

The Role of the Cerebellum in Sub- and Supraliminal Error Correction during Sensorimotor Synchronization: Evidence from fMRI and TMS

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Abstract

■ Our ability to interact physically with objects in the external world critically depends on temporal coupling between perception and movement (sensorimotor timing) and swift behavioral adjustment to changes in the environment (error correction). In this study, we investigated the neural correlates of the correction of subliminal and supraliminal phase shifts during a sensorimotor synchronization task. In particular, we focused on the role of the cerebellum because this structure has been shown to play a role in both motor timing and error correction. Experiment 1 used fMRI to show that the right cerebellar dentate nucleus and primary motor and sensory cortices were activated during regular timing

and during the correction of subliminal errors. The correction of supraliminal phase shifts led to additional activations in the left cerebellum and right inferior parietal and frontal areas. Furthermore, a psychophysiological interaction analysis revealed that supraliminal error correction was associated with enhanced connectivity of the left cerebellum with frontal, auditory, and sensory cortices and with the right cerebellum. Experiment 2 showed that suppression of the left but not the right cerebellum with theta burst TMS significantly affected supraliminal error correction. These findings provide evidence that the left lateral cerebellum is essential for supraliminal error correction during sensorimotor synchronization. ■

INTRODUCTION

Accurate sensorimotor timing and rapid error correction in response to a sensorimotor mismatch are essential in many everyday tasks. Sensorimotor timing requires the temporal coupling of motor output to sensory stimuli, whereas error correction refers to adaptive movement adjustments in response to changes in the sensory stimulus. Sensorimotor synchronization (SMS) is a simple task that can be used to study both timing and error correction. In SMS, subjects tap their finger in synchrony with a repetitive isochronous auditory or visual stimulus sequence. Previous research has shown that subjects have a tendency to tap on average 20 to 80 msec before the onset of the predicted stimulus when auditory pacing is used, demonstrating an anticipatory negative mean asynchrony (Aschersleben, 2002). The size of the negative asynchrony is influenced by the modality of the pacing stimulus and is smaller when visual pacing stimuli are used (Kolers & Brewster, 1985). Error correction is required to sustain a consistent tap–tone relationship even when the pacing stimulus is regular because of inherent variability in the motor response (Repp, 2005). Such error correction mechanisms can be explicitly

studied using a pacing sequence containing occasional local timing perturbations such as phase shifts. After such perturbations, subjects show a rapid behavioral adjustment and return to their baseline negative mean asynchrony within several taps (Repp, 2002b).

At present, it is not fully understood how the processing of errors is influenced by conscious perception of the phase shifts. Two different error correction processes have been suggested. Phase correction appears to be a largely automatic response to minor local perturbations, whereas period correction involves resetting the period of a hypothetical internal timekeeper mechanism and may be subject to conscious control (Repp & Keller, 2004; Repp, 2001b). The correction of phase shifts may rely mainly on automatic phase correction and may not be aided by conscious perception of the perturbation (Repp, 2005). However, when subjects intend not to react to perturbations, phase correction can be partially suppressed and period correction can be suppressed completely (Repp, 2002a, 2002b). This may suggest that conscious perception of the phase shift allows modulation of the error correction response.

Activation in the left sensory-motor cortex and right cerebellum is consistently reported during regular right-handed synchronization tapping in neuroimaging studies (Jäncke, Loose, Lutz, Specht, & Shah, 2000; Lutz, Specht, Shah, &

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Jäncke, 2000; Rao et al., 1997). Activation of the premotor region and inferior parietal cortices was reported in one study (Jäncke et al., 2000), but not in others. The neural correlate of error correction was investigated in two previous studies in the context of an SMS task. Lutz et al. (2000) found activations in the sensory motor cortex, SMA, and right cerebellum when comparing visually paced irregular to regular SMS performed with the right hand. Another study used positron emission tomography to demonstrate activations in frontal, parietal, BG, and cerebellar regions during the correction of predictable supraliminal shifts in a unimanual right-handed SMS task (Stephan et al., 2002). Although previous research on both regular SMS and error correction has consistently implicated involvement of the cerebellum, the exact role of the cerebellum during the correction of sub- and supraliminal perturbations in an SMS task is largely unknown.

This study adopts two complementary techniques to investigate the neural correlates of error correction of perceivable and unperceivable perturbations in the context of SMS. Of particular interest is the role of the cerebellum, as this structure is consistently activated during regular SMS (Jäncke et al., 2000; Lutz et al., 2000; Rao et al., 1997) and was also implicated in error correction (Pollok, Gross, Kamp, & Schnitzler, 2008; Stephan et al., 2002; Lutz et al., 2000). In Experiment 1, fMRI is used to investigate the neural correlates of regular SMS and error correction of sub- and supraliminal phase shifts. Effective connectivity of the cerebellum during timing and error correction is explored using a psychophysiological interaction (PPI) analysis. In Experiment 2, the causal role of the cerebellum during sub- and supraliminal error correction is examined using theta burst transcranial magnetic stimulation (TBS) (Huang, Edwards, Rounis, Bhatia, & Rothwell, 2005).

EXPERIMENT 1—fMRI

The aim of Experiment 1 was to examine the neural correlates of SMS and of the correction of unexpected subliminal and supraliminal phase shifts during SMS using fMRI. The involvement of the cerebellum was of particular interest because this structure has been associated with both timing and error correction. To investigate the contribution of the cerebellum further, we used a PPI analysis to examine changes in effective connectivity within a cerebello-cortical network during regular timing and error correction. We hypothesized that (a) the cerebellum is active during regular timing and during error correction and (b) parietal and frontal cortices are involved in the correction of supraliminal errors.

Methods

Subjects

Sixteen healthy subjects (8 men, mean age \pm SD = 25 \pm 5 years) took part in the study. All subjects were right-

handed (mean Edinburgh Handedness Inventory score of 59, range = 30–90). The subjects were naive to the experimental task, and none of them was a professional musician. The subjects had no history of psychiatric or neurological disorders.

Stimuli and Task Conditions

Subjects performed an auditory-paced SMS task inside the fMRI scanner. The pacing stimulus was a simple auditory sequence consisting of metronome tones at a frequency of 500 Hz and duration of 50 msec presented through MRI-compatible headphones. Subjects were asked to press a button using their right index finger in synchrony with the auditory stimulus, aiming for their button presses to coincide with each tone. The task consisted of three conditions: a regular condition and two irregular conditions containing perturbations of 3% (subliminal) and 15% (supraliminal) of the sequence interonset interval (IOI). In the regular condition, the pacing stimulus was isochronous with an IOI of 600 msec. In the two irregular conditions, perturbation events were introduced that shifted a single stimulus interval by 3% or 15% (18 or 90 msec, respectively) in either direction with respect to the expected time of occurrence, constituting negative and positive phase shifts. In a box-car design, a resting block (15 sec) and a tapping block (45 sec) were alternated nine times, and a further 15-sec resting block was added at the end of the final tapping block, resulting in 9 min and 15 sec total scanning time. Each tapping condition (regular, subliminal, and supraliminal) lasted for 45 sec (75 stimuli) and was repeated three times. In each of the irregular blocks, a total number of eight perturbations (four negative and four positive) of equal magnitude were introduced. Because each condition was repeated three times (in separate blocks), this resulted in 12 events for all four possible perturbations (positive and negative for subliminal and supraliminal shifts). At least seven regular stimuli occurred between two subsequent perturbations to allow subjects to reestablish synchronization before each shift. To achieve the sequences, we repeated a fixed epoch ($T - 3$ to $T + 3$ in which the shift occurs at time T) eight times, and 0, 1, or 2 tones at the standard IOI were introduced between two subsequent epochs. The order of positive and negative shifts was randomized. As such, the position of the perturbations in the sequence was semi-random, and subjects were not able to anticipate the occurrence of the next shift. To allow the subjects to focus on the synchronization task, they were not asked to report whether they were aware of perturbations. However, a previous study showed that detection of perturbations of 4% of the IOI (of 500 msec) was approximately equal to chance, whereas 90 msec shifts (18% of IOI) were detected more than 90% of the time (Repp, 2002a). Stimuli were controlled using Presentation software (version 12.8, www.neurobs.com), and behavioral responses were measured with an MRI compatible button box.

Functional Magnetic Resonance Imaging

Functional imaging data sets were acquired using a 3-T scanner (Achieva 3.0T; Philips Medical Systems, Best, The Netherlands) at the University of Sheffield. A single-shot, gradient-recalled, echo-planar technique was used to acquire 23×6 mm contiguous transverse slices at 370 time points (repetition time = 1500 msec, echo time = 35 msec, in-plane resolution = 1.8×1.8 mm, sense factor = 1.5). A standard receive-only six-channel head coil was used, and subject-specific, localized shimming was performed. Subjects viewed a projected black screen with a white fixation cross in the center through a mirror in the head coil throughout the experiment. Subjects were told that the sounds would start and asked to start tapping in synchrony with the tones as soon as it started.

Behavioral Data Analysis

From each of the nine experimental blocks, the first 10 taps were discarded to allow the subject to establish tapping synchrony. In the regular SMS condition, measures of timing performance include the mean and standard deviation of tap-tone asynchrony and of interresponse interval (IRI). These were calculated over the three regular blocks and represent the timing performance for all subjects. Sub-

sequently, error correction data from the irregular blocks were analyzed in an event-related approach including four taps before and four taps after ($T - 4$ to $T + 4$) each shifted stimulus (T). Within each subject, outlier responses (tap-tone asynchronies more than two standard deviations away from the average asynchrony) were identified separately for each position ($T - 4$ to $T + 4$) and were removed prior to averaging. To allow a direct comparison of the error correction response in all conditions, we normalized the asynchrony during T to $T + 4$ to range from baseline asynchrony to the maximum initial shift at time T , and the sign was removed (Figure 1). Baseline performance was defined as the average tap-tone asynchrony over trials $T - 4$ to $T - 1$ (Praagstra, Turgeon, Hesse, Wing, & Perryer, 2003; Repp, 2000). The resulting normalized error correction data were averaged over all trials. If the averaged normalized error correction scores represented extreme values (more than three times the interquartile range away from the group median) at three or four positions (in $T + 1$ to $T + 4$) for a single subject, these data were replaced by the group average of the value. This led to the replacement of data from two subjects in the negative subliminal condition and data from one subject from the positive subliminal condition.

To investigate the natural occurrence of error correction (i.e., after spontaneous motor variability in the absence of perturbations in the sequence), we performed a

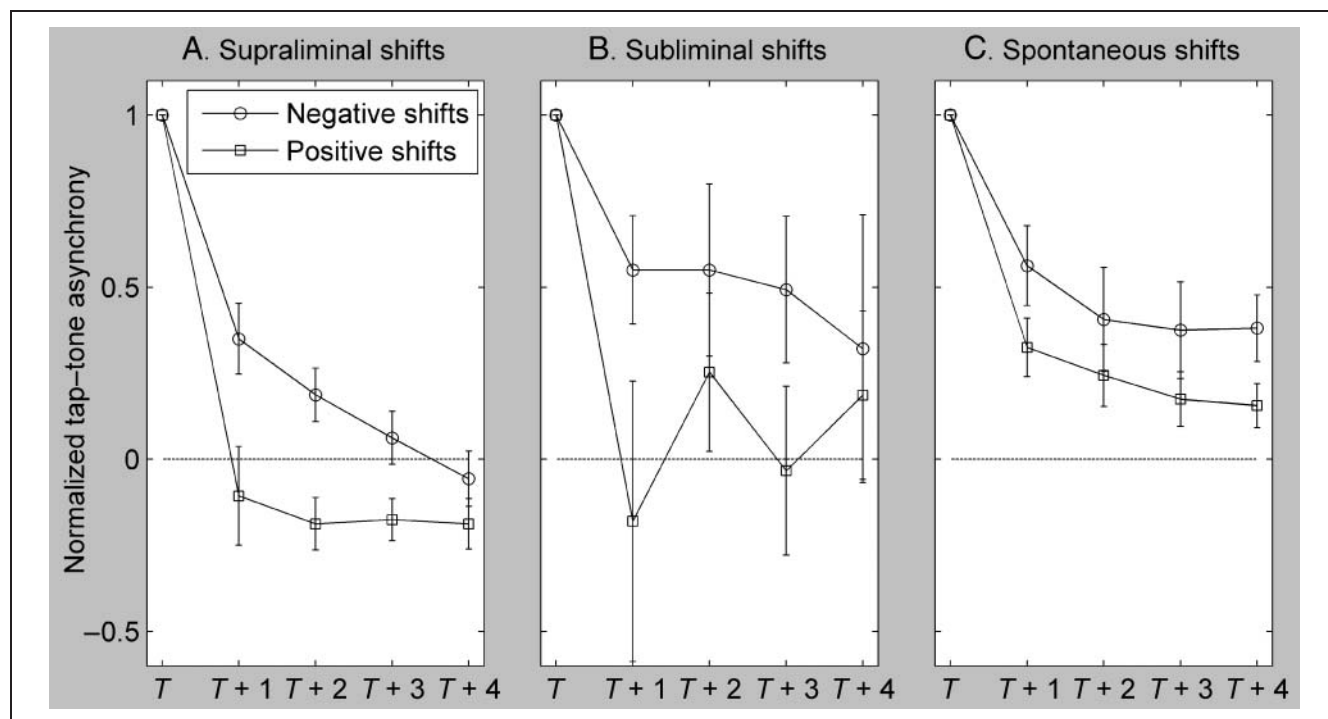


Figure 1. Normalized error correction response as a function of stimulus position after induced subliminal (A) and supraliminal (B) perturbations and spontaneous motor variability (C) in Experiment 1. Error correction of positive shifts is faster compared with negative error correction. Error correction after spontaneous large deviation from the average tap-tone asynchrony does occur, but baseline asynchrony is not achieved within four taps. Tap-tone asynchronies are shown for the time of the perturbation (T) and four subsequent taps ($T + 1 - T + 4$). The data are normalized to range from baseline asynchrony (0, dashed line) to the magnitude of the initial shift at time (T), and the sign is removed. Baseline performance is defined as the subject mean tap-tone asynchrony during $T - 4$ to $T - 1$. Spontaneous shifts are defined as deviations from the subject mean asynchrony greater than 50 msec during the standard blocks. In negative shifts (circles), the tone occurs later than expected, and in positive shifts (squares), the tone occurs earlier than expected. Error bars express a standard error.

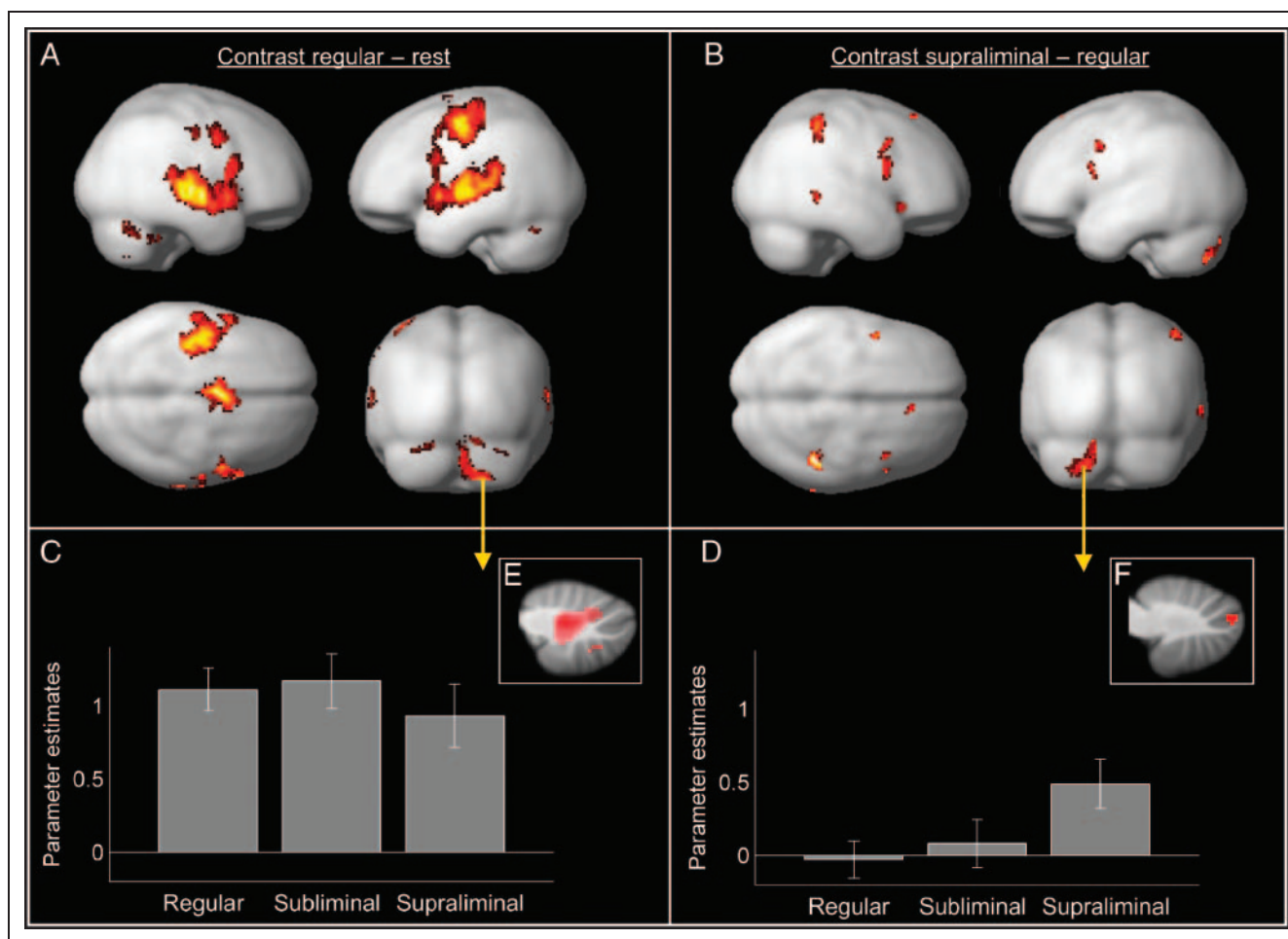


Figure 2. Functional imaging contrasts between regular tapping and rest (A) and between the supraliminal and the regular conditions (B) and associated parameter estimates (C and D) in peak cerebellar foci (E and F). fMRI activations are rendered on a normalized smooth brain surface showing (clockwise starting at the upper left corner): a sagittal view from the right and left, an axial view from the top, and a coronal view from the back. Findings are significant at $p < .001$ uncorrected and exceed a cluster-extent threshold of 20 voxels. Plots C and D show parameter estimates for the three active conditions compared with rest in two regions of peak activation in the right dentate nucleus [20 -52 -28] and left posterior cerebellar cortex [-20 -80 -44]. Error bars indicate the 90% confidence interval. In-plot figures E and F show the same fMRI activations on a sagittal slice through the cerebellum to illustrate the differential position of activation foci in the deep nuclei (right dentate nucleus) and in the cortex (left posterior cerebellar cortex). Figures E and F were created with the SUI toolbox in SPM5 (Diedrichsen, 2006).

data-driven analysis using only data from regular blocks. For each subject, the data were searched for instances (minimally five taps apart), where the asynchrony deviated from the subject's mean asynchrony by more than 50 msec. All subjects showed such spontaneous deviations; on average, 13 shifts ($SD = 5$, range = 7–21) occurred during the three regular blocks (5 in the positive direction and 8 negative). These data were analyzed in the same way as for externally induced error correction events (see above) to show the correction response to spontaneous errors (Figure 1C).

Imaging Data: Cognitive Subtraction

The imaging data were analyzed using SPM5 (<http://www.fil.ion.ucl.ac.uk/spm>). Motion correction was performed by realigning the images to the central image with a six-parameter

(rigid body) spatial transformation. Further preprocessing stages involved normalization into standard space and smoothing using Gaussian kernels of 5-mm FWHM. On an individual level, statistical analysis was based on the general linear model using the boxcar design convolved with a canonical hemodynamic response function, creating contrast images for all conditions. Thereafter, a one-sample t test was performed to obtain second-level group results (Figure 2A and B). Subsequently, parameter estimates were derived from single-voxel locations to allow closer investigation of activation patterns in several ROIs. These locations were experimentally informed Montreal Neurological Institute coordinates resulting from local maxima in second-level functional contrasts (regular–rest for right cerebellar ROI and supraliminal–regular for left cerebellar ROI). Figure 2C and D shows parameter estimates for the contrasts between all active conditions (regular, subliminal, and supraliminal) and rest.

To further investigate the lateralization of cerebellar activation, we performed a laterality analysis. Parameter estimates were extracted for a 5-mm sphere centered on the left cerebellar ROI $[-20 -80 -44]$ and on the mirrored right cerebellar region $[20 -80 -44]$. A paired t test was performed to analyze whether there was a statistically significant difference between the parameter estimates indicating a lateralization of activation.

Imaging Data: Normalization to Cerebellar Template

Individual subject contrast images resulting from first-level general linear model analysis were normalized to a spatially unbiased template of the human cerebellum with the use of the SUIT toolbox in SPM5 (Diedrichsen, 2006). In each subject, the cerebellum and the brainstem were isolated on the basis of a segmentation algorithm, and functional images were normalized to the SUIT template using nonlinear deformation. The subsequent cerebellar contrast images were smoothed and entered into a second-level one-sample t test producing group results to create Figure 2E and F.

Imaging Data: PPI Analysis

To further investigate the role of the cerebellum during supraliminal error correction, we performed a PPI analysis (Friston et al., 1997) using SPM5. For each subject, a left cerebellar seed ROI was identified by locating the suprathreshold voxel nearest to the group ROI (left cerebellar local maxima in supraliminal–regular contrast $[-20 -80 -44]$). A suitable ROI in the left posterior cerebellar cortex was located from the first-level contrast

(supraliminal–regular) for all subjects. The zero-mean corrected first principle component was extracted from all voxels in a radius (5 mm) centered on the subject-specific ROI to form the physiological time course. The PPI term was produced by convolving the physiological time series with a psychological vector that described the paradigm (1 for the supraliminal condition, -1 for regular tapping). The interaction term was entered at the first level as the effect of interest, and the psychological and the physiological time series were entered as effects of no interest. Subject-specific interaction contrasts were entered into a second-level one-sample t test to achieve group results (Figure 3). The identical PPI analysis was also performed with a seed ROI in the right cerebellum. Here, subject-specific physiological time series were extracted from a radius centered on the nearest suprathreshold voxel to the group ROI $[4 -68 -16]$ in the regular–rest contrast.

Results and Discussion

During regular blocks, taps preceded the tones by an average of 53 msec, demonstrating an anticipatory negative mean asynchrony. The standard deviation was 45 msec as calculated by averaging the within-block SD over three regular blocks and over all subjects. The average IRI was 600 msec (group-averaged within-block $SD = 45$ msec). In the subliminal condition, the average tap–tone asynchrony was 65 msec (group-averaged within-block $SD = 43$ msec), and the IRI was 600 msec (group-averaged within-block $SD = 37$ msec). During supraliminal blocks, the average tap–tone asynchrony was 53 msec (group-averaged within-block $SD = 56$ msec) and the average IRI was 599 msec (group-averaged within-block $SD = 50$ msec).

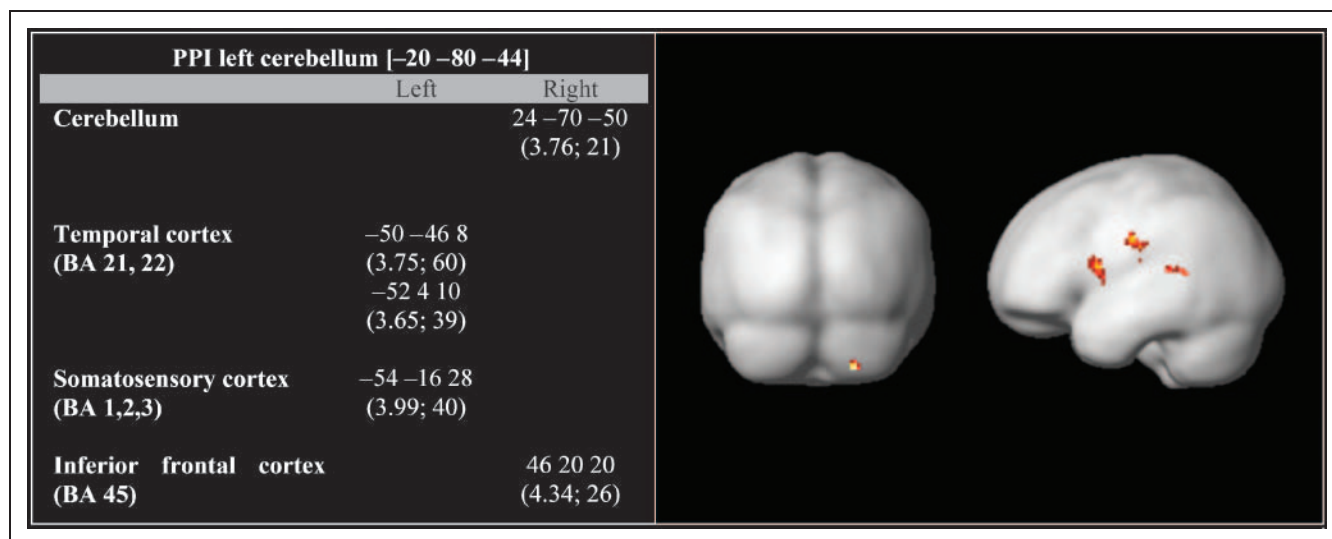


Figure 3. PPI analysis results with a seed ROI in the left cerebellum $[-20 -80 -44]$. In the table, Montreal Neurological Institute coordinates of local maxima are provided (x, y, z , in millimeters), and values in parentheses provide corresponding Z scores and cluster sizes (voxels). Areas that display enhanced effective connectivity with the left cerebellum during the supraliminal condition compared with regular SMS are shown on a normalized smooth brain surface showing a coronal view from the back (left) and a sagittal view from the left (right). Findings are significant at $p < .001$ uncorrected and exceed a cluster-extent threshold of 20 voxels.

Event-related error correction analysis revealed a behavioral error correction response in all four possible phase shifts (Figure 1). The average number of outlier responses removed was 3.4 ($SD = 2$) of 108 responses. There was no difference in the number of outlier responses removed from the analysis between the conditions ($p > .2$). A three-way repeated measures ANOVA on the normalized relative asynchrony with factors direction (positive or negative), size (subliminal or supraliminal), and position ($T + 1$ to $T + 4$) indicated a significant main effect of direction, $F(1, 15) = 5.59, p = .032$, such that the correction of negative shifts was less efficient than of positive shifts. Furthermore, there was a main effect of size, $F(1, 15) = 8.20, p = .012$, in which baseline performance was achieved faster after the correction of supraliminal errors compared with subliminal error correction. The main effect of position did not reach significance ($p > .5$), and none of the interactions were significant ($p > .1$).

Subliminal phase shifts (18 msec) fall within the range of tapping variability ($SD = 46$ msec) as opposed to supraliminal shifts (90 msec). In view of this, we analyzed the behavioral response after extreme cases of motor variability (deviations from the mean asynchrony greater than 50 msec) and compared this with the error correction response to phase shifts introduced in the pacing stimulus (Figure 1C). Error correction after spontaneous motor variability is apparent, but baseline asynchrony is not achieved within the four taps after the deviation. Hence, it may well be that this form of “error correction” after spontaneous motor variability is better interpreted as a general regression to the mean asynchrony.

Functional imaging data from all three experimental conditions were contrasted with baseline rest, and the subliminal and supraliminal error correction conditions were contrasted with regular SMS. Compared with baseline rest, the regular condition showed activations in the right premotor cortex, left primary motor cortex, bilateral primary auditory cortices, and right cerebellum extending to vermis (Figure 2A, Table 1). The subliminal condition compared with regular SMS did not produce any significant activations. The contrast between the supraliminal and the regular conditions revealed that bilateral frontal cortices, right inferior parietal cortex, and left cerebellum were significantly activated during the supraliminal condition (Figure 2B, Table 1). To investigate whether subliminal error correction may lead to less activity in the same circuitry, we lowered the significance threshold of the comparison between subliminal correction and regular tapping ($p < .01$ uncorrected). Lowering the threshold resulted in scattered activity that was not consistent with the contrast between supraliminal and regular tapping. In summary, the right cerebellum is active in all three conditions compared with rest, whereas the left cerebellum is only engaged in the condition including perceivable shifts.

A laterality analysis was performed to compare activation in the left cerebellar local maximum with the mirrored right cerebellar region in the contrast between

the supraliminal and the regular conditions. Results of the laterality analysis confirm that the cerebellar activation during the supraliminal conditions was significantly left lateralized, $t(1, 15) = 4.47, p < .001$. The lateralization of cerebellar activation is also confirmed by the parameter estimates for the two local maxima in the left and right cerebellar hemispheres (Figure 2C and D). Furthermore, when the subtraction results are normalized to a template confined to the cerebellum, a dissociation in activation foci is highlighted: Activation in the right cerebellum is mainly located in the dentate nucleus, whereas activity on the left-hand side is confined to the cortex (crus I, Figure 2E and F).

Functional imaging data were further analyzed in a PPI analysis using a seed ROI in the left cerebellum. Group results are summarized in Figure 3. The PPI analysis identifies brain areas that exhibit enhanced connectivity with the left cerebellum during the condition that included supraliminal perturbations compared with regular tapping. Significantly enhanced connectivity with the left cerebellum was observed in the frontal, auditory, and sensory cortices and in the right cerebellum. The same PPI analysis was also performed using a seed ROI in the right cerebellum. Results show no change in effective connectivity of the right cerebellum during supraliminal tapping compared with regular SMS.

In summary, we found involvement of the cerebellar vermis and right cerebellar dentate in all active conditions compared with rest. The left lateral cerebellar cortex was activated only during the condition that required supraliminal error correction. Furthermore, the left cerebellum exhibited enhanced functional connectivity with a cerebello-cortical network during supraliminal error correction compared with regular timing. These findings suggest that the left cerebellum may play an essential role during supraliminal error correction.

EXPERIMENT 2—TBS

Results from Experiment 1 indicated that the left cerebellum is involved only during the correction of supraliminal phase shifts. In Experiment 2, we investigated the effect of TBS over the medial, left lateral, and right lateral cerebellum on error correction performance. On the basis of Experiment 1, we hypothesized that suppression of the left cerebellum would impair supraliminal error correction, whereas suppression of the medial or right cerebellum would not affect error correction performance.

Methods

Subjects

Forty right-handed healthy subjects (mean age $\pm SD = 23 \pm 5$ years) took part in the study. They were students from the University of Sheffield. All were randomly assigned to one of four experimental groups: (1) medial

Table 1. Statistical Contrasts between Regular, Subliminal, and Supraliminal Conditions and Rest and between the Supraliminal and the Regular Conditions

	<i>Regular–Rest (Figure 2A)</i>		<i>Subliminal–Rest</i>		<i>Supraliminal–Rest</i>		<i>Supraliminal–Regular (Figure 2B)</i>	
	<i>Left</i>	<i>Right</i>	<i>Left</i>	<i>Right</i>	<i>Left</i>	<i>Right</i>	<i>Left</i>	<i>Right</i>
Cerebellum	–24 –66 –26 (5.23; 292)	4 –68 –16* (6.07; 2157)	–24 –62 –26 (4.23; 61)	4 –66 –22 (4.86; 1424)	–18 –72 –32 (5.29; 798)	12 –52 –22 (5.42; 1946)	–20 –80 –44* (4.46; 161)	
				36 –58 –36 (4.58; 25)		0 –56 –2 (4.16; 21)		
				12 –66 –50 (4.10; 118)				
Temporal cortex	–54 –20 0 (5.63; 4871)	60 –18 –2 (5.94; 2381)	–48 –22 2 (5.55; 1576)	62 –18 –4 (5.65; 522)	–52 –20 0 (5.58; 6229)	64 –16 –2 (6.03; 3440)		34 18 –10 (4.21; 25)
			–34 –64 8 (3.69; 22)	46 0 –4 (3.95; 59)				66 –42 0 (3.53; 23)
			–58 8 4 (3.51; 25)	42 –16 –20 (4.30; 29)				
Motor cortex	–48 –8 54 (5.41; ^a)		–44 –14 52 (5.04; 1057)		–42 –6 54 (4.71; ^a)			
Parietal cortex					–44 –40 46 (4.80; 392)	42 –38 38 (4.60; 282)		50 –40 54 (4.34; 247)
Frontal cortex				54 4 44 (4.17; 121)		34 20 –6 (5.29; 1766)	–48 4 40 (4.54; 34)	42 8 34 (4.23; 45)
							–48 10 22 (3.43; 26)	6 30 58 (3.86; 22)
								52 10 16 (3.63; 68)
Premotor cortex/ SMA (BA 6)	–4 –4 54 (5.16; 837)	54 0 40 (4.32; 169)	–4 –6 56 (4.01; 90)			12 4 64 (4.39; 798)		
		62 –14 44 (4.58; 35)						
Thalamus	–16 –22 –2 (4.23; 104)	22 8 –16 (4.35; 390)	–14 –24 –2 (4.12; 43)					
BG		32 18 6 (3.57; 42)	–26 2 –8 (5.09; 385)	20 4 8 (3.89; 121)				

Montreal Neurological Institute coordinates of local maxima are provided (*x y z*, in millimeters) for all clusters that were significant at $p < .001$ uncorrected and exceed a cluster-extent threshold of 20 voxels. Values in parentheses provide corresponding *Z* scores and cluster sizes (voxels). Voxel locations marked with an asterisk (*) are used as seed ROIs in the PPI analysis. BA = Brodmann's area.

^aMotor cortex local maxima included in left temporal cortex clusters.

cerebellar TBS, (2) left cerebellar TBS, (3) right cerebellar TBS, and (4) sham TBS. The groups were matched for age (mean age \pm SD: Group 1 = 22 ± 6 years, Group 2 = 22 ± 2 years, Group 3 = 24 ± 6 years, and Group 4 = 24 ± 6 years) and sex (six men and four women in each group).

Stimuli and Task Conditions

All subjects performed an identical auditory-paced SMS task before and after TBS. As in Experiment 1, four different perturbations (subliminal: 3%, 18 msec and supraliminal: 15%, 90 msec in both positive and negative direction) were introduced into an otherwise regular auditory pacing sequence consisting of metronome tones presented at an IOI of 600 msec (frequency of 500 Hz and duration of 50 msec). The occurrence of sub- and supraliminal perturbations was intermixed within blocks to further avoid anticipation effects. After an initial 30-sec practice block, subjects performed a total of three 5-min SMS blocks with period of rest in between. At the beginning of each 5-min block, 10 regular tones were presented to allow subjects to synchronize their tapping to the regular pacing stimulus, and these data are excluded from all further analysis. After the initial 10 tones, a fixed epoch ($T - 4$ to $T + 4$ in which the shift occurs at time T) was repeated eight times for each of four different shifts in pseudorandomized order. Between two subsequent epochs, two to six stimuli at the standard IOI were introduced to avoid predictability of the next perturbation. Hence, over the three 5-min blocks, a total of 24 event-related error correction responses were obtained for each of the four shift conditions. Data analysis was identical to that of Experiment 1 and was based on an event-related approach including four taps before and four taps after ($T - 4$ to $T + 4$) each shifted stimulus (T). As with Experiment 1, if average normalized error correction scores represented extreme values (more than three times the interquartile range away from the group median) at three or four positions (in $T + 1$ to $T + 4$) for a single subject, these data were replaced by the group average of the value calculated within the relevant cerebellar TBS group. This led to the replacement of data from two subjects in the pre-TBS positive subliminal condition.

TBS Protocol

After completion of the full SMS task, the TBS procedure was explained to the subjects in detail, and any questions were answered. Subsequently, the resting motor threshold of each subject was determined using the thumb movement visualization method (Pridmore, Fernandes Filho, Nahas, Liberatos, & George, 1998). Each subject then received 40 sec of continuous TBS (Huang et al., 2005). A total of 600 pulses were applied at 80% of the resting motor threshold using a 70-mm figure-of-eight coil

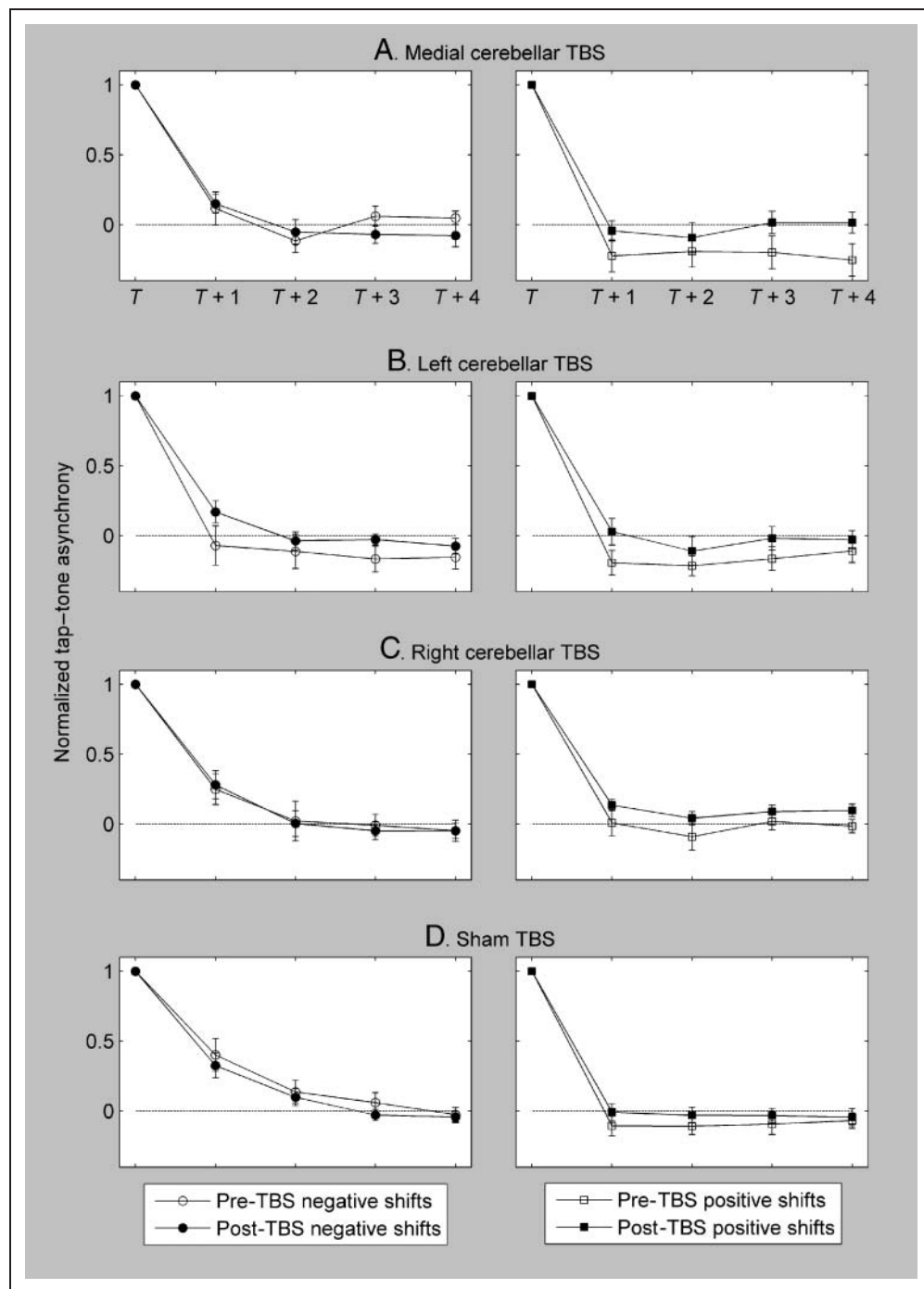
and a Magstim Super Rapid stimulator (Magstim Company, Whitland, UK). The target TBS locations were (1) the medial cerebellum (1 cm below inion), (2) the left lateral cerebellum (1 cm below inion and 3 cm left of midline), (3) the right lateral cerebellum (1 cm below inion and 3 cm right of midline), or (4) the sham TBS (1 cm below inion) (Lee et al., 2007; Theoret, Haque, & Pascual-Leone, 2001). The coil was positioned vertically with the handle pointing upward (Lee et al., 2007). For sham TBS, the coil was held at 90° angle to the scalp over the medial cerebellum. During and after TBS, none of our subjects reported any adverse effects.

Results and Discussion

To assess whether there were any differences in error correction performance between the four different TBS groups before stimulation, we performed a multivariate general linear model with a fixed factor for the TBS group and within-subject factors for direction (positive and negative), size (subliminal and supraliminal), and position ($T + 1$ to $T + 4$). The results indicate a trend-level effect of TBS group on pre-TBS performance ($p = .073$, Figure 4). Closer investigation of individual subject performance showed that the difference in pre-TBS performance was explained by two outlier subjects (one subject from the left and one from the medial cerebellar TBS groups). There was no significant difference in pre-TBS performance when data from these two subjects were removed ($p > .1$). Because the removal of these subjects did not affect the significance of the TBS findings, data from all subjects were included in the results presented below.

To compare error correction performance before and after TBS of the cerebellum, we performed a repeated measures ANOVA with within subject factors for TBS (before and after stimulation), direction (positive and negative), and position ($T + 1$ to $T + 4$) separately for the subliminal and supraliminal conditions on normalized error correction values for each group. In the left cerebellar TBS group, results indicate a trend-level main effect of TBS, $F(1, 9) = 4.84, p = .055$, and a significant TBS by position interaction, $F(3, 27) = 3.31, p = .035$. Post hoc analysis indicated that there was a significant effect of left cerebellar TBS at $T + 1$ ($p = .013$) but not at $T + 2$ to $T + 4$ ($p > .09$). At $T + 1$, the average normalized error correction value increased from -0.13 to 0.09 (Figure 4B). Left cerebellar TBS did not affect subliminal error correction performance ($p > .2$). By contrast, suppression of the right cerebellum did not change error correction of sub- or supraliminal phase shifts (Figure 4C). In the medial cerebellar TBS group, there was a trend-level TBS by direction interaction, $F(1, 9) = 3.75, p = .085$. Post hoc analysis showed a trend-level difference between performance before and after TBS during positive supraliminal error correction ($p = .09$) but not during negative supraliminal error correction ($p > .3$, Figure 4A). Further investigation showed a significant effect

Figure 4. Normalized error correction response as a function of stimulus position before and after suppression of the medial (A), left (B), and right (C) cerebellum with theta burst TMS and after sham TBS (D). Suppression of the medial cerebellum (A) only affected the correction of positive (right) supraliminal phase shifts. Suppression of the left cerebellum (B) affected supraliminal error correction of positive and negative shifts. TBS over the right lateral cerebellum (C) had no effect on error correction performance. Tap-tone asynchronies are shown for the time of the perturbation (T) and four subsequent taps ($T + 1$ to $T + 4$). The data are normalized to range from baseline asynchrony (0, dashed line) to the magnitude of the initial shift at time (T), and the sign is removed. Baseline performance is defined as the subject mean tap-tone asynchrony during $T - 4$ to $T - 1$. Performance before TBS (open circles and squares) is compared with post-TBS performance (filled circles and squares). In negative shifts (left side, circles), the tone occurs earlier than expected, and in positive shifts (right side, squares), the tone occurs later than expected. Error bars express a standard error.



of medial cerebellar TBS at time $T + 1$ on positive supraliminal error correction ($p = .045$) but not at the other time points ($p > .1$) and no effect on negative supraliminal error correction at any time point ($p > .1$). Medial cerebellar TBS did not affect subliminal error correction. There were no significant changes in error correction performance after sham TBS (Figure 4D). In the data set, the number of outlier error correction responses removed from the analysis was not statistically different between the conditions ($p > .4$) and was not affected by TBS ($p > .7$). The average number

of outlier error correction responses removed across subjects was 10.4 ($SD = 2.4$) of 216 total responses.

In summary, suppression of the left cerebellum significantly affected supraliminal error correction at the tap immediately after the phase shift. Suppression of the right cerebellum did not affect error correction performance. As such, the findings of Experiment 2 support results of Experiment 1 and provide further evidence that the left cerebellar cortex is necessary for the correction of supraliminal phase shifts during SMS.

GENERAL DISCUSSION

This study investigated the role of the cerebellum during sub- and supraliminal error correction in the context of an SMS task. Imaging results from Experiment 1 indicate a functionally lateralized response such that the right cerebellar dentate and vermis are activated in all SMS conditions compared with rest, whereas the left posterior cerebellar cortex is only engaged during the correction of large, supraliminal phase shifts. Furthermore, the left cerebellum exhibited enhanced connectivity with a cerebello-cortical network including the right lateral frontal cortex and the right cerebellum during the condition that included supraliminal error correction compared with regular SMS. In Experiment 2, TBS applied to the left cerebellum significantly affected the correction of positive and negative supraliminal errors, which confirms the causal contribution of the left cerebellum to the supraliminal error correction process.

The imaging results of Experiment 1 show that the right cerebellum is activated in all experimental conditions compared with rest (Figure 2C). The activation is mainly localized in the right dentate nucleus extending to the vermis (Figure 2E). The finding of persistent right cerebellar dentate activation closely replicates an earlier fMRI study investigating right-handed SMS and continuation (Rao et al., 1997). It is possible that cerebellar activation ipsilateral to the moving limb is related to movement control, in line with a traditional view of the cerebellum (Ramnani, 2006). However, activation of the right cerebellum during SMS may play a critical role in the timing of movement. There is neuroimaging evidence to suggest that the right cerebellum is essential for perceptual timing even when little or no movement is required (Lewis & Miall, 2003). Furthermore, it was shown in two independent rTMS studies that suppression of the right, but not the left, cerebellum affects perceptual timing abilities (Fierro et al., 2007; Lee et al., 2007). Nonetheless, future research will be needed to differentiate conclusively between the control of timing and movement within the cerebellum. For example, the present study may be replicated using the left hand to examine whether the right cerebellum is consistently activated during movement timing.

The left cerebellum was only involved during the condition that included error correction of perceivable changes in the pacing stimulus (Figure 2D). In contrast to the right dentate activation, activity in the left cerebellar hemisphere was located exclusively in the cortex (Figure 2F). The finding of involvement of the left lateral cerebellum during the correction of supraliminal errors closely replicates earlier findings (Stephan et al., 2002). Furthermore, our PPI results showed that during supraliminal error correction the left cerebellum displayed enhanced effective connectivity with a cerebello-cortical network that included the frontal and sensory cortices and the right cerebellum (Figure 3). The pattern of task-dependent effective connectivity between the left cerebellum and the auditory, sensory, and frontal cortices has, to our knowledge, not been shown in pre-

vious studies. Although the functional significance of this cerebello-cortical network is currently unclear, it may be that sensory input from the auditory and somatosensory domains are rapidly integrated in the frontal region and passed to the left cerebellum to facilitate prompt behavioral error correction. Further research will be needed to fully understand the function of the emerging cerebello-cortical network during supraliminal error correction. Lastly, the findings of Experiment 2 show that suppression of the left lateral cerebellum significantly affected the correction of supraliminal errors at the tap immediately after the perturbation (Figure 4), whereas suppression of the right cerebellum did not affect error correction performance. Hence, Experiment 2 provides evidence that the left cerebellum causally contributes to supraliminal error correction.

In both experiments, behavioral error correction occurred after subliminal perturbations. Yet no left cerebellar activation was found during subliminal error correction compared with regular SMS in Experiment 1. Furthermore, in Experiment 2, the correction of subliminal phase shifts was not affected by any of the TBS protocols. These findings suggest that the mechanism of subliminal error correction differs from that of supraliminal error correction. Repp (2005) previously proposed that synchronization during regular SMS is achieved through a continuous phase resetting mechanism. In the phase resetting hypothesis, the timing of each response is calculated on the basis of the previous pacing tone rather than the tap-tone asynchrony. Phase resetting after a perturbation that falls below the perceptual threshold is not different from phase resetting after a tone at the regular interval. Hence, the use of the same neural mechanism to achieve both regular SMS and subliminal error correction may explain why there was no additional brain activation during subliminal error correction in Experiment 1 and why cerebellar TBS did not affect subliminal error correction in Experiment 2. The phase resetting hypothesis is also consistent with the finding that spontaneous error correction was less efficient than induced error correction (because baseline asynchrony was not achieved within four taps; Figure 1C). This less efficient response to spontaneous shifts is expected if response timing is relative to the previous pacing tone rather than to the tap-tone asynchrony. Overall, these findings provide evidence that the correction of subliminal shifts may be achieved by a continuous phase resetting process that also controls accurate timing during regular SMS.

In addition to involvement of the left cerebellum, inferior parietal and frontal areas were activated during the condition that involved perceivable phase perturbations in Experiment 1. These results replicate findings by Stephan et al. (2002). However, the PPI analysis did not show increased connectivity between the left cerebellum and the parietal-frontal network. The lack of effective connectivity between the left cerebellum and the parietal-frontal cortices may suggest that the parietal-frontal network is engaged in more cognitive processes associated with the perception of errors rather than behavioral error correction. Consistent

with our interpretation, a number of studies have indicated the role of the parietal-frontal network in error perception. One study investigated the perception of supraliminal irregularities in pitch and duration of an auditory sequence (Molholm, Martinez, Ritter, Javitt, & Foxe, 2005), and another study looked at awareness of behavioral errors in a go/no-go task (Hester, Foxe, Molholm, Shpaner, & Garavan, 2005). Both studies showed activation in a parietal-frontal network similar to our findings, but without involvement of the cerebellum. Activation of a parietal-frontal network during the perception of irregularities and during awareness of behavioral errors may suggest that these regions are involved in conscious error detection. The right-hemispheric lateralization of parietal-frontal activation in Experiment 1 of our study provides further evidence that these areas are associated with conscious error detection. The right parietal and frontal areas are thought to play a role in directing attention (Posner & Raichle, 1994) and processing sensory feedback (Coull & Nobre, 2008), whereas the left cerebral hemisphere may be specialized in movement control (Serrien, Ivry, & Swinnen, 2006) and temporal attention (Coull & Nobre, 1998). In summary, activation of a parietal-frontal network during the condition that included supraliminal phase shifts may be related to conscious detection of supraliminal irregularities and of behavioral errors. Furthermore, the lack of cerebellar activation (despite cerebellar coverage) during the detection of irregularities and of behavioral errors (Hester et al., 2005; Molholm et al., 2005) supports the hypothesis that the left posterior cerebellum plays a crucial role in error correction rather than in the detection of perceptual mismatch or of sensorimotor error.

Behavioral data from both experiments show that the correction of positive shifts is faster than that of negative shifts (Figure 1). A similar dichotomy in error correction response was previously suggested (Praamstra et al., 2003) but was not seen in other similar studies (Repp, 2000, 2001a). Using electroencephalography, it has been shown that error-related negativity (associated with committing a behavioral error) is only present for positive supraliminal shifts and not for negative supraliminal shifts or subliminal shifts of either direction (Praamstra et al., 2003). The difference in error-related negativity for positive and negative supraliminal shifts suggests that the correction of these may be achieved by fundamentally different neural mechanisms. Although the experimental paradigm used in Experiment 1 did not allow a direct comparison between positive and negative shifts, the findings in Experiment 2 provide evidence that different neural mechanisms are involved in the correction of supraliminal positive and negative phase shifts. Experiment 2 shows that suppression of the medial cerebellum affects the correction of only positive phase perturbations, whereas left cerebellar suppression affects both positive and negative error correction. A previous study showed differential effects of unexpectedly early and late tone onsets in a temporal discrimination task (McAuley & Jones, 2003). Here, the discrimination threshold (i.e., the

minimum time difference required to differentiate between two durations) was significantly larger when a comparison interval was presented unexpectedly early with respect to a context rhythm. The different behavioral effects of early and late stimulus presentation may be due to the temporal expectancy created by the entrainment of an internal oscillator with an external rhythm (Large & Jones, 1999). In line with the above studies, we suggest that after positive shifts during SMS an expectancy mechanism may be used to prepare the correction response. In response to negative shifts, the expectancy mechanism may not be utilized as the errors should be corrected reactively (similar to a simple RT task). The results of Experiment 2 suggest that the medial cerebellum may play a role in the expectancy mechanism because suppression of the medial cerebellum affected only positive error correction. Future studies are needed to specifically test this hypothesis.

There are some methodological issues to consider in interpreting our results. The experimental design of Experiment 1 did not allow a direct comparison between positive and negative error correction. However, the TBS results of Experiment 2 provide evidence that the neural mechanisms for positive and negative error correction may differ. Future research may wish to investigate the difference between the correction of positive and negative supraliminal phase shifts using fMRI. Furthermore, the criterion used to find extreme cases of motor variability (deviations from mean asynchrony greater than 50 msec) may be considered arbitrary. However, it was chosen because it is similar to the group-averaged standard deviation of the asynchrony during regular taps (45 msec) and because it falls above the threshold for conscious perception (Repp, 2002a). The data were also analyzed adopting the criteria of 50-msec deviation from the target IRI (<550 or >650 intertap interval), which yielded similar results. Lastly, it is possible that the lack of right cerebellar activation during supraliminal error correction in Experiment 1 is associated with sensitivity issues because the right cerebellum is already significantly activated during all conditions compared with rest. Future research may wish to replicate our findings during left-handed SMS to exclude this possibility. Such research should also aim to extend scanning time to increase statistical power whilst maintaining sufficient levels of task performance. In addition, future research on the role of cortical regions in the emerging cerebello-cortical network is needed to gain a complete understanding of supraliminal error correction.

Conclusions

The current study aimed to investigate the neural networks for error correction of sub- and supraliminal phase shifts during SMS. The functional imaging results of Experiment 1 indicate two neural networks: (1) the primary motor and sensory cortices and the right cerebellar dentate

nucleus are involved in regular motor timing and correction of subliminal errors, and (2) the inferior parietal and frontal cortices and the left posterior cerebellar cortex are engaged during the detection and correction of perceivable errors. A PPI analysis furthermore shows that the left cerebellum exhibited enhanced connections with frontal, auditory, and sensory cortices and with the right cerebellum during supraliminal error correction compared with regular SMS. Experiment 2 shows that suppression of the left, but not the right, lateral cerebellum significantly affects supraliminal error correction. Taken together, the results of Experiments 1 and 2 provide evidence for a crucial role of the left cerebellum in conscious error correction but not in the correction of subliminal errors. Furthermore, findings of both experiments highlight differences between the response to positive and the negative shifts. We suggest that temporal expectancy may be used to correct positive shifts, and the medial cerebellum may play a role in temporal expectancy mechanisms. Negative shifts, on the other hand, may be corrected reactively.

Acknowledgments

J. Bijsterbosch was supported by a Medical Research Council PhD studentship.

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