Evidence for Anticipatory Motor Control within a Cerebello-Diencephalic-Parietal Network

Bettina Pollok[1], Joachim Gross[1,2], Daniel Kamp[1], and Alfons Schnitzler[1,3]

Abstract

■ The posterior parietal cortex and the cerebellum are assumed to contribute to anticipatory motor control. Thus, it is reasonable that these areas act as a functional unit. To identify a neural signature of anticipatory motor control, 11 healthy volunteers performed a bimanual finger-tapping task with respect to isochronous (i.e., regular) and randomized (i.e., irregular) auditory pacing. Neuromagnetic activity was recorded using a 122-channel whole-head neuromagnetometer. Functional interaction between spatially distributed brain areas was determined by measures of tap-related phase synchronization. Assuming that (i) the cerebellum predicts sensory events by an internal model and (ii) the PPC maintains this prediction, we hypothesized that functional interaction between both structures varies depending on the predictability of the pacing signal. During isochronous pacing, functional connectivity within a cerebello-diencephalic-parietal network before tap onset was evident, suggesting anticipatory motor control. During randomized pacing, however, functional connectivity after tap onset was increased within a parietal–cerebellar loop, suggesting mismatch detection and update of the internal model. Data of the present study imply that anticipatory motor control is implemented in a network-like manner. Our data agree well with the hypothesis that functional connectivity in a cerebello-diencephalic-parietal loop might be crucial for anticipatory motor control, whereas parietal–cerebellar interaction might be critical for feedback processing. ■

INTRODUCTION

Appropriate timing represents a fundamental prerequisite for the successful interaction with our social and physical environment. Fast movements cannot be executed under feedback control alone because biological feedback loops are too slow (van Beers, Baraduc, & Wolpert, 2002; Kawato, 1999). Thus, the central nervous system is assumed to predict sensory events. Such anticipatory control is based on the learned relationship between patterns of afferent and efferent signals (Wolpert & Flanagan, 2001; Wolpert, Miall, & Kawato, 1998; Wolpert, Ghahramani, & Jordan, 1995). Hence, anticipatory motor control requires (i) prediction of sensory events and (ii) an update of this prediction determined by sensory feedback.

Computations required for these processes have been attributed principally to two brain structures, the cerebellum and the posterior parietal cortex (PPC; for an overview, see Blakemore & Sirigu, 2003). A specific significance of the left superior PPC in evaluating the congruency between active movements and visual feedback of the actual outcome has been nicely shown (MacDonald & Paus, 2003). In this study, MacDonald and Paus (2003) demonstrated that repetitive transcranial magnetic stimulation (rTMS) over the left PPC results in disturbed mismatch detection between expected and actual sensory consequences of a movement. Hence, it has been argued that the superior PPC is involved in the comparison between sensory and motor information by maintaining the anticipated sensory consequences of a movement (MacDonald & Paus, 2003; Wolpert, Goodbody, & Husain, 1998). Alternatively, it has been demonstrated that PPC neurons can predict sensory changes prior to intended eye movements (Duhamel, Colby, & Goldberg, 1992; for an overview, see Andersen, Snyder, Bradley, & Xing, 1997), suggesting that the PPC might be key for anticipatory movement control as well.

A specific role of the cerebellum for predicting somatosensory consequences of voluntary movements has been proposed in several studies (Diedrichsen, Verstynen, Lehman, & Ivry, 2004; Blakemore, Frith, & Wolpert, 2001; Babin-Ratte, Sirigu, Gilles, & Wing, 1999; Blakemore, Wolpert, & Frith, 1999; Miall, Keating, Malkmus, & Thach, 1998; for overviews, see Blakemore & Sirigu, 2003; Miall & Reckess, 2002; Wolpert, Miall, et al., 1998; Ivry & Keele, 1989). Moreover, it has been demonstrated that the cerebellum is crucial for the prediction of sensory events even when a movement is not required (Tesche & Karhu, 2000). Thus, independent of a motor response, prestimulus cerebellar activity seems to reflect the prediction of any sensory input with high temporal acuity (Tesche &

[1]Heinrich Heine University, Duesseldorf, Germany, [2]University of Glasgow, UK, [3]University of Wales, Bangor, UK

Karhu, 2000). Along this line, Martin et al. (2006) nicely demonstrated that the amount of prestimulus activation within the cerebellum predicts reaction times, suggesting that an entrainment might be achieved by the prediction of sensory events.

Miall et al. (1998) reported an increase of simple cerebellar spike activity preceding about 150 msec that of complex spikes. This delay can be explained under the assumption that simple spike activity represents a predictive signal, whereas complex spikes indicate an error detection mechanism (Miall et al., 1998). This result suggests that cerebellar activity changes observed in several imaging studies (for an overview, see Blakemore & Sirigu, 2003) might represent prediction of sensory events as well as error detection. Because both processes (i.e., anticipation and error detection) might take place in identical brain structures separated by a small time delay of a few 100 msec, methodological approaches with high temporal resolution (i.e., within the range of milliseconds) are necessary to disentangle the functional contribution of the cerebellum and the PPC to anticipatory motor control. Thus, investigation of functional connectivity—and more specifically, investigation of the time course of synchronization—could help to unravel the functional contribution of the PPC and the cerebellum to anticipatory motor control.

Assuming that the cerebellum predicts sensory events, and the PPC maintains this prediction until actual sensory feedback is available, we hypothesized that coherence between both structures should be increased in two time windows: in a first window, before the actual outcome of the movement occurs as a signature of anticipation, and in a second window, after movement execution indicating error detection. To test this hypothesis, we investigated the oscillatory network associated with a simple finger-tapping task during isochronous and randomized pacing. Because the occurrence of the pacing signal in time during isochronous pacing is exactly predictable, anticipation should be evident in this condition. On the other hand, error detection should prevail during randomized pacing. Thus, we expected differences of the time course of functional interaction depending on the predictability of the pacing signal. More specifically, during isochronous pacing, we hypothesized increased functional interaction between the cerebellum and the PPC before tap onset as compared to unpredictable pacing as a signature of anticipation. In contrast, increased functional interaction between both structures after tap onset was expected during randomized pacing, representing error detection and update of the prediction for the next trial.

METHODS

Subjects and Paradigm

Eleven healthy, right-handed volunteers (6 men) participated in the present study. Data of one other subject were excluded from further analysis because the electromyographic (EMG) signal was not recorded continuously for the whole measurement period. Mean age was 30.2 ± 1.5 years (mean ± *SEM*) and overall age ranged between 22 and 38 years. Subjects gave their written informed consent prior to the magnetoencephalography (MEG) measurement. They were naïve with regard to the purpose of the experiment. The study was approved by the local ethics committee and was in accordance with the Declaration of Helsinki.

Subjects performed a bimanual finger-tapping task with respect to (i) isochronous pacing and (ii) randomized pacing in successive runs for 4 min, respectively. During isochronous pacing, subjects synchronized finger taps of the index fingers of both hands to an auditory pacing signal (500 Hz, 10 msec duration). The pacing signal was presented with a constant interstimulus interval (ISI) of 800 msec. Thus, in this condition, the auditory stimulus was exactly predictable. During randomized pacing, the auditory signal was presented with ISIs of 600, 800, or 1000 msec. Because ISIs were completely randomized, occurrence of the auditory stimulus was less predictable. In this condition, subjects were instructed to react as fast as possible as soon as the pacing signal occurred. The order of experimental runs was counterbalanced across subjects. In both conditions, subjects performed simultaneous bimanual brisk alternating finger flexions and extensions of their index fingers. We chose a bimanual task because, in a previous study (Pollok, Sudmeyer, Gross, & Schnitzler, 2005), evidence for a hemispheric asymmetry during a bimanual synchronization task was obtained, which does not occur during the same but unimanual task (Pollok, Gross, Müller, Aschersleben, & Schnitzler, 2005).

The pacing signal was delivered by a synthesizer (HP 33120A) and was presented binaurally through plastic tubes. Handedness was assessed using the Edinburgh inventory (Oldfield, 1971).

Data Collection

Subjects were comfortably seated in a magnetically shielded room while performing their tasks. Both arms rested on wooden panels fixed laterally to the chair. A short training period preceded the MEG measurement. The onset of finger taps was determined by photoelectric barriers mounted on a pad for each hand. Tap onset was measured on surface contact of each index finger. Neuromagnetic activity was measured with a helmet-shaped, 122-channel, whole-head neuromagnetometer (Neuromag). Simultaneously, we recorded muscle activity using surface EMGs placed on the first dorsal interosseus (FDI) muscle of both hands, respectively. MEG and EMG signals were recorded with a bandpass filter of 0.03–330 Hz, digitized with 1000 Hz, and stored digitally for off-line analysis. Eye blinks were recorded with vertical electrooculogram.

High-resolution T1-weighted magnetic resonance images (MRI) were obtained from each subject. Coregistration between MRI and MEG data was achieved by localizing three anatomical landmarks (nasion, left and right preauricular points) in each individual and by measuring the magnetic signals of four coils placed on the scalp. EMG signals were high-pass filtered at 20 Hz to remove movement artifacts and were rectified to enhance the firing rate information of muscle activity (Myers et al., 2003).

Data Analysis

For the identification of oscillatory activity associated with task execution, we used the analysis tool *Dynamic Imaging of Coherent Sources* (DICS; Gross et al., 2001). By using a spatial filter algorithm and a realistic head model, DICS allows the detection of cerebromuscular and cerebrocerebral coherence within the entire brain. After applying a Hanning window, fast Fourier transform (FFT) was applied to all EMG and MEG signals using the Matlab FFT function (www.mathworks.com). Values were calculated with a resolution of 1.3 Hz. FFT was calculated on 256 samples. Windows overlapped with half the FFT size. Cross-spectral density was computed to all signal combinations and averaged across the whole measurement period. Finally, a spatial filter was applied to voxels of the entire brain in order to create tomographic maps of coherent activity. Voxel size was $6 \times 6 \times 6$ mm. In a first step, we identified the brain area showing strongest coherence to muscle activity. We identified this source as reference region for the detection of further brain areas. Cerebromuscular coherence was calculated at movement frequency (i.e., 1.2 Hz). Additionally, coherence between the MEG and the pacing signal was calculated at this frequency. Coupling between brain areas was calculated at alpha (8–12 Hz) and beta (13–24 Hz) frequency, respectively. These frequency ranges were chosen because coupling and power at both frequencies have been shown to be closely related to motor control (for an overview, see Schnitzler & Gross, 2005). For cerebromuscular and cerebrocerebral coherence, the voxel showing the strongest coherence toward the reference region was identified and used for further analysis. The exact DICS procedure has been described in detail elsewhere (Gross et al., 2001).

We identified the position of each source in three-dimensional space. Mean localization maps of identified sources were calculated after normalization of individual anatomic and functional data using SPM99 (Wellcome Department of Cognitive Neurology, Institute of Neurology, University College London; www.fil.ion.ucl.ac.uk/spm).

We calculated the phase synchronization index (SyI) with respect to tap onset to obtain information about synchronization changes in time. SyI quantifies phase coupling between different brain regions (Rosenblum & Kurths, 1998). It is computed as the absolute value of the sum of phase differences of both regions divided by the number of epochs. Phase information was derived from the Hilbert transform of the bandpass filtered signals. SyI values can range between 0 and 1 indicating perfect phase locking (i.e., 1) or no phase locking (i.e., 0). SyI was calculated for each condition and for each connection. Values were calculated with a resolution of 1.7 msec at alpha and beta frequencies, respectively. The maximum peak amplitude, and its latency, was determined in each individual and in each connection and was averaged across subjects.

Because we were interested in differences of movement-related functional interplay between both experimental conditions, data were analyzed with respect to tap onset. They were calculated across subjects and are based on mean individual values. For all statistics, nonparametric test procedures were chosen. Paired comparisons were calculated using Wilcoxon test for dependent samples. For correlation analysis, we used Spearman's rank-order correlation. All statistics were calculated one-tailed because a priori hypotheses were tested. Alpha adjustments for all repeated test procedures were achieved with the sequentially rejective Bonferroni correction (Holm, 1979).

RESULTS

Behavioral Data

The handedness test revealed a mean laterality quotient of 98.6 ± 0.7 (mean ± *SEM*; range 95.0–100.0), suggesting that all subjects were strictly right-handed. During isochronous pacing, subjects demonstrated the well-known negative asynchrony, suggesting that finger taps of both hands led over the pacing signal. Mean values are −62.0 ± 11.3 msec (right hand) and −63.6 ± 12.3 msec (left hand). Randomized pacing was associated with reaction times of 132.7 ± 13.2 msec (right hand) and 126.4 ± 11.9 msec (left hand). No significant differences between both hands in either condition were evident (Wilcoxon test: $p > .1$). To investigate whether subjects tend to predict the pacing signal in the 1000-msec ISI, we calculated the reaction times separately for the three ISIs during randomized pacing. However, no differences were evident [136.4 ± 13.7 msec (600 msec), 137.0 ± 13.8 msec (800 msec), 136.6 ± 13.7 msec (1000 msec)].

The Oscillatory Network

In all subjects, the source showing the strongest coherence to FDI muscle was localized within the contralateral primary sensorimotor (S1/M1) hand area. Defining S1/M1 of each hemisphere as reference region, we localized coherent activity within the bilateral premotor cortex (PMC), the supplementary motor area (SMA), the PPC, the cerebellum, and the diencephalon. We would like to stress that due to the reduced spatial resolution of MEG data in deep brain structures, an exact localization

within the diencephalon is not possible. Therefore, the detected source might be due to activation within the thalamus and/or the basal ganglia.

Additionally, with respect to the pacing signal, oscillatory activity within the superior temporal sulcus of each hemisphere corresponding to the auditory cortex was localized. With the exception of both auditory sources, which were detected in 10 subjects, the other sources were evident in all subjects. Mean source localizations across all subjects as revealed by SPM99 are illustrated in Figure 1 and the appendant coordinates according to Talairach and Tournoux (1988) are summarized in Table 1.

Table 1. Talairach Coordinates of Detected Sources

Source	*x (mm)*	*y (mm)*	*z (mm)*	*BA*
M1 left	−38	−28	64	3
M1 right	36	−24	64	4
PMC left	−52	8	32	9
PMC right	46	26	36	9
SMA	−4	−4	68	6
PPC left	−30	−50	66	7
PPC right	22	−64	64	7
Auditory cortex left	−58	−18	2	22
Auditory cortex right	58	−20	12	41
Diencephalon left	−12	−16	14	
Diencephalon right	22	−16	10	
Cerebellum left	−38	−72	−42	
Cerebellum right	22	−78	−42	

Talairach coordinates of mean source localizations for brain areas occurring consistently across subjects.

Synchronization Index

Tap-related SyI was calculated for all source combinations. Analysis revealed a main peak in a time window between 200 msec before and 200 msec after tap onset. This peak was identified by visual inspection in individual data. Figure 2 depicts SyI between certain brain areas in one representative subject. These data indicate that, between two taps, SyI strength varies with clear discernible peaks. However, despite a maximum peak, synchronization is evident during the entire time course (i.e., from tap to tap). This figure furthermore indicates that differences between both experimental conditions occur in a subset of functional connections only.

In a further step, we identified the main peak in each individual and each source combination to estimate its latency and SyI strength at alpha and beta frequency, respectively. Mean group data comparing SyI strength

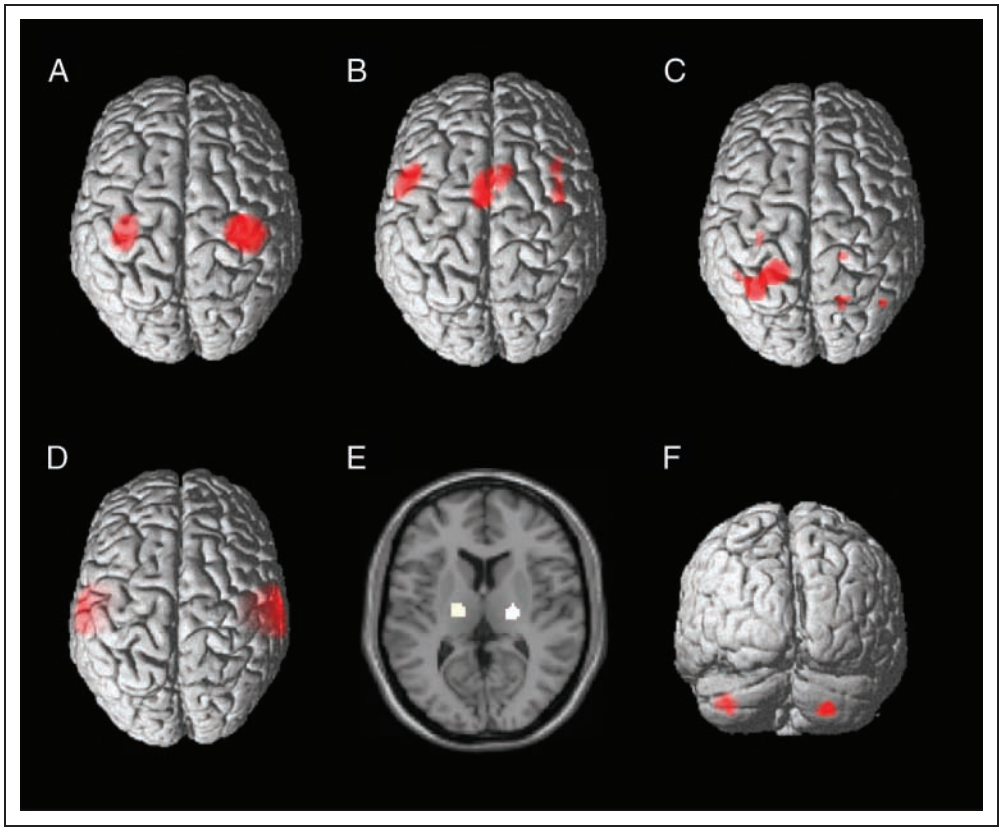

Figure 1. Mean source localizations of coherent activity at alpha and at beta frequencies. Sources being consistently evident across subjects were localized within bilateral (A) primary sensorimotor cortex (S1/M1), (B) premotor cortex (PMC) and supplementary motor area (SMA), (C) superior posterior parietal cortex (PPC), (D) auditory cortex, (E) diencephalon, and (F) cerebellum. Functional data were normalized and superimposed on a normalized brain using SPM99. Please note that S1/M1 was localized with respect to contralateral FDI, whereas auditory sources were identified with regard to the pacing signal. All other sources were localized with respect to S1/M1.

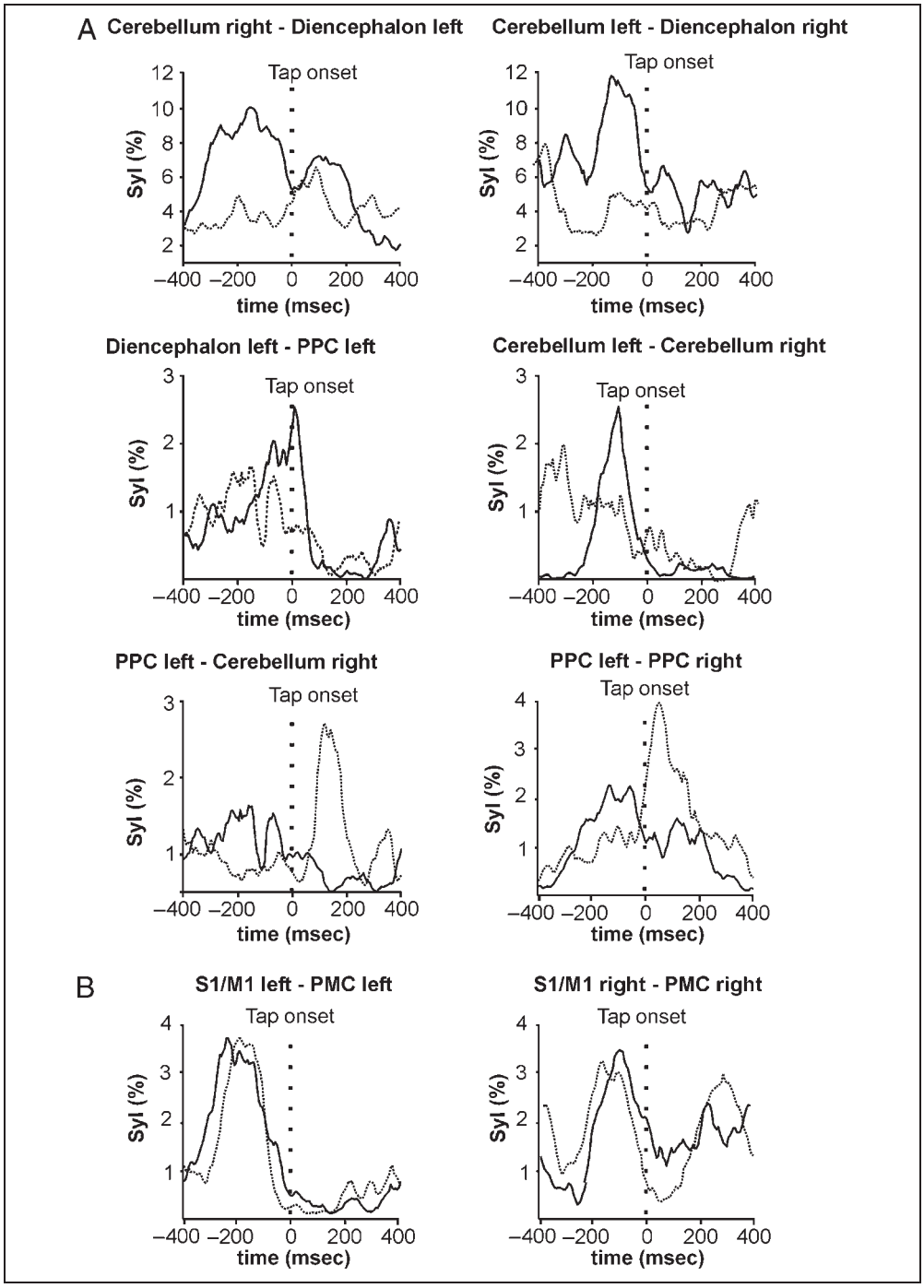

Figure 2. Synchronization index (SyI) for selected functional connections in one single subject during isochronous (solid line) and randomized pacing (dotted line). (A) Functional connections showing significant differences between isochronous and randomized pacing, whereas (B) depicts two connections, without differences between both experimental conditions. SyI can range between 0 indicating no phase synchronization and 1 representing perfect phase locking. The dotted vertical line indicates tap onset. Please note that in a time window between 200 msec before and 200 msec after tap onset, a discernible peak was evident. Peak latency and amplitude were detected in each individual and used for further statistical analyses.

between isochronous and randomized pacing are summarized in Figure 3.

As compared to randomized pacing, during isochronous pacing, SyI at alpha frequency was significantly stronger (i) between the right cerebellum and a source within the left diencephalon at −133 ± 18.9 msec and (ii) between the left diencephalon and the left PPC at −27.7 ± 16.1 msec. In contrast, SyI was stronger during randomized pacing (i) between the left PPC and the right cerebellum at 148.1 ± 20.0 msec and (ii) between the bilateral PPC at 53.2 ± 22.5 msec after tap onset. Within the contralateral hemisphere, comparable results were evident: During isochronous pacing, SyI was stronger between the left cerebellum and a source within the right diencephalon at −148.7 ± 14.8 msec and between the right diencephalon and the right PPC at 27.2 ± 23.0 msec. Moreover, SyI between bilateral cerebellar sources was significantly stronger at −168.6 ± 17.8 msec during this condition. However, no differences occurred between the right PPC and the left cerebellum ($p > .1$). To test whether this result might indicate a hemispheric asymmetry of functional interaction, we compared SyI

strength between the right cerebellum–left PPC and the left cerebellum–right PPC. Analysis did not reveal significant differences ($p > .2$).

At beta frequency, we observed stronger SyI during isochronous pacing between the left diencephalon and the left S1/M1 at −125.4 ± 9.6 msec and between the source within the right diencephalon and the right S1/M1 at −125.5 ± 13.4 msec. Statistical analysis revealed no significant latency differences between both conditions ($p > .2$). Figure 4 depicts mean latencies.

All in all, the analysis revealed differences of SyI strength between isochronous and randomized pacing in certain connections at alpha as well as beta frequencies. Figure 5 schematically summarizes differences of SyI strength as a measure of functional interaction.

Interestingly, no significant differences of phase synchronization between the auditory cortex and the cerebellum, or the auditory cortex and the PPC was evident ($p > .05$).

In a further step we calculated the correlation between SyI peak amplitudes showing significant differences between the two tasks and performance (i.e., negative asynchrony and reaction times). We found the performance to be significantly correlated with SyI between the left PPC and the right cerebellum (Spearman's $\rho = .62$; $p = .003$) and with SyI between the bilateral PPC ($\rho = .60$; $p = .003$). Accordingly, a significant correlation of SyI between the bilateral PPC and between the left PPC and the right cerebellum ($\rho = 0.50$; $p = .03$) was evident. Furthermore, SyI between the right cerebellum and the source within the left diencephalon and between this diencephalic activation and the left PPC was significantly correlated (rho = .64; $p = .001$). Additionally, a negative correlation between the left diencephalon

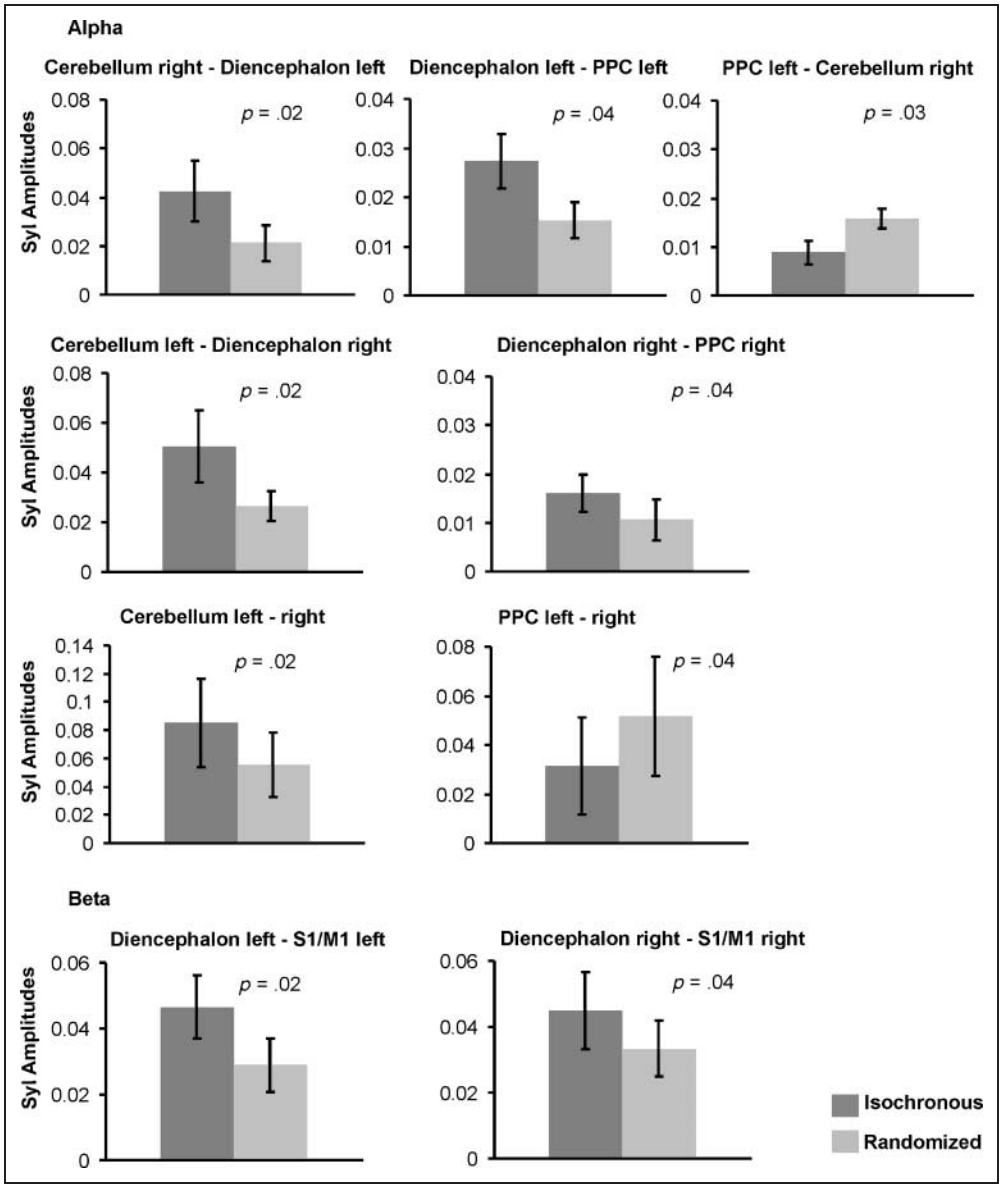

Figure 3. Mean SyI values estimated during isochronous and randomized pacing. In each individual dataset, SyI peaks were determined and averaged across subjects. For statistical analyses, Wilcoxon test for dependent samples was performed for comparison between isochronous and randomized pacing. For all repeated measurements, alpha adjustments were calculated. All p values are one-tailed. Error bars depict *SEM*. Please note that the ordering of the plots is arbitrary and does not reveal information about the directionality of information flow within the brain.

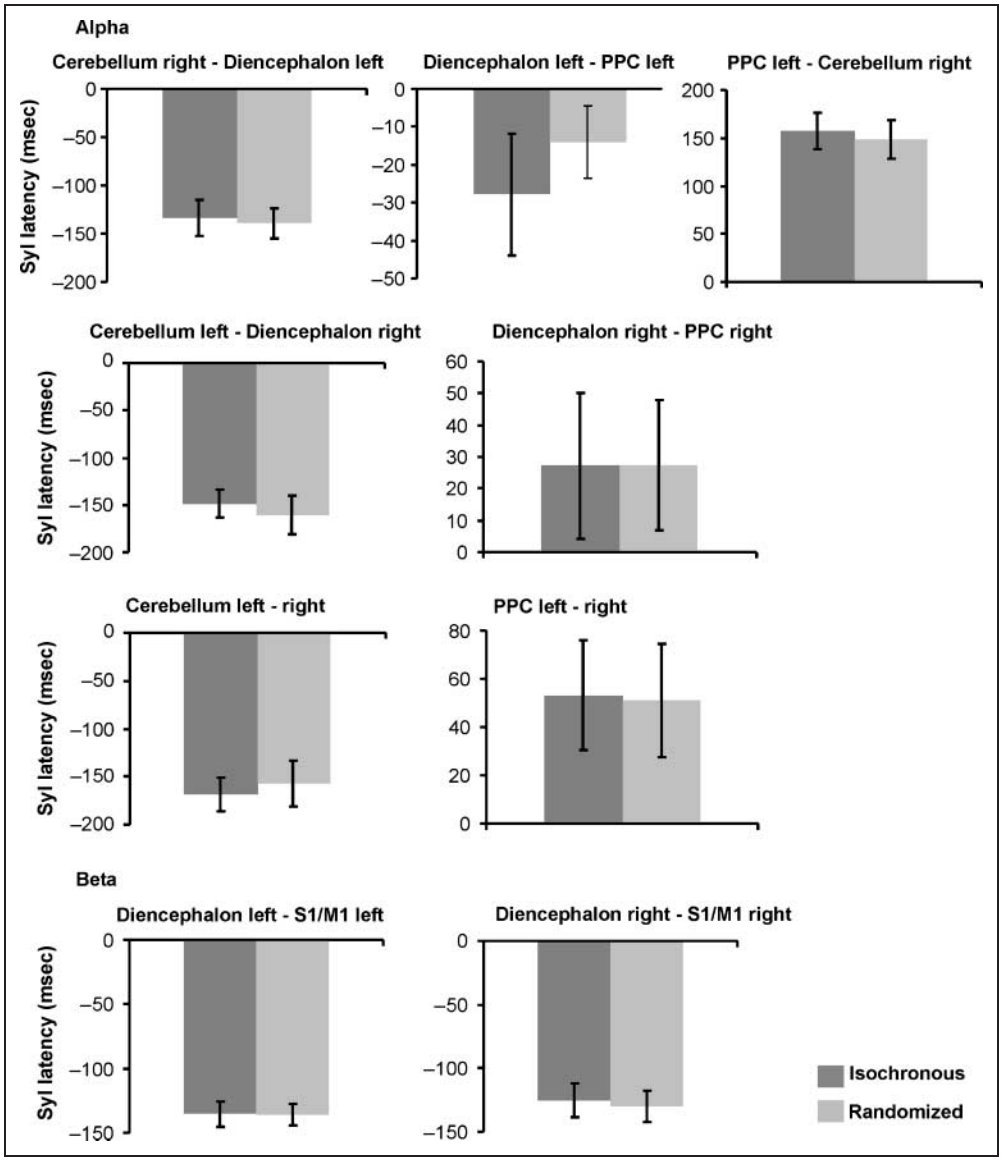

Figure 4. Mean SyI peak latencies during isochronous and randomized pacing. Latencies were determined when SyI peaks were maximal. Values are demonstrated for those connections in which significant SyI amplitude differences between both conditions were evident. Please note that in none of the conditions did significant latency differences occur (Wilcoxon test: $p > .2$). Error bars depict *SEM*. Again the ordering is arbitrary.

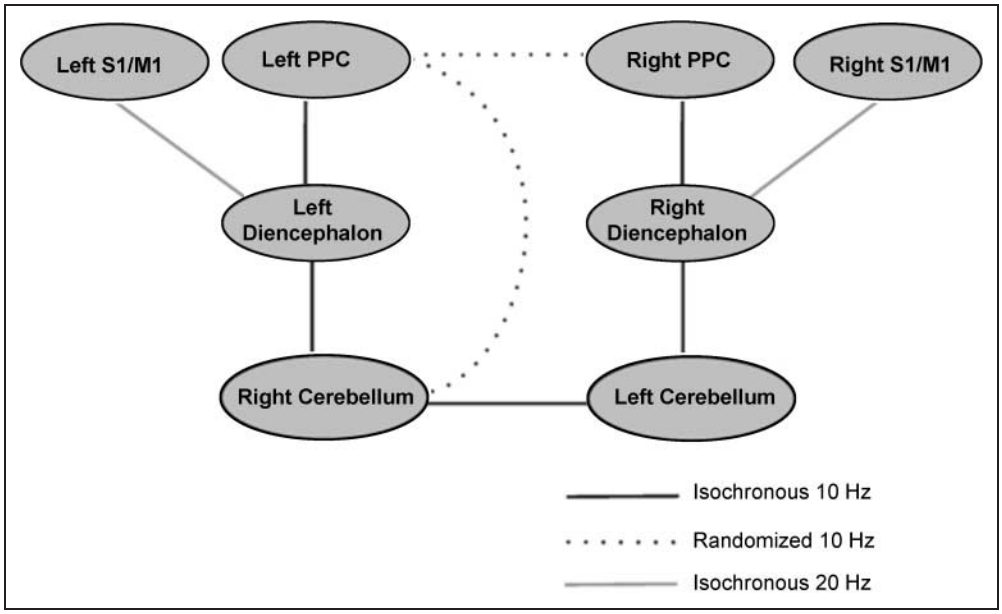

Figure 5. Summary of anticipatory motor control and feedback processing. Solid lines indicate stronger SyI values before tap onset as a measure of anticipation. Dotted lines delineate stronger SyI values after tap onset, indicating feedback processing. Black lines represent SyI at alpha frequency, whereas gray lines depict SyI at beta frequency. Please note that the demonstrated connections indicate SyI differences between experimental conditions but they do not represent the functional network of motor control.

and the left PPC, and the left PPC and the right cerebellum ($\rho = -.392$; $p = .04$) occurred. All calculated correlations are listed in Table 2.

Finally, we compared SyI amplitudes before tap onset (i.e., in a time window in which the cerebellum–diencephalon subnetwork is maximally synchronized) with those following the tap (i.e., in a time window, in which the PPC–cerebellum subnetwork shows strongest synchronization). This analysis was performed to elucidate whether the cerebello-diencephalon-PPC and the PPC–cerebellum networks showed their maximum synchronization at separate times. Analysis showed that before tap onset SyI between the cerebellum and the diencephalon was significantly stronger as compared to the post tap interval, in which the PPC–cerebellum was maximally synchronized. In contrast, SyI between the PPC and the cerebellum post-tap interval was significantly stronger as compared to the pre-tap interval, in which SyI within the cerebellum–diencephalon–PPC loop reached its maximum (Figure 6).

DISCUSSION

At least two mechanisms determine voluntary movements: feedback processing and anticipatory motor control. Previous studies suggest that the cerebellum anticipates sensory events, whereas the PPC maintains this information suggesting that both areas act as a processing circuit (Rao et al., 1997). We hypothesized that increased functional connectivity between both areas before tap onset indicates anticipatory motor control, whereas increased functional connectivity after tap onset represents error detection and processing of feedback information, possibly indicating an update of the internal model. Anticipatory motor control was expected to be primarily evident during isochronous pacing because during this condition the pacing signal was exactly predictable. In contrast, feedback processing was expected to prevail during randomized pacing because the pacing signal was less predictable. In this condition, subjects were required to initiate their finger movement after the auditory signal has occurred, resulting in mismatch between onset of the auditory signal and the finger tap. Evidence in favor of our hypothesis was obtained by showing that synchronization within a cerebello-diencephalic-parietal network was significantly stronger at about 150–20 msec before tap onset during isochronous pacing. In contrast, synchronization between the PPC and the cerebellum about 150 msec after tap onset was significantly stronger during randomized pacing. Although the present data support our hypothesis, we would like to stress that the criticality of a given network to behavior is always hard to interpret.

Behavioral Data

Analysis revealed the well-known negative asynchrony during isochronous presentation of the pacing signal, indicating that the tap precedes the auditory signal for 20–60 msec (for a review, see Repp, 2005). During randomized pacing, reaction times were at about 130 msec, indicating that anticipation was evident even in this condition. One critical point in the present procedure is that by using three ISIs only, subjects might be able to predict at least the longest ISI (i.e., 1000 msec). Thus, in this condition, fastest reactions are expected. To investigate whether subjects tend to predict the 1000 msec ISI, we calculated the reaction times separately for the three ISIs. Because no significant differences were evident, we can rule out the possibility that subjects were able to predict the occurrence of the auditory signal in this condition.

The Oscillatory Network

Analysis revealed that bimanual task execution is associated with oscillatory activity in a cerebello-diencephalic-cortical network oscillating at alpha as well as at beta frequencies. This network comprises the bilateral cerebellum, S1/M1, PMC, PPC, and SMA. Additionally, bilateral activation within the diencephalon occurred. This result replicates previous findings and is in line with the assumption that these constituents form a functional network controlling voluntary as well as involuntary movements (for overviews, see Carson, 2005; Schnitzler & Gross, 2005; Cardoso de Oliveira, 2002; Swinnen, 2002; Rao et al., 1997).

Synchronization Index

Analysis of the synchronization index revealed differences between both conditions at alpha and beta frequencies, respectively. At alpha frequency, SyI differences between both conditions occurred within a cerebello-diencephalic-parietal and within a parietal–cerebellar loop. Differences within the beta range were evident between the diencephalon and S1/M1. Although the exact functional meaning of both frequency ranges is still a debated issue, spontaneous oscillations observed in the Rolandic fissure at alpha frequency have been related to somatosensory processing, whereas those at beta frequency are assumed to represent motor control (for a review, see Hari & Salmelin, 1997). Along this line, coherence between the cerebellum and the PPC observed in the present data might suggest processing of somatosensory information, whereas coherence between the diencephalon and S1/M1 at beta frequency agrees well with motor control function.

We found significant SyI differences between both conditions in a time window between 200 msec before and 200 msec after tap onset. However, we would like to stress that these time windows depict differences between conditions only. Thus, results do not mean that (i) at other times synchronization is not evident and that (ii) prediction is exclusively related to isochronous pacing and error detection to randomized pacing.

Table 2. Correlation between Behavior and SyI Values

	Behavior	*Cer Right–Thal Left*	*Thal Left–PPC Left*	*PPC Left–Cer Right*	*Cer Left–Thal Right*	*Thal Right–PPC Right*	*Cer Left–Cer Right*	*PPC Left–PPC Right*	*Thal Left–S1/M1 Left*	*Thal Right–S1/M1 Right*
Behavior		rho = −.02	rho = −.04	**rho = .6**	rho = −.028	rho = −.27	rho = −.08	**rho = .60**	rho = −.26	rho = −.21
		p = .38	p = .06	***p* = .003**	p = .20	p = .25	p = .72	***p* = .003**	p = .24	p = .34
Cer right–Thal left			**rho = .64**	rho = .13	rho = .36	rho = .08	rho = −.24	rho = .31	rho = .14	rho = −.24
			***p* = .001**	p = .57	p = .10	p = .74	p = .28	p = .19	p = .52	p = .28
Thal left–PPC left				**rho = −.39**	rho = −.03	rho = .35	rho = .42	rho = −.33	rho = −.16	rho = −.10
				***p* = .04**	p = .90	p = .13	p = .07	p = .14	p = .49	p = .66
PPC left–Cer right					rho = .01	rho = −.31	rho = .02	**rho = .5**	rho = −.13	rho = −.34
					p = .96	p = .24	p = .94	***p* = .03**	p = .6	p = .14
Cer left–Thal right						rho = .16	rho = −.13	rho = −.22	rho = .23	rho = .01
						p = .51	p = .58	p = .33	p = .12	p = .96
Thal right–PPC right							rho = .26	rho = −.23	rho = .32	rho = .21
							p = .30	p = .33	p = .17	p = .34
Cer left–Cer right								rho = .15	rho = −.13	rho = −.03
								p = .52	p = .60	p = .88
PPC left–PPC right									rho = −.24	rho = −.24
									p = .28	p = .24
Thal left–S1/M1 left										rho = .11
										p = .62

Spearman's rank-order correlation between behavioral data and all SyI values showing significant SyI − amplitude differences between randomized and isochronous pacing. Values printed in **bold** indicate significant correlations.

Cer = cerebellum; PPC = posterior parietal cortex; Thal = thalamus; S1/M1 = primary sensorimotor area.

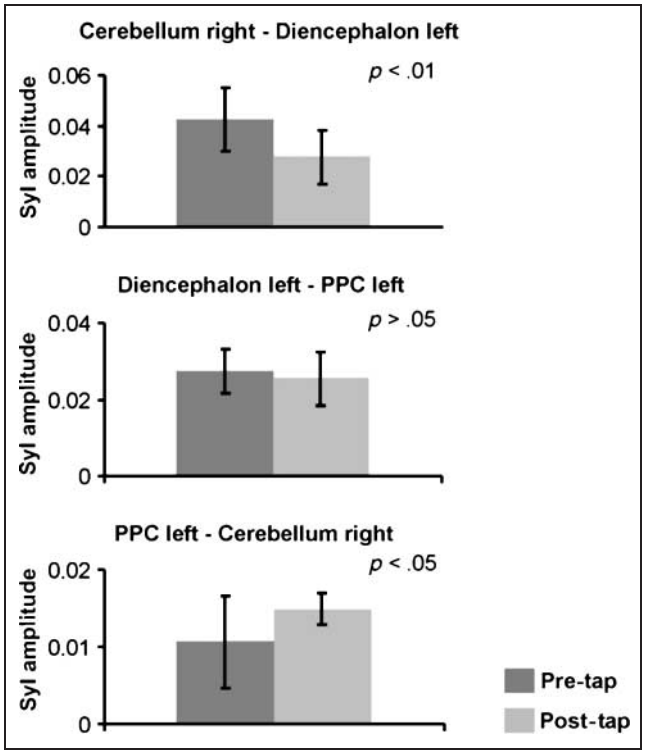

Figure 6. Comparison of SyI amplitudes before and after tap onset. Data indicate SyI amplitudes at times when the cerebellum–diencephalon–PPC and the PPC–cerebellum subnetworks reach the strongest synchronization, respectively. Please note that synchronization between the right cerebellum and the left diencephalon was significantly reduced at the time when synchronization between the left PPC and the right cerebellum reaches its maximum and vice versa. Thus, both subnetworks are maximally synchronized at separate times.

Comparing SyI amplitudes before and after tap onset revealed that at least synchronization between the cerebellum, the diencephalon, and the PPC on the one hand and between the PPC and the cerebellum on the other hand seems to be temporally specific. This analysis showed that, in a time window, in which one subnetwork is maximally synchronized, synchronization within the other network is reduced. However, it should be stressed that such temporal specificity did not occur between the diencephalon and the PPC. Although we do not have an explanation for this result, data suggest that both networks—at least partly—are characterized by temporal-specific synchronization supporting our hypothesis that both subnetworks might subserve different functions. All in all, data of the present study are in line with the hypothesis that, during isochronous tapping, anticipation might prevail, whereas during randomized pacing, error detection overweights.

Our data suggest that synchronization between the PPC and the cerebellum increases around tap onset—an event critical for the required tasks. This observation is in line with the idea that the cerebellum is crucial for anticipation of sensory events as well as for error detection. However, the time delays within the cerebellum demonstrated in the present study are at odds with those reported by Miall et al. (1998). Whereas these data suggest a time delay between complex and simple spikes of about 150 msec, the present data reveal a minimum time delay between prediction and feedback processing within the cerebellum of about 280 msec. This might be due to the fact that, in the present study, peak latencies were compared, whereas Miall et al. compared time windows. Thus, a direct matching between results from both studies could not be expected. Nevertheless, both studies agree well with the hypothesis that the cerebellum might be involved in anticipatory motor control as well as in feedback processing.

Functional Interplay between the PPC and the Cerebellum

In the present study, subjects were required to tap with respect to an explicit timing signal. A specific significance of the cerebellum for such tasks is well established (reviewed in Ivry, Spencer, Zelaznik, & Diedrichsen, 2002; Ivry, 1997). The cerebellum influences the cerebral cortex via a cerebello-thalamo-cortical pathway (for a review, see Horne & Butler, 1995). Conversely, the cerebellum receives back information from the cortex via the pons (for an overview, see Eccles, Ito, & Szentagothai, 1967). Thus, there is a close reciprocal connection between the cerebellum and the cerebral cortex.

Present data suggest a specific significance of functional connectivity between the PPC and the cerebellum for the execution of cued movements. Whereas the cerebello-diencephalic-parietal loop might subserve anticipatory motor control, the parieto-cerebellar loop seems to be related to feedback processing. Present data demonstrate that SyI strength between the right cerebellum and the left diencephalon is significantly correlated with SyI between the left diencephalon and the left PPC. Thus, functional connectivity between these structures seems to be closely related.

A specific significance of the right cerebellum has been established showing stronger right cerebellar activity in the prediction of sensory consequences of one's own movements using positron emission tomography (Blakemore et al., 2001; Kinoshita, Oku, Hashikawa, & Nishimura, 2000). Specifically, Blakemore et al. (2001) demonstrated that a discrepancy between actual and predicted sensory events is associated with increased right cerebellar activity. The authors concluded that the right cerebellum might signal discrepancies between the prediction and the actual sensory feedback. However, from positron emission tomography data, no information about the time course of activation can be derived. Thus, it is not yet clear whether the demonstrated activation changes are due to prediction or to mismatch detection. Data from Tesche and Karhu (2000), as well as from Martin et al. (2006), using MEG, demonstrate

significant prestimulus activation within the cerebellum strongly supporting the hypothesis that the cerebellum is key for the prediction of sensory events. Interestingly enough, such prestimulus activation has been shown even during passive stimulation (Tesche & Karhu, 2000), suggesting that cerebellar activity reflects the level of expectancy of sequentially presented stimuli.

It has been shown that rTMS over the PPC results in disturbed detection of such discrepancy (MacDonald & Paus, 2003). Thus, there is evidence that the PPC contributes to mismatch detection as well. Our data imply that functional connectivity between the cerebellum and the contralateral PPC might play a critical role for the anticipation of sensory events as well as for feedback processing. Two functional interpretations of this interplay seem to be apparent: Firstly, as suggested by MacDonald and Paus (2003) and Wolpert, Goodbody, et al. (1998), the PPC might maintain an internal representation of anticipated sensory events, which might be transferred to the cerebellum where a comparison between prediction and actual feedback takes place. However, if this were the case, no differences of functional connectivity strength would be expected between isochronous and randomized pacing. Secondly, the PPC maintains the prediction but also compares the predicted with the actual sensory events and sends this information to the cerebellum in order to update the prediction for the next trial. Along this line, one would expect stronger coherence between the cerebellum and the PPC in those cases, in which the prediction and the actual sensory consequences do not fit. Additionally, increased functional connectivity should be evident as soon as sensory feedback is available on a central level, (i.e., at about 100 msec after tap onset; Pollok, Muller, Aschersleben, Schnitzler, & Prinz, 2004; Pollok et al., 2003). Indeed, data of the present study favor this hypothesis because (i) increase of functional connectivity was evident during randomized pacing, and (ii) increase of functional connectivity between the PPC and the cerebellum occurred at about 140 msec after tap onset (i.e., about 270 msec after the tone onset). Thus, the data of the present study are in line with the hypothesis that the PPC maintains an internal representation of the prediction and, moreover, compares this prediction with the actual sensory feedback. By means of functional connectivity, the outcome of this process might be transferred toward the cerebellum where the prediction for the next trial is updated.

Further evidence for this hypothesis comes from the observation (i) that SyI between the left PPC and the right cerebellum was significantly correlated with performance accuracy. This result implies that the less accurate subjects perform (i.e., the larger the distance between tap and auditory signal), the stronger the synchronization between both structures after tap onset. Furthermore, (ii) analysis showed the left diencephalon–left PPC SyI to be negatively correlated with SyI between the left PPC and the right cerebellum. This result is in line with the idea that inappropriate anticipation—as indicated by weaker phase synchronization between the diencephalon and the PPC—should result in mismatch between anticipated and actual sensory feedback—demonstrated by stronger coupling between the PPC and the cerebellum. All in all, these data support the hypothesis that the PPC plays a crucial role for the detection of mismatch between anticipated and actual sensory events. Additionally, the PPC has been identified as an area of cross-modal processing (e.g., Di, Brett, & Barth, 1994; for a review, see Andersen et al., 1997). Thus, it is likely that information about the occurrence of the auditory signal might be processed within this areas as well. Consequently, a comparison between the predicted somatosensory consequences of the movement, the actual somatosensory feedback, and the actual auditory information might take place within the PPC. Interestingly, the present data did not reveal evidence for significant phase synchronization differences between the PPC and the auditory cortex or between the cerebellum and the auditory cortex. Although surprising at first glance, this result might be simply explained by the fact that the present data were analyzed with respect to tap onset. Due to the behavioral variability in both tasks (i.e., the varying temporal distance between tap and tone onset), stimulus-related phase differences might have vanished.

Analysis does not reveal evidence for neural activation within the pons. We rather found the PPC to be directly connected with the cerebellum, which is at odds with known anatomic connections. This might be due to the fact that signals in brain areas remote from the sensors—such as the pons—cannot be detected sufficiently well by the MEG device used in the present study. Thus, although coherent activation within the pons was not detected, it is likely that the apparent direct cerebellar–parietal connection is transferred via this area.

Interestingly, the data suggest a hemispheric asymmetry of feedback processing: Whereas during randomized pacing SyI between the left PPC and the right cerebellum was stronger as compared to isochronous pacing, no differences between the right PPC and the left cerebellum occurred. Although this result does not rule out a functional connection between both brain areas, it implies that this connection might be functionally less relevant for feedback processing—at least in a bimanual task. Thus, one might wonder how mismatch between actual and anticipated feedback detected in the right cerebral hemisphere might be processed. Data of the present study suggest that this takes place via a functional connection between the bilateral PPC. Thus, mismatch might be transferred from the right via the left PPC toward the right cerebellum. Evidence for this hypothesis is obtained by showing that SyI between the bilateral PPC is significantly correlated with that between the left PPC and the right cerebellum. Finally, the left cerebellar hemisphere is provided with this information by intercerebellar coherence. Interesting enough, SyI between

bilateral cerebellar hemispheres was stronger during isochronous pacing.

These results support a superior role of the left PPC and functional coupling between bilateral cerebellar hemispheres at least for the temporal control of simultaneous bimanual movements. Although surprising at first glance, both results are in line with the literature. A superior role of the left PPC for the production of manual sequences has been evidenced in patient (Haaland & Harrington, 1994; Harrington & Haaland, 1991) as well as in imaging (Schluter, Krams, Rushworth, & Passingham, 2001) and TMS (Schluter, Rushworth, Passingham, & Mills, 1998) studies. More specifically, the left PPC is assumed to be crucial for the control of movements, which require precise timing abilities (Schluter et al., 2001). Schluter et al. (2001) demonstrated left hemispheric PPC activation associated with a choice reaction time task, irrespective of whether the task was performed with the left or the right hand. Consequently, impaired manual sequence production has been shown after left posterior hemisphere lesions (Harrington & Haaland, 1991). Finally, results from Sirigu et al. (1996) imply that the left, but not the right, PPC plays a crucial role for the generation of a mental movement representation.

Functional connectivity between bilateral cerebellar hemispheres has been evidenced in previous MEG studies (Pollok, Butz, Gross, & Schnitzler, 2006; Pollok, Sudmeyer, et al., 2005). These data led to the hypothesis that such intercerebellar coupling might be crucial for the stabilization of simultaneous bimanual movements performed with respect to an explicit timing signal. It is a well-established phenomenon that during such tasks behavioral variability is reduced as compared to unimanual performance (reviewed in Ivry, 1997). A specific significance of the cerebellum for this bimanual advantage has been demonstrated (for an overview, see Ivry, 1997). Along this line, a superior role of the right cerebellar hemisphere for such simultaneous movements has been established using fMRI (Ullen, Forssberg, & Ehrsson, 2003). Data of the present study imply that the right cerebellar hemisphere receives information from the bilateral PPC, which might be used for the update of the prediction. For the next trial, these information are transferred toward the left cerebellum, possibly to obtain behavioral pattern stabilization between both hands.

Conclusion

Data of the present study imply that anticipatory motor control is implemented in a network-like manner. Our data agree well with the hypothesis that functional connectivity in a cerebello-diencephalic-parietal loop might be crucial for anticipatory motor control, whereas parietal–cerebellar interaction might be critical for feedback processing. Although the criticality of a given network to behavior is hard to demonstrate, the present data are in line with the idea that the PPC and the cerebellum act as a functional unit, however, subserving different functions.

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Reprint requests should be sent to Bettina Pollok, Department of Neurology, MEG-Laboratory, Heinrich Heine University, Moorenstr. 5, 40225 Duesseldorf, Germany, or via e-mail: bettina.pollok@uni-duesseldorf.de.

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