European Journal of Neuroscience, Vol. 16, pp. 1609–1619, 2002

The roles of the cerebellum and basal ganglia in timing and error prediction

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Keywords: attention, fMRI, predictability, striatum, switching

Abstract

Recent evidence that the cerebellum and the basal ganglia are activated during the performance of cognitive and attention tasks challenges the prevailing view of their primary function in motor control. The specific roles of the basal ganglia and the cerebellum in cognition, however, have been difficult to identify. At least three functional hypotheses regarding their roles have been proposed. The first hypothesis suggests that their main function is to switch attentional set. The second hypothesis states that they provide error signals regarding stimuli or rewards. The third hypothesis is that they operate as an internal timing system, providing a precise representation of temporal information. Using functional magnetic resonance imaging, we tested these three hypotheses using a task-switching experiment with a 2×2 factorial design varying timing (random relative to fixed) and task order (unpredictable relative to predictable). This design allowed us to test whether switching between tasks, timing irregularity and/or task order unpredictability activate the basal ganglia and/or the cerebellum. We show that the cerebellum is primarily activated with timing irregularity while the anterior striatum is activated with task order unpredictability, supporting their distinctive roles in two forms of readjustment. Task order unpredictability alone, independent of reward delivery, is sufficient to induce striatal activation. In addition, activation of the cerebellum and basal ganglia were not specific to switching attention because these regions were both activated during switching between tasks and during the simultaneous maintenance of two tasks without switching between them.

Introduction

The basal ganglia and the cerebellum are known to be involved in motor control because of the motor deficits resulting from their dysfunction. This motor function has been supplemented in recent years by numerous studies showing that the basal ganglia and the cerebellum are also involved in a wide range of nonmotor, cognitive tasks (Leiner *et al*., 1991; Ivry, 1996; Middleton & Strick, 2000). Although several studies have contrasted the roles of the cerebellum and of the basal ganglia in motor control and learning (Jueptner & Weiller, 1998; Doya, 2000), it has been difficult to distinguish their specific roles in cognitive performance. Three main hypotheses have been offered.

The first hypothesis is that the cerebellum and basal ganglia mediate switching attentional set (Akshoomoff & Courchesne, 1992; Owen *et al*., 1993; Hayes *et al*., 1998; Le *et al*., 1998). Indeed, both cerebellar lesions patients (Courchesne & Allen, 1997) and parkinsonian patients showed impaired performance in switching attention set or switching between tasks (Gotham *et al*., 1988; Eslinger & Grattan, 1993; Owen *et al*., 1993; Hayes *et al*., 1998; Cools *et al*., 2001b). FMRI studies also support the view that the lateral cerebellar hemisphere is activated in shifting attention (Le *et al*., 1998), but no specific basal ganglia activation was found for switch as compared to repeat trials during task switching (Dove *et al*., 2000; Sohn *et al*., 2000).

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Received 3 May 2002, revised 28 July 2002, accepted 6 August 2002

The second hypothesis is that the cerebellum and the basal ganglia code prediction errors (Fiez *et al*., 1992; Kawato & Gomi, 1992; Schultz & Dickinson, 2000; Ivry & Fiez, 2001). Evidence that the cerebellum codes prediction errors was first proposed for the motor domain, based on the fact that the cerebellum modifies its output with unexpected sensory input (Marr, 1969; Albus, 1971; Kawato & Gomi, 1992). This error-correction function has been extended to the cognitive domain, the cerebellum providing a more general error-correction role, in modifying internal thought (Bracke-Tolkmitt *et al*., 1989; Canavan *et al*., 1994; Courchesne & Allen, 1997; Hikosaka *et al*., 1999; Tamada *et al*., 1999; Doya, 2000; Imamizu *et al*., 2000; Blakemore *et al*., 2001; Ivry & Fiez, 2001). Evidence that the basal ganglia code an error prediction is mainly based on the fact that monkey's striatum codes a prediction error of reward delivery (Schultz, 2000; Schultz & Dickinson, 2000). A recent fMRI study in humans confirms this hypothesis, the ventral striatum being activated by reward unpredictability (Berns *et al*., 2001). However, it is unclear whether striatal activity necessarily requires reward delivery or whether the crucial factor is unpredictability itself.

The third hypothesis is that the basal ganglia and the cerebellum operate as an internal timing system, providing the precise representation of temporal representation across various tasks. Cerebellar patients have difficulty with perceptual tasks requiring precise timing (Ivry, 1996, 1997) and Parkinson's disease patients often underestimate time intervals (Pastor *et al*., 1992; Harrington *et al*., 1998). Direct evidence that the cerebellar neocortex is essential for timing the interval between stimulus and response in eyeblink conditioning has been provided by extensive neurophysiological and lesion studies in the rabbit.

doi:10.1046/j.1460-9568.2002.02212.x

Although cerebellar function is also associated with associative learning and sensorimotor coordination (Marr, 1969; Albus, 1971; Thach, 1998; Miall *et al*., 2001), we concentrate on testing the three theories mentioned above because they concern both the basal ganglia and the cerebellum. The goal of this study was thus to test whether activation of the cerebellum and basal ganglia are specific to switching attention between tasks, to error prediction or to timing irregularity. To address these questions, we conducted a task-switching fMRI experiment using a 2 × 2 factorial design varying timing (fixed relative to random) and task order (predictable relative to unpredictable).

Materials and methods

Subjects

Eight healthy subjects (mean age 25 years; range 20–31) with at least a high school education were recruited following procedures approved by the Institutional Review Board. All subjects were native speakers of English and strongly right-handed, as measured by the Edinburgh handedness inventory (mean score 90.5). None of the subjects presented with an abnormal neurological history. One or two days before the MR session, subjects participated in a behavioural testing session during which they were trained to perform each of the tasks and were required to attain an overall accuracy score > 90% to participate in the fMRI experiment.

Stimuli and task conditions

Subjects responded to visually presented letters (vowels or consonants, either in lower or upper case, in red or in green) by pressing response buttons with their right or left hand (Fig. 1). There were eight conditions, each cued by a distinct visual instruction, consisting of two conditions used for baseline (Task A, vowel-consonant discrimination; Task B, case discrimination), four tasks switching conditions (obtained by crossing the task order and timing factors) and two conditions used for control (Union task, A or B) (see full description below). The tasks were administered in six scanning runs. Each condition was included once in each run as a block of 24 trials for a total of 192 trials/run. Each run was pseudo-randomly ordered so that each condition appeared at different serial positions within a run and two conditions never appeared twice in immediate succession to prevent confounding order effects. Control tasks or tasks used for baseline alternated with switch conditions.

Sustained attention tasks (Baseline)

In the 'vowel–consonant' condition, subjects had to press the right button if the letter was a vowel and the left if the letter was a consonant. In the 'case discrimination' condition, subjects had to press the right button if the letter was in upper case and the left if the letter was in lower case. In both of these conditions, the colour of the letters was irrelevant. The baseline was composed of the mean of these two discrimination tasks [(A + B)/2]. In both of these two conditions, the colour of the stimuli (appearing every 2.5 s) alternated every three letters.

Switching tasks

In the 'switching' conditions, subjects had to take into account the colour of the letters to know which task to perform. If the letter was red, subjects had to perform the vowel–consonant condition (i.e. to respond with the right button if the letter was a vowel and with the left if it was a consonant). Conversely, if the letter was in green, subjects had to perform the case discrimination task (i.e. to respond with the right button if the letter was in upper case and with the left if it was in lower case). There were four different switch conditions: 'fixed predictable', 'random predictable', 'fixed unpredictable', 'random unpredictable'). In the fixed conditions the stimuli appeared every 2.5 s whereas, in the random condition, the timing between two stimuli was pseudo-randomized (2.5 s ±260, ±390, ±510 ms). In the predictable condition, a switch between tasks occurred every three stimuli and was pseudo-randomized in the unpredictable condition. Across each condition, the number of red/green letters (12 of each), of switches (11) and of left/right responses (12 of each) was consistently maintained.

Control condition

The mean of the following two conditions was used to control for the active maintenance of the two task sets without switching between them. In both of these conditions, subjects had to press the right button if the letter was a vowel or was in upper case (and if both were true) and the left button otherwise (Union condition). In the first control condition stimuli appeared every 2.5 s while, in the second control, the timing between two stimuli was pseudo-random every 2.5 s ± 260, 390 or 510 ms. In both of these control conditions, the colour of the letter was irrelevant and changed pseudo-randomly. Stimulus duration was 500 ms in all conditions.

This design allowed us to test the three hypotheses mentioned in the introduction. If the cerebellum and/or the basal ganglia are specific to switching attention between tasks, they should be more activated by task switching than by maintaining two task sets without switching between them. Furthermore, if the cerebellum and/or the basal ganglia are specific to timing adjustment, they should be activated by the main effect of timing irregularity (random > fixed timing conditions) because the uncertainty of the temporal relationship between events is maximal in the random condition. Behaviourally, a timing operation may be revealed either by slower reaction times (RTs) in the random compared to the fixed timing conditions or by a reduction in RTs with an increasing time lag in the random timing condition. The latter possibility is likely to occur if subjects use the probabilistic information conveyed by the passage of time to predict the likelihood of stimulus presentation (i.e. the more time the subjects have, the more probable the stimulus occurrence). In both cases, the main effect of timing irregularity (random > fixed timing) should reveal brain regions that attempt but fail to predict the timing of stimulus presentation [at least for short interstimulus intervals (ISIs)]. Conversely, the main effect of task order unpredictability (unpredictable > predictable task order) should reveal brain regions activated in error prediction, because more adjustment to the current task is needed when task order is unpredictable than when it is fully predictable. Indeed, subjects may constantly try to anticipate the following task. Thus, when task order is unpredictable, discordance between subject's expectation and the effective task to perform will result in error correction. In contrast, when task order is predictable, routine preparation for the whole sequence of tasks is possible and no error signal needs to be emitted.

Apparatus

Stimuli were generated by a PC computer using the Expe6 software package (ftp://ftp.lscp.ehess.fr/pub/expe6/) and projected onto a screen at the subjects' feet. Subjects viewed the stimuli through a mirror attached to the head coil. Subjects' behavioural responses were recorded when they pressed one of two MRI-compatible response buttons held in each hand.

Data analysis

Behavioural analysis

RT and percentage of errors were analysed with a MANOVA including the two factors of Task Order (predictable vs. unpredictable) and Timing (fixed vs. random).

Imaging data

High-resolution structural images were obtained using a standard 1.5 GE whole-body signa scanner with an RF head coil. For each subject, six time series of 180 whole-brain images (four first images removed) were obtained with a gradient-echo, echo-planar scanning sequence (TR 3 s, TE 40 ms, flip angle 90°; FOV 24 cm, acquisition matrix 64 × 64, 22 axial slices, thickness 6 mm). Each run was pseudo-randomly ordered according to a latin square design so that each condition appeared only once at different serial positions within a run and that baseline/control and switch conditions alternated. The order of runs was also counterbalanced across subjects. Using SPM96 with modified memory-mapping procedures, for each subject, the series of functional images for the six runs was realigned, normalized to the Montreal Neurological Institute template, smoothed with a Gaussian filter (10-mm FWHM kernel), and finally scaled across scans. Then, the data from all subjects were pooled and statistical parametric maps were computed from local MR signals using linear multiple regression with conditions, modelled as two temporal basis functions, and runs as covariates (Friston *et al*., 1991). Only regions formed by more than four adjacent active voxels (voxel size 4 mm^3) were reported (extend threshold $P < 0.5$). In accordance with our hypotheses, only cerebellar and subcortical regions are reported ($Z > 3.09$, i.e. $P < 0.001$, uncorrected for multiple comparisons).

Mean values are quoted ± SEM.

Results

Behavioural data

Behavioural results are depicted in Fig. 2. There was a significant response time cost (RT difference between switch and no switch trials) in all task-switching conditions [$F_{1,7} = 32.2$; $P < 0.001$] (main effect of Switch). Furthermore, performance was significantly worse when the order of the tasks was unpredictable than when it was predictable (RT = 932.2 ± 130.1 vs. 818 ± 142.9 ms, $F_{1,7} = 14.4$, $P < 0.01$; 4.7 ± 3.1% of errors vs. 3.9 ± 3.4%, $F_{1,7} = 5.7$, $P < 0.05$; main effect of Task Order). Finally, no main effect of Timing was found: fixed timing, compared to random timing, did not significantly reduced the error rate (3.8 ± 3.4% vs. 4.8 ± 3.3%, $F_{1,7} = 2.0$, $P = 0.19$) nor the RTs (865.6 ± 138.1 vs. 884.6 ± 123.8 ms, $F_{1,7} = 2.2$, $P = 0.18$). No interaction reached statistical significance. The mean RTs of the individual tasks used for baseline and control were: vowel/consonant, 717.3 ± 100.1 ms; case discrimination, 656.5 ± 89.8 ms; first union, 778 ± 115.2 ms; second union, 747.1 ± 79.2 ms.

It is possible that the different time lags between stimuli in the random timing conditions induce different types of behaviour (e.g. subjects may be better prepared with long than with short ISIs) which may not be observed by directly comparing the fixed to the random timing conditions. In order to better understand the contribution of the various time lags in random timing, we thus performed an additional three-factors repeated-measures ANOVA only for the two random-timing switching conditions, which included task order (Predictable vs. Unpredictable), time lag (five intervals of 408 ms from 1480 to 3520 ms) and switch (no switch vs. switch trials). As before, we found a main effect of Switch ($F_{1,7} = 15.3$, $P < 0.01$) and a main effect of Task Order ($F_{1,7} = 9.5$, $P < 0.05$). There was a trend toward a reduction of RTs with time lag ($F_{4,28} = 2.2$, $P = 0.09$); this trend became significant ($F_{4,56} = 3.2$, $P < 0.05$) in another analysis adding seven pilot subjects. No interactions were found between these factors. Error rates did not show any significant main effect or interactions.

To ensure that the control condition effectively induced the subjects to maintain two tasks in memory without switching between them, we directly compared the control and the switching conditions. RTs were significantly slower in the task-switching conditions averaged together (mean 875.0 ± 129.9 ms) than in the control condition (mean 763.2 ± 96.1 ms; $F_{1,7} = 34.8$; $P < 0.001$), indicating that the switching conditions demanded additional cognitive processes over those needed for the control task. Furthermore, subjects did maintain two task-sets simultaneously in memory in the control condition because, if subjects coded the control condition as a single stimulus–response mapping, they should have directly associated the lower case consonants to a left motor response and other letters to a right button press. However, RTs were not faster for lower case consonants than for other letters (vowels and upper case consonants) ($F_{1,7} = 0.95$; $P = 0.4$).

Imaging data

Tables 1 and 2 present results from all the brain regions activated in the different conditions. In the following, we focus on subcortical and cerebellar activation to test our hypotheses. First, we investigated which cerebellar and subcortical regions were significantly activated in all switching conditions averaged together relative to baseline ($Z > 3.09$, i.e. $P < 0.001$, uncorrected). Activation was found in the cerebellar hemispheres (lobules VI, VIIIA, VIIIB, Crus I, in Schmahmann's nomenclature; Schmahmann *et al*., 1999), the vermis (lobules VII, VIII) (Fig. 3), the thalamus and the caudate nucleus (Fig. 4). We plotted the activation of each task-switching condition separately relative to baseline at the peak of activation of each of these brain regions ($Z > 3.09$, i.e. $P < 0.001$, uncorrected) (Figs 3 and 4, bottom).

In order to control for the higher working memory load necessary to keep both task sets active during the task-switching conditions, we also examined the voxels commonly activated by each task-switching condition relative to the control condition, which required subjects to maintain two task-sets in memory without switching between them. This was done by selecting the voxels activated in all task-switching conditions averaged together relative to baseline ($Z > 3.09$, $P < 0.001$, uncorrected for multiple comparisons) which were also activated in each individual task-switching condition compared separately to baseline ($Z > 2.33$, $P < 0.01$, uncorrected). None of the brain regions mentioned above (caudate nucleus, thalamus and cerebellum) were significantly activated in this comparison ($Z < 1.7$, $P > 0.05$, uncorrected). Furthermore, all these brain regions were significantly activated in the control condition relative to baseline ($Z > 3.09$, i.e. $P < 0.001$, uncorrected), indicating that they were not specifically activated during task switching (graph bars in Figs 3 and 4).

The main effect of task-order unpredictability (subtraction of the two task-switching conditions with predictable order from the two with unpredictable task order) activated the anterior putamen bilaterally ($Z > 3.09$, i.e. $P < 0.001$, uncorrected) (Table 1, Fig. 5). No significant activation was found in the cerebellum.

The main effect of timing irregularity (subtraction of the two task-switching conditions with fixed timing from those with random timing) was to activate the right posterior cerebellar hemispheres (VI/

TABLE 1. Foci of activations in the different statistical contrasts

		All task-switching conditions averaged together vs. baseline				Main effect of irregular timing				Main effect of unpredictable task order			
Anatomical structure	(Brodmann's area)	*x*	*y*	*z*	*Z*-value	*x*	*y*	*z*	*Z*-value	*x*	*y*	*z*	*Z*-value
Cerebellum													
Left cerebellar hemisphere		–28	–68	–40	6.72								
		–44	–64	–28	6.68								
Right cerebellar hemisphere		32	–64	–32	3.71	28	–60	–32	4.96				
						20	–40	–44	5.56				
Vermis (VIIB/VIIIB)		0	–68	–32	5.80								
Basal ganglia													
Left Caudate nucleus		–16	–16	24	5.15								
Right Caudate nucleus		16	4	20	5.13								
Left Putamen										–20	4	0	3.66
Right Putamen										20	16	0	4.60
										16	8	–4	4.51
										12	–4	–8	3.83
Thalamus													
Left thalamus (vl)		–12	–16	8	4.78								
Right thalamus (dm)		28	–12	8	4.79								
Frontal													
L sFG	(BA 6)	–28	4	56	7.56								
L mFG	(BA 8/9/44)	–40	20	32	7.18					–44	16	32	5.79
R mFG	(BA 8/9/46)	48	16	40	7.77								
		60	28	32	6.47								
R iFG	(BA 44/45)									36	24	20	6.21
L Somato-motor area	(BA 4)									–28	–16	60	5.16
R Somato-motor area	(BA 4)									20	–16	68	6.21
Parietal													
L IPS	(BA 7/40)	–36	–56	52	8.36					–32	–56	48	6.10
R IPS	(BA 7/40)	36	–60	44	8.05					40	–48	48	5.74
Temporal gyrus													
L iTG	(BA 20)									–52	–28	–12	6.64
R iTG	(BA 37)	52	–56	–4	7.54					52	–56	–4	7.54
Insula													
L INS										–20	24	–4	5.59
R INS										28	28	4	5.37
L m occip. gyrus	(BA 18/19)									–28	–88	4	6.19
R m occip. gyrus	(BA 18/19)									28	–84	–8	5.38

All areas were significant at $P < 0.001$ (uncorrected for multiple comparisons); *x*, *y*, and *z* are standardized stereotaxic coordinates of Talairach and Tournoux. Abbreviations: L, left; R, right. sFG, superior frontal gyrus; mFG, middle frontal gyrus; IPS, intra-parietal sulcus; INS, insula; iTG, inferior temporal gyrus; sTG, superior temporal gyrus; Somatosens. cx, somatosensory cortex; occip. gyrus, occipital gyrus; vl, ventro-lateral, dm, dorso-medial.

TABLE 2. Areas revealing interactions between task order and timing

	Talairach coordinates			
Anatomical structures	*x*	*y*	*z*	*Z*-value
Frontal cortex				
Right PM/Motor cx (BA 4/6)	52	–8	28	6.5
Left Motor cx (BA 4)	–44	–12	32	6.1
Right mFG (BA 9/46)	40	28	28	6.5
Left mFG (BA 9/46)	–36	28	24	5.8
Left fronto-polar cx (BA 10)	–28	48	8	5.2
Pre-SMA	–4	12	56	4.9
Cingulate cortex				
Anterior cingulate (BA 24)	4	28	16	5.4
Basal ganglia				
Right Caudate nucleus	16	12	4	3.79
Left Putamen	–24	–8	–4	4.08
Right Putamen	20	–4	4	3.68
Temporal gyrus				
Right mTG (BA 19/37)	40	–72	4	5.7
Left mTG (BA 37)	–52	–36	–8	4.8

BA, Brodmann's area; mFG, medial frontal gyrus; mTG, middle temporal gyrus; PM, pre-motor cortex; *x*, *y*, *z*, Talairach coordinates. All areas were significant at $P < 0.001$ (uncorrected for multiple comparisons).

VIIB/Crus I) (Schmahmann *et al.*, 1999) and the dentate nucleus ($Z > 3.09$, i.e. $P < 0.001$, uncorrected) (Table 1, Fig. 6). No significant activation was found in the basal ganglia.

Brain regions showing interactions between the timing and task-order factors ($Z > 3.09$, i.e. $P < 0.001$, uncorrected) activated the right head of the caudate nucleus and the posterior putamen bilaterally (Table 1, Fig. 7). No interactions were found in the cerebellum.

Finally, we investigated whether the combination of task order and timing unpredictability activated specific subcortical regions relative to baseline ($Z > 3.09$, i.e. $P < 0.001$, uncorrected). We found that the task-switching condition with unpredictable task order and random timing specifically activated the substantia nigra (Fig. 8).

Functional connectivity analysis

In order to better understand what the basal ganglia/cerebellum do with task order/timing information, we performed a functional connectivity analysis on our data. This analysis allows us to point out which brain regions correlate with the cerebellum and the basal ganglia in each task-switching condition. For each subject, we measured the mean blood oxygenation level-dependent (BOLD)

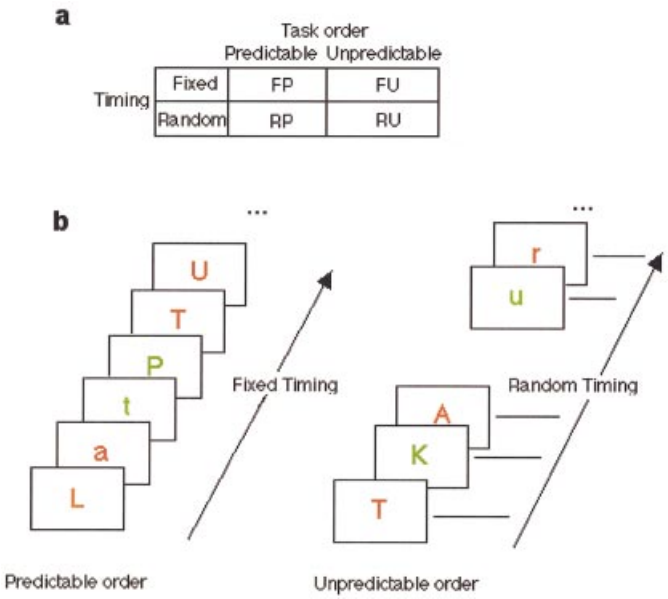

FIG. 1. (a) Table describing the 2 × 2 factorial design. The two factors of interest were timing (Fixed, 2.5 s; Random, 2.5 s ± 260, 390 or 510 ms) and task order (Predictable, switch on every second trial; Unpredictable). The factors were crossed to produce four distinct task-switching conditions: Fixed timing Predictable order (FP), Fixed timing Unpredictable order (FU), Random timing Predictable order (RP), Random timing Unpredictable order (RU). (b) Stimuli and timing. Subjects responded to visually presented letters by pressing response buttons with their right or left hand. Subjects had to switch between two letter-discrimination tasks depending upon the colour of the letter. If the letter was red, subjects performed a vowel–consonant discrimination task (Vowel, right; Consonant, left). If the letter was green, subjects performed a case-discrimination task (Upper case, right, Lower case, left). Two (FP and RU) of the four possible tasks switching conditions are represented in examples. (Left) Stimuli in the predictable task order condition with fixed timing. (Right) Stimuli in the unpredictable task order condition with random timing.

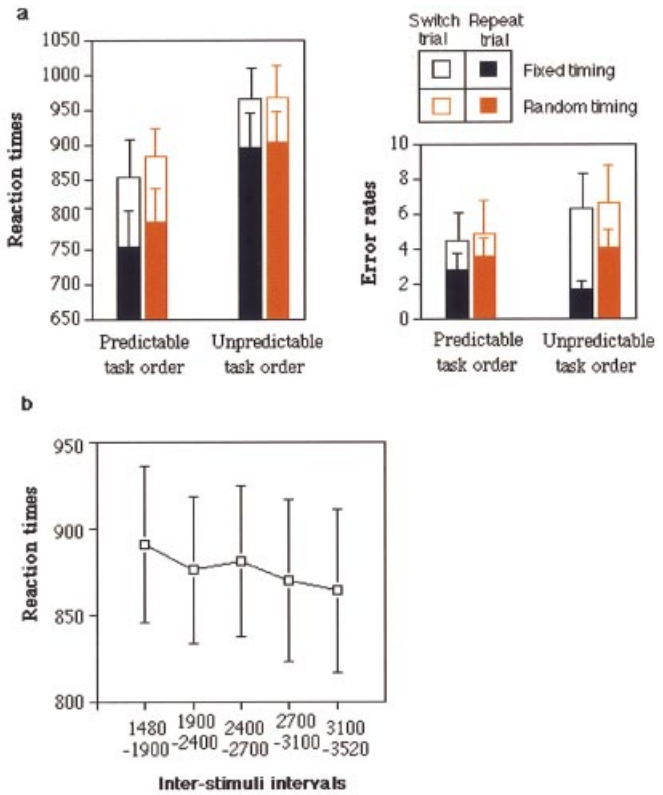

FIG. 2. (a) Mean response time (left) and error rates (right) averaged across subjects in the various tasks switching conditions for the repeat and switch trials. Mean response time was examined for correct response trials only. (b) Response time for each of the five intervals grouping the different ISIs of the two task-switching conditions with random timing. Errors bars represent SEM. The random timing condition 2.5 s ± 260, 390 or 510 ms creates the following ISIs: 1480, 1600, 1720, 1730, 1850, 1980, 2250, 2370, 2380, 2500, 2620, 2630, 2750, 3020, 3150, 3270, 3280, 3400 and 3520 ms.

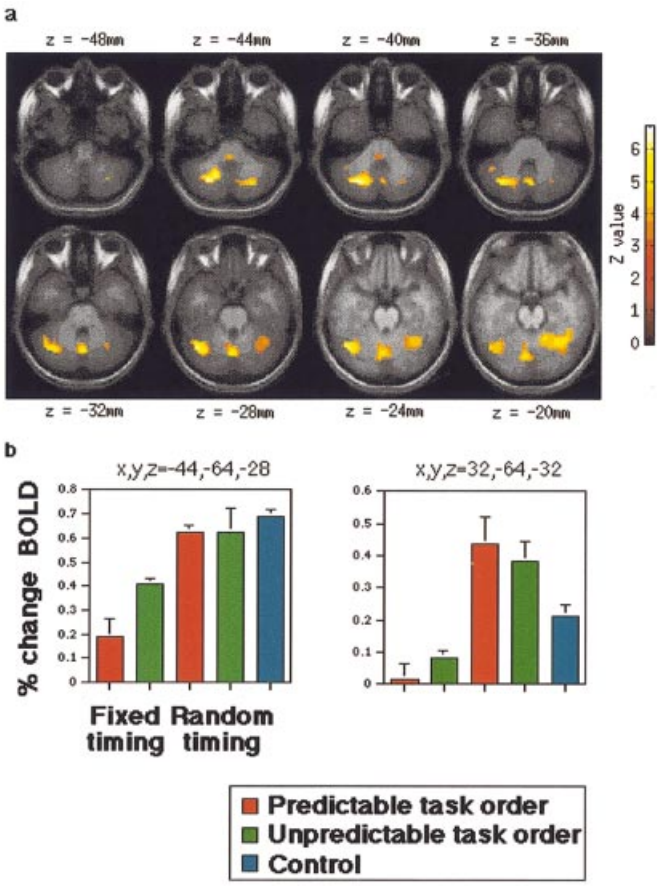

FIG. 3. (a) Data for cerebellar regions significantly activated in all tasks switching conditions relative to baseline (mean of the two discrimination tasks) were superimposed on the mean structural MRI slices averaged across subjects. Slices are shown in neurological convention. The *Z*-values for the regional maxima are listed in Table 1. (b) Percentage of signal change relative to baseline for each task-switching condition and for the control condition at the peak of activation in the cerebellar hemispheres. Error bars indicate SEM.

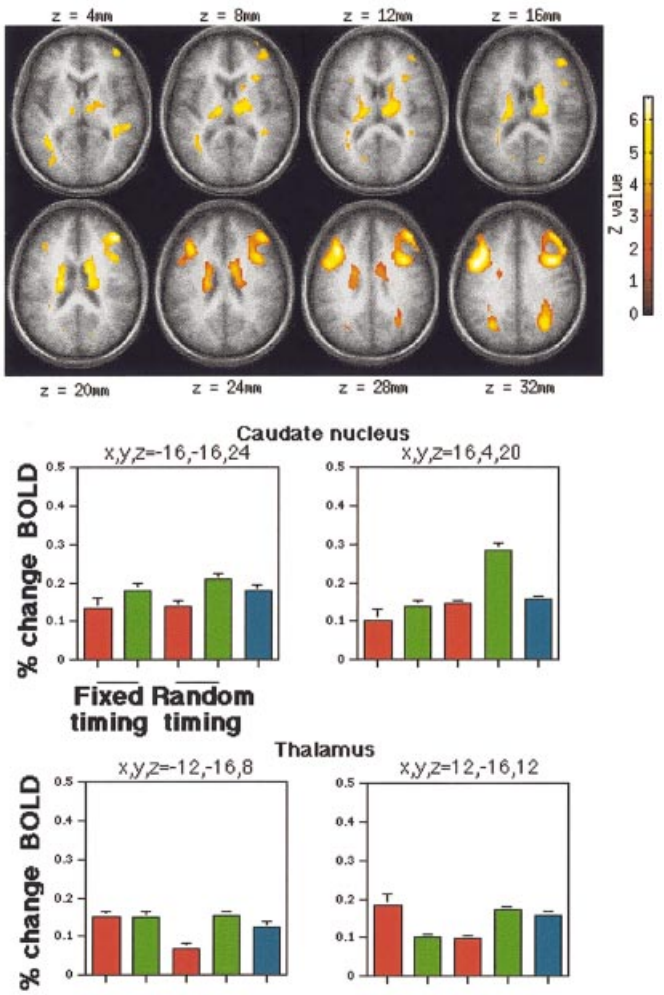

FIG. 4. (Top) Data for striatal and thalamic regions significantly activated in all tasks switching conditions relative to baseline were superimposed on the mean structural MRI slices averaged across subjects. Slices are shown in neurological convention. The *Z*-values for the regional maxima are listed in Table 1. (Bottom) Percentage of signal change relative to baseline for each task-switching condition and for the control condition in the caudate nucleus and thalamus. Error bars indicate SEM.

signal in each task-switching condition relative to baseline at the peak of activation of the following brain regions activated by all task-switching conditions relative to baseline (Table 1): the dorsolateral prefrontal cortex (DLPFC) (x,y,z = 48,16,40; x,y,z = –28,4,56), the intraparietal sulcus (IPS) region (x,y,z = –36,56,52; x,y,z = 36,60,44), the pre-supplementary motor area (pre-SMA) (x,y,z = –4,16,52), the caudate nucleus (x,y,z = –16,16,24; x,y,z = 16,4,20) and the cerebellum (x,y,z = –28,68,40; x,y,z = 32,64,32; x,y,z = 0,68,32). In each task-switching condition, we then performed correlations between each of these brain regions. We focused on brain regions correlating with the caudate nucleus in the unpredictable task order conditions and with brain regions correlating with the cerebellum in the random timing conditions (Fig. 9). Figure 9a represents the pattern of activation in the different task-switching conditions relative to baseline ($Z > 3.09$, i.e. $P < 0.001$, uncorrected) and Fig. 9b (top) represents the matrix of interregional correlations (R^2). In order to clarify the results, we also collapsed together the data from left and right hemispheres in these brain networks (Fig. 9b, bottom).

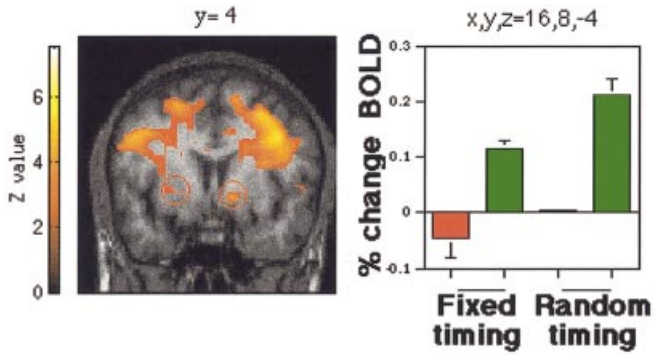

FIG. 5. (Left) Main effect of task order unpredictability superimposed on a normalized coronal MRI slice of one subjects. (Right) Percentage of signal change relative to baseline for each task-switching condition in the right anterior putamen. Error bars indicate SEM.

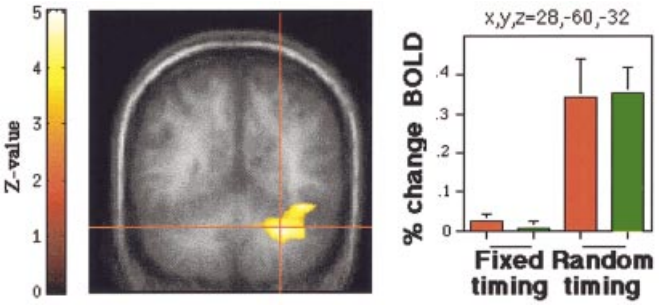

FIG. 6. (Top) Main effect of timing irregularity superimposed on the mean structural MRI slices averaged across subjects. The *Z*-values for the regional maxima are listed in Table 1. (Bottom) Percentage of signal change relative to baseline for each task-switching condition in the right cerebellar hemisphere. Error bars indicate SEM.

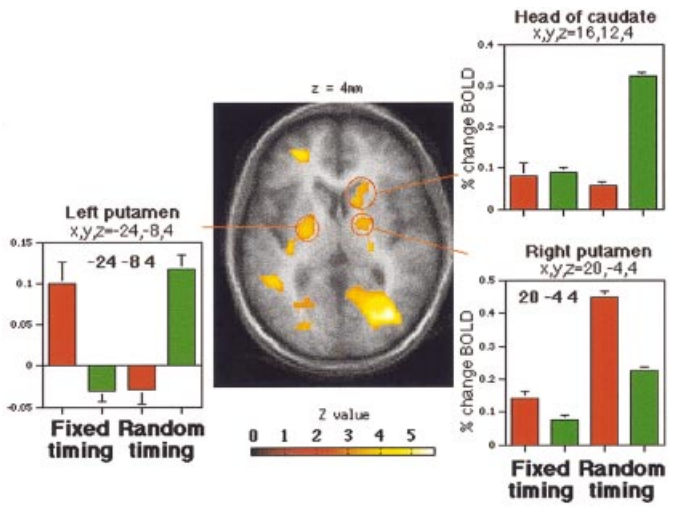

FIG. 7. Interactions between task order and timing superimposed on normalized structural MRI slices averaged across subjects. Percentage of signal change relative to baseline for each task-switching condition is shown at the peaks of striatal activation. Error bars indicate SEM.

When task order was unpredictable (and timing was fixed or random), the caudate activation positively correlated with activation of the DLPFC and the cerebellum. In addition, when both task order was unpredictable and timing was random, the caudate activation

correlated with the pre-SMA and the IPS. Thus, the caudate nucleus communicates information relative to task order unpredictability to a number of cortical regions.

When timing was random (and task order was predictable or unpredictable), the cerebellum activation positively correlated with the DLPFC, the IPS and the caudate activation. In addition, when both timing and task order were unpredictable, the cerebellum activation positively correlated with the pre-SMA activation.

Discussion

Our results show that both the cerebellum and the striatum were activated bilaterally by all tasks switching conditions relative to baseline (Figs 3 and 4). These activations cannot be attributed to motor function because identical motor responses were required for the task-switching and baseline conditions. Activations of the cerebellum and basal ganglia do not support the switching attention hypothesis because these brain regions were also activated by a control condition requiring maintenance of two task-sets without switching between them (Figs 3 and 4). Rather, our results show that the cerebellum and the basal ganglia are differently sensitive to the unpredictability of task order and timing during the processing of sequences of tasks. The anterior striatum was activated by the main effect of task order unpredictability (Fig. 5). In contrast, the right posterior cerebellar hemisphere and dentate nucleus were activated by the main effect of timing irregularity (Fig. 6).

Brain regions activated with task order unpredictability or timing irregularity may, in part, be due to a form of oddball response. However, it should be kept in mind that in classical oddball paradigms both the timing and the type of stimulus (target or distractor) are unpredictable (and thus confounded) while our study dissociated the two components of timing and task order unpredictability. Event-related potential (ERP) studies of the oddball paradigm have revealed that rare target stimuli generate the P3b event-related potential (Clark *et al*., 2000). Moreover, oddball paradigms that have investigated the neural responses to infrequent stimuli in the auditory or visual domains found a large degree of spatial overlap primarily in the bilateral cerebellum and the frontal and parietal areas, as well as in the supramarginal gyrus, frontal operculum and insular cortex bilaterally (Linden *et al*., 1999; Clark *et al*., 2000; Stevens *et al*., 2000). Although we limit our discussion to the cerebellum and the basal ganglia in the present paper, we have previously described and discussed the roles of distinct prefrontal regions and of the intraparietal cortex with task order predictability/unpredictability and timing regularity (Dreher *et al*., 2002).

Our results that the cerebellum and basal ganglia are not specific for switching attention are in accordance with the fact that cerebellar patients are not impaired on attention tasks that require rapid visual orienting between spatial positions (Dimitrov *et al*., 1996; Helmuth *et al*., 1997; Yamaguchi *et al*., 1998). Although early studies reported attentional deficits in cerebellar patients (Courchesne *et al*., 1994; Courchesne & Allen, 1997), it has recently been proposed that these deficits might be secondary to the coordination of motor responses (Ravizza & Ivry, 2001; Bischoff-Grethe *et al*., 2002). The observation that the basal ganglia are not specific for switching between tasks is also provided by several event-related fMRI studies directly comparing switch to repeat trials (Kimberg *et al*., 2000; Sohn *et al*., 2000). Furthermore, early-stage medicated Parkinson's disease patients performed normally in switching attention between tasks in which verbal responses were given (Rogers *et al*., 1998). Although patients with Parkinson's disease have also been reported to have impaired performance in switching attention set (Taylor *et al*., 1986; Gotham *et al*., 1988; Eslinger & Grattan, 1993; Owen *et al*., 1993; Hayes *et al*., 1998) or switching between tasks (Cools *et al*., 2001b), this impairment may reflect a dopaminergic deficit (Hayes *et al*., 1998; Cools *et al*., 2001a,b), a difficulty to instantiate a new attentional set (Owen *et al*., 1993), or may be related to the disrupted forms of motor output (Robertson & Flowers, 1990). The dopaminergic deficit interpretation seems especially pertinent because several studies reported improved performance in Parkinson's disease patients after dopaminergic medication (Hayes *et al*., 1998; Cools *et al*., 2001a).

When compared to baseline, all task-switching conditions averaged together not only activated the cerebellum and the striatum but also recruited a bilateral prefronto-parietal network (Table 1, Fig. 9a). This network is typically reported in functional neuroimaging experiments using attention tasks, working memory tasks and dual-tasks (Cohen *et al*., 1997; Nobre *et al*., 1997; Adcock *et al*., 2000; Bunge *et al*., 2000), indicating that this network is not specific to task switching.

Task order unpredictability activates the anterior striatum

Increased response times on both the switch and repeat trials of the unpredictable task order conditions show that unpredictability was related to the overall structure of the sequence of tasks. This confirms a recent behavioural study (Sohn & Carlson, 2000). The anterior putamen activation found with task order unpredictability (Fig. 5) is in accordance with the observation that striatal neurons detect unpredicted reward events, irrespective of the specific behavioural situation in which such events occur (Ravel *et al*., 2001). A previous fMRI study has shown that unpredictability of reward delivery in humans activates the ventral striatum (Berns *et al*., 2001) but could not specify whether this activation was specific to the unpredictability of the reward delivery or to the unpredictability of the sequence itself. Our results suggest that reward delivery is unnecessary for activation of the anterior striatum and that unpredictability of task order alone is sufficient to induce this activation. However, the role of dopamine cannot be totally excluded in our study, even though no reward was delivered. Indeed, the discharges of midbrain dopamine neurons have properties similar to the reward prediction error of temporal difference reinforcement learning models (Schultz & Dickinson, 2000; Schultz, 2000). Dopamine neuron activity serves as an effective reinforcement signal for learning sensorimotor associations in the striatum. It is thus possible that the dopamine signal is required with unpredictable sequences, especially with combined unpredictability of task order and timing. Confirming this view, substantia nigra activation was found when comparing the switching condition with unpredictable task order and random timing to the baseline (Fig. 8).

When considering other brain regions activated with task order unpredictability, we found a large network including the right inferior frontal gyrus (BA 45), the left middle frontal gyrus (BA 9), the intraparietal cortex bilaterally and the inferior temporal cortex (BA 20 and BA 37) (Table 1, and see Dreher *et al*., 2002). This confirms that the basal ganglia is not the only brain region coding the error signals (Schultz & Dickinson, 2000; Schultz, 2000). Our results are also consistent with recent studies showing that decision-making in the presence of uncertainty involves a fronto-parietal network (Paulus *et al*., 2001; Huettel *et al*., 2002) and that the dorsolateral prefrontal cortex is associated with the adjustment of inferential learning on the basis of unpredictability during a causal associative learning task (Fletcher *et al*., 2001). At the outset, when all associations were unpredictable, DLPFC activation was maximal. This response

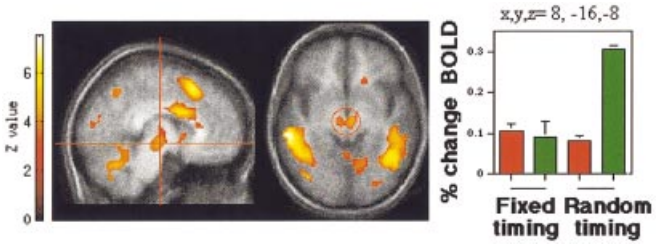

FIG. 8. (Left) Substantia nigra activation found in the task-switching condition with unpredictable task order and random timing relative to baseline superimposed on a normalized axial MRI slice averaged across subjects. (Right) Percentage of signal change relative to baseline for each task-switching condition. Error bars indicate SEM.

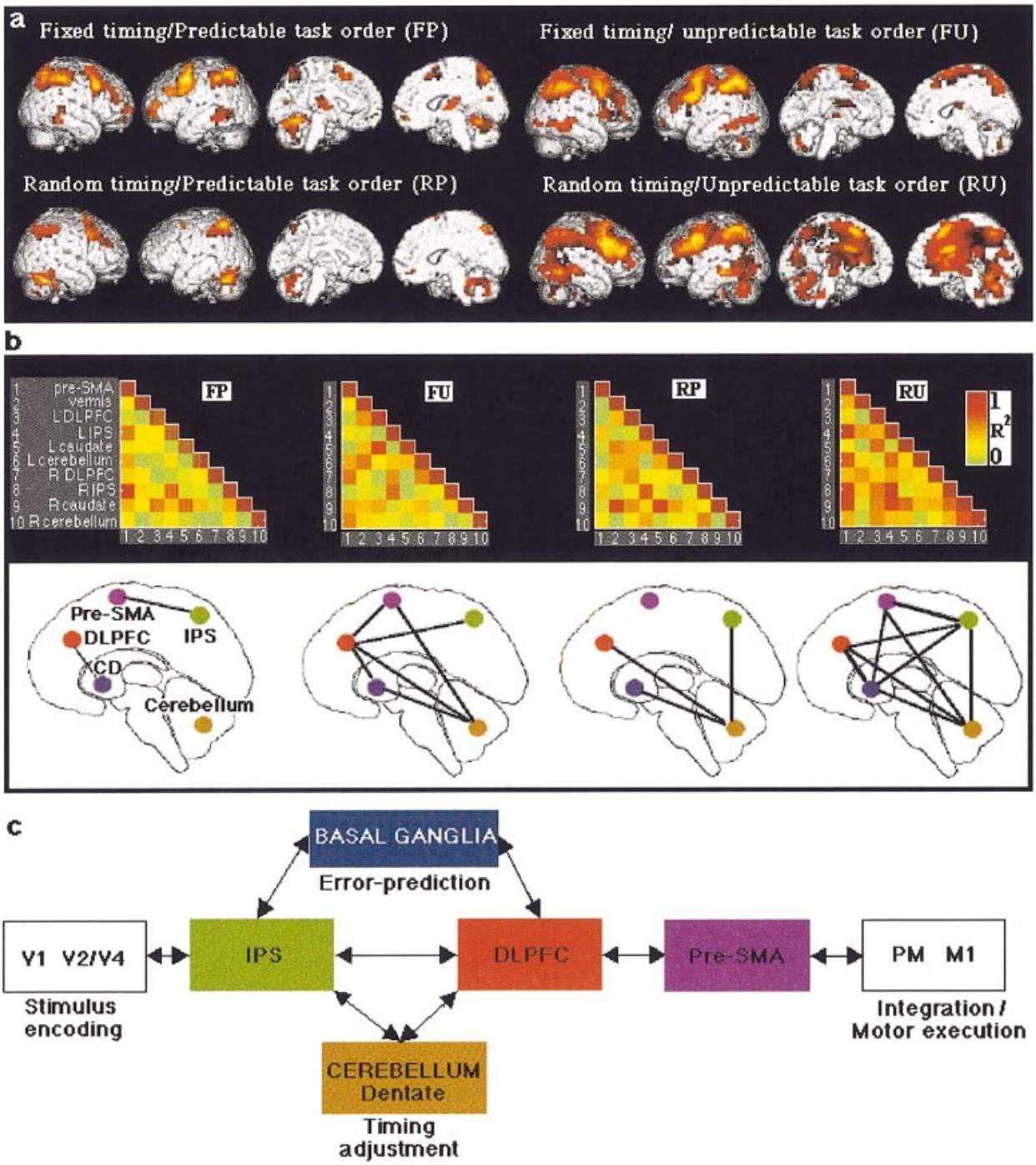

FIG. 9. (a) Pattern of brain activation in the different task-switching conditions relative to baseline ($Z > 3.09$, i.e. $P < 0.001$, uncorrected). (b) Results of the functional connectivity analysis. (Top) Matrix of interregional correlations in the different task-switching conditions. The correlation coefficients R^2 are represented as colour gradations. (Bottom) To summarize the results in a lateral view of the brain, data from the left and right hemispheres were collapsed together. The connection between two brain regions indicate correlation coefficients $R^2 > 0.5$ when collapsing together the two hemispheres across the brain regions found in all task-switching conditions relative to baseline. (c) Hypothetical processes performed by the components of the bilateral prefronto-parietal network. The cerebellum is assumed to compute timing adjustment and the basal ganglia to react to task order unpredictability.

attenuated with learning but, subsequently, activation in the DLPFC was evoked by surprise violations of the learned association.

Cerebellar hemisphere activation with timing adjustment

Our behavioural analysis of the random-timing task-switching conditions suggests that a timing operation was elicited by the ISI manipulation. Indeed, there was an important trend toward a reduction of RTs with time lag, suggesting that subjects could use the probabilistic information conveyed by the passage of time to predict the likelihood of stimulus presentation (i.e. the more time the subjects had, the more probable the stimulus occurrence). A similar result has recently been reported (Meiran *et al*., 2000). Therefore, the increased cerebellar activation found in random relative to fixed timing may be attributed to the fact that the cerebellum tries to predict the timing of stimulus presentation, yet fails to do it for short ISIs (resulting in a prediction error because the actual outcome at short ISI differs from the predicted timing outcome).

However, we can't rule out the possibility that, even if the trials were blocked by duration of ISI, subjects would take longer to perform the tasks at short ISIs than at long ones. Thus, it is possible that the longer RT for short ISIs may be caused by a refractory period in task performance rather than a lack of time necessary to make a prediction about stimulus onset (Meiran *et al*., 2000). At the same time, subjects may anticipate (predict) when random events will happen and look for a pattern in random timing onset.

There is a large body of evidence that is consistent with the hypothesis that the posterior part of the cerebellum is related to timing adjustment (Ivry *et al*., 1988; Ivry, 1997). Bilateral lesions of the lateral part of the posterior lobe of the cerebellum induce deficits in monitoring and reproducing timing (Ivry *et al*., 1988; Nichelli *et al*., 1996; Ivry, 1997). Studies of eyeblink conditioning also showed that the posterior cerebellum plays a critical role in precise timing adjustment (Yeo & Hardiman, 1992; Gruart & Yeo, 1995). Similarly, the lateral cerebellar cortex and cerebellar vermis contribute to a supramodal (auditory and visual) production of a timed motor response, particularly when it is novel or complex (Penhune *et al*., 1998). Although these studies support the cerebellar timing hypothesis, they provide little insight into what particular regions within the cerebellar hemispheres are most critical for timing processes. Our results show that the right cerebellar hemisphere (lobules VI/VII/Crus I) may be particularly suited to perform this function. Moreover, the posterior cerebellar activation which we found is consistent with a division of the cerebellum made according to a rostro-caudal axis. The posterior lobe, especially HVI–HVIIa, has been linked to such higher order functions as attention and working memory (Allen *et al*., 1997; Desmond *et al*., 1997), while the anterior lobe represents movement execution. The absence of anterior cerebellar hemisphere activation in our study is explained by the fact that the same motor responses were needed in all tasks, and were subtracted in the contrast.

The timing adjustment hypothesis may be considered as a particular case of a more general error correction process. However, our results show the distinct nature of the signal processed by the cerebellum and the basal ganglia: the cerebellum adjusts to timing information while the striatum adjusts to task order predictability (Fig. 9c). This distinction is relative for the striatum because the head of the caudate nucleus and bilateral putamen showed an interaction between timing and task order (Fig. 7).

It should also be noted that the cerebellum does not work in isolation, despite the fact that no other brain region than the cerebellum was activated with random relative to fixed timing (Fig. 9b). Indeed, our functional connectivity analysis showed that when timing was random (and task order was predictable or unpredictable), the cerebellar activation positively correlated with the DLPFC, the IPS and the caudate activation. Thus, the cerebellum is likely to share timing information with these brain regions, which is consistent with their known anatomical connectivity (Middleton & Strick, 2000; Clower *et al*., 2001; Middleton & Strick, 2001).

An alternative view of the discrimination of temporal intervals, the basis of prediction in the random timing condition, is to consider it a fine-scale discrimination of sensory information (Gao *et al*., 1996). If so, then cerebellar activity could, in part, reflect the sensory processing necessary to predict time onset. Finally, it may be noted that although the cerebellar neural circuitry involved in storage of memories for learned motor responses (e.g. eyelid conditioning) is now well known (Medina *et al*., 2002), the exact mechanisms underlying the cerebellar timing function remain unclear. A recent study indicated that the conditioned response expression and timing are dissociable and involve different inhibitory inputs (Bao *et al*., 2002).

Comparing the neural basis of sequences of tasks and sequences of movements

Several studies support distinct roles for the basal ganglia and the cerebellum in learning motor sequences (Jueptner & Weiller, 1998; Doya, 2000). Doya and collaborators suggested that the cerebellum is involved in supervised learning and the basal ganglia in reinforcement learning. Jueptner proposed a double dissociation between selection of movements, which requires the basal ganglia but not the cerebellum, and sensory information processing, which involves the cerebellum but not the basal ganglia. Unlike these studies comparing the roles of the basal ganglia and the cerebellum in motor learning, our study is the first to directly compare the roles of the basal ganglia and of the cerebellum in processing sequences of cognitive tasks. The main difference between motor sequences and cognitive sequences is that, in motor sequences, one act leads to the next in a chain-like fashion. In contrast, during sequences of tasks, decisions (e.g. between two motor responses) need to be taken following rules of the type: 'if the letter is red, is it a vowel'? Unlike previous studies comparing the roles of the basal ganglia and the cerebellum in motor learning, our results suggest a distinction in the pattern of brain activation between unpredictability of task order and timing irregularity.

The question of whether the factors of order and timing involve the same neural basis for sequences of movements and for sequences of tasks is still unanswered. A 2×2 factorial design varying task order and timing predictability has previously been used for sequences of simple finger movements cued by the colour of two stimuli (Sakai *et al*., 2000). It is, however, difficult to directly compare our results with those of this study because no analysis of the main effects of stimulus order and timing irregularity was performed. This study reported bilateral posterior cerebellar hemisphere activation when the timing was random and no cerebellar activation with unpredictability of the order of the movement ('response selection'). In addition, no basal ganglia activation was found with response selection uncertainty (Sakai *et al*., 2000). However, the role of the basal ganglia in unpredictable sequences of movements requires further investigation. Indeed, at the beginning of learning a motor sequence the anterior striatum is activated (Grafton *et al*., 1992; Petersen *et al*., 1998; Hikosaka *et al*., 1999). This activation decreased when motor sequence become more automatic while activation of the posterior striatum increased. Similarly in our study, when task order cannot be learned (unpredictable order), the anterior striatum was activated while a decrease of activation was found when task order was

overlearned predictable task order. This suggests that both motor and task sequences may require the anterior striatum when they are unpredictable. Further studies directly comparing motor and cognitive sequences are needed to solve this issue (Koechlin *et al*., 2002)

To conclude, our study provides new evidence that the cerebellum and striatum are involved not only in the control of movements but also in the sequencing of cognitive tasks. The cerebellum is primarily activated by timing irregularity while the basal ganglia show a more complex pattern of activation, the anterior striatum being activated by task order unpredictability while the head of the caudate nucleus and the posterior putamen responding to an interaction between timing and task order. Furthermore, task order unpredictability alone, independently of reward delivery, is sufficient to induce striatal activation.

Acknowledgement

This research was supported by a postdoctoral fellowship from the FYSSEN foundation to J.-C.D.

Abbreviations

DLPFC, dorsolateral prefrontal cortex; fMRI, functional magnetic resonance imaging; IPS, intraparietal sulcus; ISI, interstimulus interval; pre-SMA, pre-supplementary motor area; RT, reaction time.

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