cerebellum for feed-forward prediction.

The present study has shown that distributed brain regions, including the cerebellum, are involved in temporal processing in the subsecond range. The activity in the peri-sylvian regions, especially the insula, in both the motor and the sensory timing tasks suggests that time information given as visual stimuli might be internally recorded in an auditory-phonological form. The superior lateral cerebellar hemispheres may play a central role in the processing of internal representations of subsecond time periods.

Bilaterally separate lateral cerebellar activations, the left cerebellar region for motor timing and the right cerebellar region for sensory timing, indicate multiple instantiations of cerebellar time modules. However, the functional difference between the right and the left cerebellum for temporal processing remains to be clarified in the future studies. Most importantly, the present study suggested that subsecond time processing without accompanying spatial information processing is achieved by the interactions between the SMA and the cerebellum.

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