# A PET STUDY OF HUMAN SKILL LEARNING: CHANGES IN BRAIN ACTIVITY RELATED TO LEARNING AN ORIENTATION DISCRIMINATION TASK

**Christine Schiltz**[1], **Jean-Michel Bodart**[1], **Christian Michel**[2] **and Marc Crommelinck**[1]

([1]Laboratory of Neurophysiology, U.C.L., Brussels, Belgium; [2]PET Unit, U.C.L., Louvain-la-Neuve, Belgium)

## Abstract

Using $^{15}$O-water 3D positron emission tomography we investigated the effect of training in orientation discrimination upon cerebral activity in healthy human adults. When subjects are trained in this discrimination task, they learn the visuo-motor stimulus-response association required by the task and they increase their perceptual abilities in orientation discrimination. The present study was designed to investigate the rCBF modifications related to both these learning processes induced by training in orientation discrimination. PET data were acquired on two separate days (before and after training). Comparing the activation pattern related to orientation discrimination before and after the training period we observed activity decreases located in the left cerebellar cortex, in the right precentral gyrus and bilaterally in the fusiform gyri. The only region showing an activity increase was located in the body of the right caudate nucleus. These findings confirm the role of the neostriatum in skill learning and highlight the importance of mechanisms resulting in cortical and cerebellar neuronal activity decreases in this type of learning.

Key words: training, visual cortex, cerebellum, caudate nucleus

## Introduction

Initiated by the description of the tragically famous case of H.M. (Milner, 1962), the study of preserved abilities in amnesic patients has led to the distinction between two different memory systems (Squire, Knowlton and Musen, 1993): the declarative and the non-declarative system. The former system concerns facts and events, whereas the latter encompasses skill and habit learning, priming, simple classical conditioning and non-associative learning (habituation and sensitization). The present study focuses on skill learning and thus concerns the non-declarative memory system. In skill learning, subjects perform a challenging task on repeated trials and learning is quantified by the improvement in speed and accuracy achieved across task repetitions. It is sensible to distinguish between high-level cognitive skills (Van Lehn, 1996) and low-level motor, visuo-motor (Brooks, 1986) and perceptual (Gibson, 1953)

skills. Recently, positron emission tomography (PET) and functional magnetic resonance imaging studies have started to investigate the changes in regional cerebral blood flow (rCBF) related to low-level skill learning in healthy human adults.

Here, we investigate the neuronal correlates of low-level skill learning using PET and visual orientation discrimination, a paradigm which requires subjects to discriminate the orientation of a stimulus (e.g. a grating) with respect to a reference. Our orientation discrimination task, which we already used in a previous study (Schiltz, Bodart, Dubois et al., 1999), has two important features: subjects have to discriminate large, suprathreshold orientation differences during the PETscanning sessions and they have to communicate their decision by a motor response in a limited time period (600 ms) and at a very high frequency (72 stimulus-response associations per minute). When naive subjects are trained in this task, they first rapidly increase their response accuracy from 80% to approximately 95% of correct responses. With further extensive training, performance remains stable in the suprathreshold task, but subjects significantly improve their ability to discriminate fine orientation differences. Therefore, in this particular task, we distinguish between two different learning phases in which different types of learning predominate. Such a two-phase learning model is in line with the proposition made by several research groups that skill learning proceeds through two consecutive stages (Karni and Sagi, 1993; Polat and Sagi, 1994; Karni, Meyer, Jezzard et al., 1995; Ahissar and Hochstein, 1996; Karni, Meyer, Rey-Hipolito et al., 1998; Petersen, Van Mier, Fiez et al., 1998). According to these authors the first (early) stage takes place during the first few hundred trials and leads to the acquisition of a task-relevant routine. The second (late) stage requires thousands of training trials and changes the strength of the links between the specific task related sensory (or motor; see Karni et al., 1998) units. In the early phase of our experiment, learning mainly concerns the visuo-motor stimulus-response association and has been termed conditional motor learning by Passingham (1993). Indeed, in our suprathreshold task, the orientation difference is easily discriminated, but performance is initially limited by the speed constraint of the arbitrary sensori-motor association. The rapid decrease in error rate observed during the early phase is typical for this kind of learning, as discussed by Honda, Deiber, Ibanez et al. (1998). In the late phase of our study, learning mainly affects the visual processing required for the orientation discrimination task. This perceptual learning is, to a large extent, specific for the location and orientation of the stimulus used during the training (Mayer, 1983; Schiltz et al., 1999; Schoups, Vogels and Orban, 1995; Shiu and Pashler, 1992; Vogels and Orban, 1985).

Our previous study (Schiltz et al., 1999) focused on the late learning phase in order to study exclusively the rCBF changes related to the perceptual learning induced by training in orientation discrimination. This was done by using a pretraining, which took place before the first day of PETscanning. During this pretraining the early learning phase took place and thus subjects had learned most of the visuo-motor association at the moment of the first PETscanning. The changes we observed were all activation decreases in the striate and extrastriate visual cortex, as well as in the cerebellum. The aim of the present study was to

investigate rCBF changes induced by training in orientation discrimination, including the rCBF modifications due to learning of the visuo-motor stimulus-response association occurring in this task. Since most of the latter changes occur in the early learning phase, the first scan in the current experiment had to take place before this phase. Consequently, we scanned the subjects on the day of their first contact with the orientation discrimination task, immediately after a minimal familiarization period. Thus, in this first PET session response accuracy was only approximately 80% of correct responses. After an intensive training in orientation discrimination a second PET session then took place during which subjects scored almost perfect (i.e. ≥ 95% of correct responses). This gain in accuracy between PET sessions contrasts with the constant performance level of our previous study. During the latter study subjects scored almost perfect (i.e. ≥ 95% of correct responses) in both PET sessions, since they had already practised the discrimination task during the pretraining phase taking place before the first PET session.

In both imaging sessions of the present experiment, we used discrimination of grating orientations as experimental condition and passive viewing of a uniform texture as a control condition. To highlight the effects of training in orientation discrimination we compared the activation in orientation discrimination relative to control before and after training. The observation that training in orientation discrimination decreases the neuronal activity in early visual areas (V1, V2, V3) and in the cerebellum confirmed our previous results (Schiltz et al., 1999). In addition, and contrary to our previous study, we also observed a learning-related activity decrease in the primary motor area, as well as an activity increase in the caudate nucleus. These findings are consistent with those described in recent imaging studies concerning low-level skill learning (for references see Discussion). A preliminary account of these data has been published in an abstract form (Schiltz, Bodart, Dubois et al., 1998).

## Materials and Methods

### *Subjects*

Six male, right-handed (Oldfield, 1971), healthy volunteers, ranging in age from 23 to 28 years, participated in the experiment as subjects. All had a normal visual acuity, had no history of neurological disorders, were drug free and had a normal MRI. The study was approved by the ethical committee of the Catholic University of Louvain medical school and all subjects gave their written informed consent.

### *Experimental Paradigm*

#### *Stimulus Characteristics*

The stimuli were presented on a monochrome monitor (frame refresh rate of 70 Hz), within a circular aperture of 4° diameter cut into a mask covering the display screen. Subjects viewed the display binocularly at a distance of 113 cm, in a dimly lit room and fixated a red target spot of 0.2° diameter, located in the center of the circular aperture. Fixation was controlled by electro-oculogram. Two different types of stimuli were presented to the subjects for 300 ms. Each stimulus presentation was followed by a black screen which lasted for 533 ms. The randomly textured pattern stimuli (Figure 1) consisted of

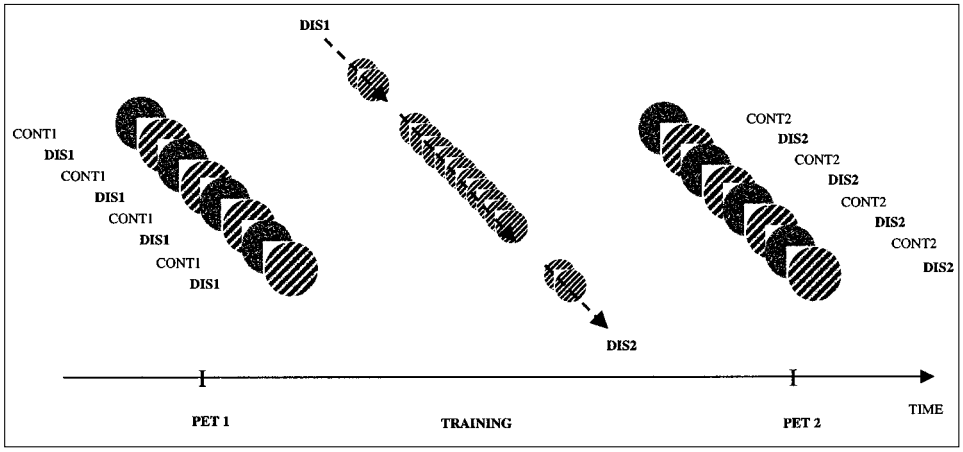


Fig 1 – *Schematic of the time course of the experiment. The moment of the two PETscanning sessions and the training period are indicated. The convention for labeling the experimental conditions is listed.*

equal proportions of black and white pixels. The mean luminance of these stimuli was 10 cd/m$^2$. The grating stimuli (Figure 1) were high contrast (94%), square wave, 1 cycle/° gratings of the same mean luminance (10 cd/m$^2$). In order to eliminate cues other than orientation, the phase was randomized between trials and noise was superimposed on the edges of the bars. A reference orientation tilted 45° or 37° clockwise from the vertical orientation was assigned pseudorandomly to each subject.

*Task Description*

Subjects performed three tasks, amongst which the two following were included in the present study: orientation discrimination (DIS), which served as experimental task and passive viewing of randomly textured stimuli (CONT), which served as control task. In both tasks, subjects had to maintain their gaze on the fixation target, while holding a response key in each hand. Stimuli were presented in blocks of 100 trials, at a rate of 72 trials per minute. After each stimulus presentation, a black screen was displayed until the next stimulus appeared.

In CONT subjects viewed the randomly textured pattern and performed no additional task. In DIS subjects viewed the gratings. The orientation of the gratings was varied pseudorandomly and the subjects performed an orientation discrimination task on them. Subjects saw only one grating at a time and they had to give a response after each grating presentation. During one half of the presentations the reference grating was presented and during the other half a grating tilted clockwise from the reference orientation. Subjects had to press the right key in the presence of the gratings with the reference orientation and the left key in the presence of the gratings tilted clockwise. The responses had to be given by key press within a period of 600 ms after stimulus onset. Auditory feedback was given: a high-pitched tone signaled a correct response, a low-pitched tone signaled an incorrect response. In the CONT condition pseudo-feedback was given (80% 'correct' response tones and 20% 'incorrect' response tones). According to the stage of the experiment (for details cf. "Time course of the experiment"), the orientation difference ($\delta$) between the grating and the reference orientation ranged from 20° to 1°. Table I lists the components involved in the two experimental tasks. The third task which subjects performed during scanning was a passive viewing of gratings. We discarded this condition in the present study since it was not possible to assess reliably whether the subjects were covertly performing the orientation discrimination task on the gratings or whether they were just passively viewing the gratings.

TABLE I
*Components of the Two Experimental Tasks*

| Component | Task | |
|---|---|---|
| | CONT | DIS |
| Auditory stimuli | + | + |
| Visual stimuli | + | + |
| Oriented gratings | | + |
| Motor response | | + |

*Time Course of the Experiment*

The experiment consisted of three phases: the first PET data acquisition, the training in DIS and the second PET data acquisition. These three phases are schematically represented in Figure 1.

During both *PET data acquisitions* subjects performed each condition four times. Thus a total of 12 scans was acquired during each PET session, but, as indicated above, only 8 of these scans were used in the present study. The task order was pseudo-random, but identical during both scanning sessions, for each subject. The only difference between the two sessions consisted in the level of expertise in the DIS task, which subjects had acquired during the training period. DIS1 and CONT1 will refer to the experimental tasks when performed during the first day of PETscanning (i.e., before training). DIS2 and CONT2 will refer to the tasks when performed in the second PET session (i.e., after the training). The first PETscanning was preceded by a brief habituation period lasting maximally 20 minutes. This period aimed to familiarize the subjects with the task and allow them to perform above chance level during PETscanning, optimally reaching a performance exceeding 75% correct responses with a $\delta$ of 15°. Three of the six subjects (CE, PY, PP) succeeded in reaching the criterion and performed on average 400 (SD 200) trials. The three other subjects (WK, MW, LM), on the other hand, were not able to reach the criterion in the fixed period, after having performed 600 trials. During PETscanning, the $\delta$ used in the DIS task was set to 15° for the three subjects reaching the above-mentioned criterion and to 20° for the three other subjects. Once determined for each subject, $\delta$ was kept constant on both scanning days.

During the *training period* which extended over a period of 25 (SD 8) days, subjects were trained in DIS. The training consisted in 10 sessions of 1000 trials each, at a maximum rate of one session per day. Each session lasted about 40 minutes. Training started with the $\delta$ (15° or 20°) used during the scanning sessions and was reduced by 1°, each time subjects reached a performance level of 80% correct discriminations in three consecutive blocks. The training was extensive in order to assure that all subjects had improved their performance in DIS significantly on the second day of PETscanning.

*Psychophysical Assessment on Scanning Days*

During the PETscanning, the percentage of correct responses per block (1 block = 100 trials) was measured. We also recorded the response times (RTs), but due to a computer fault the only data available were the average RTs from each scanning day of four subjects. In addition, on both scanning days each subject's orientation just noticeable difference (JND) was determined outside the scanner using a constant stimulus method (Gescheider, 1985). Using a least-square procedure, the data were fitted to a sigmoid function, and the 75% correct threshold was computed (Wetherhill and Lewitt, 1965).

*Data Acquisition and Image Reconstruction*

Measurements of local radioactivity uptake were made using a ECAT Exact HR PET tomograph (CTI/ Siemens Knoxville TN), which provided 47 slices equally spaced by 3.125

mm. Data were acquired in 3D mode (septa retracted), in a 60s frame, following a bolus injection (over 10 s) of 8 mCi of $H_2{}^{15}O$. All tasks started simultaneously with the tracer injection and the integrated counts accumulated during 60 s scans were used as an index of rCBF (Mazziotta, Huang, Phelps et al., 1985). Head attenuation was corrected using a transmission scan obtained with 3 rotating rod sources loaded with 5 mCi $^{68}Ge$. Since relative radioactivity uptake was measured, emission data were not corrected for scattered radiation. If one assumes similar scatter contribution in all conditions, this approach minimizes the variance of the individual relative blood flow measurements (Votaw, 1996). Images were reconstructed in 3D using the Kinahan and Rogers (1990) reprojection algorithm. Forty-seven slices were reconstructed with a Hann filter in both tomographic and axial directions with a cutoff at 5.5 mm and an in-plane pixel size of 2 mm. This resulted in an effective spatial resolution of 6 to 7 mm in all 3 directions. The time interval between successive emission scans was 15 minutes, which allowed decay of residual radioactivity. Scans were oriented along the orbitomeatal line and images of the entire brain were obtained. During the scans subjects were asked not to speak and not to perform any particular mental operations, except those necessary for the task at hand. Visual fixation was controlled online by electrooculogram. The subject's head was fixed using a rigid head holder, covered with foam and elastic straps. Landmarks made along the scanner laser lines allowed precise control of the head position during the experiment.

For each subject, T1-weighted MRI data were obtained from a 0.5 Tesla Philips Gyroscan imager. Data were acquired with a Fast Field Echo 3D protocol (repetition time = 30 ms, echo time = 13 ms, flip angle = 30°) and reconstructed with a voxel size of 0.86 × 0.86 × 2.0 mm.

### *Image Analysis*

Image analysis was performed using SPM96 implemented in Matlab (Mathworks Inc.). The results were displayed with an interactive image display software developed in-house (Michel, Sibomana, Bodart et al., 1995) using IDL language (IDL, Research System Inc.). Using the automated image registration algorithm AIR (Woods, Cherry and Mazziotta, 1992), the PET images were realigned to the first scan, using a rigid body transformation. Then, the images were spatially normalized to fit into the Talairach and Tournoux (1988) coordinate system (voxel size: 2 × 2 × 2 mm). Finally, the images were smoothed using an isotropic Gaussian filter of 15 mm FWHM and corrected for global activity by proportional scaling (Friston, Frith, Liddle et al., 1990). To identify the regions showing significant rCBF changes, statistics were computed on a voxel-by-voxel basis, using the general linear model (Friston, 1995). The resulting voxel sets of each contrast constitute a statistical parametric map of the t-statistic SPM{t}, which were then transformed to the unit normal distribution SPM{Z}.

Each individual MRI was interactively realigned with the PET images (using IDL software) displayed with a contours exchange program, according to the principles described by Pietrzyck, Herholz, Fink et al. (1994) and spatially normalized using the same transformations as those applied to the PET images. Finally the sum of all 6 individual MRIs was computed. To permit an accurate anatomical definition of the activations, SPM{*Z*} were fused with the summed MRI and displayed as volume images in three orthogonal sections, using IDL software.

### *rCBF Comparisons*

To identify the regions involved in DIS independently of the effect of training, we compared the cerebral activity during DIS to the activity during CONT both before and after training and we retained only the regions which were significant at both skill levels. Concretely, we used the contrasts (DIS1-CONT1) and (DIS2-CONT2) and masked the first contrast with the second. The masking function implemented in SPM96 simply eliminates voxels from a chosen contrast if they do not survive a defined Z-score in another contrast. The threshold of significance in both individual contrasts was set to $Z > 4.4$, corresponding to an omnibus p value at the voxel level of $p < 0.05$. In order to provide complete

information concerning the task effects, we will list in one table (Table III) those regions showing significant task effects only before training, only after training and at both skill levels.

We then compared the task-related activation pattern obtained before training with the one obtained after training in DIS. Given the assumption that the major task-related between-day differences were due to the training this comparison allowed us to identify those regions showing activity changes induced by the training. The contrast (DIS2-CONT2)-(DIS1-CONT1) identified the training-related activity increases apparent in DIS. Its negative counterpart (DIS1-CONT1)-(DIS2-CONT2) tested for activity decreases.

The two latter contrasts were considered with the use of a masking procedure. By eliminating voxels from a chosen contrast if they do not survive a defined Z-score in another contrast, the use of a mask reduces the number of voxels to which the contrast of interest is applied and consequently increases the sensitivity within the surviving regions. In the present study we used the contrasts testing for a task effect before and after training as masks. Concretely, the contrast testing for training-related increases in DIS was masked with (DIS2-CONT2) and the contrast testing for decreases was masked with (DIS1-CONT1). With the masking procedure (the masking contrasts were thresholded at a Z-score of $Z > 4.4$), the search volume was reduced to 15873 voxels when testing for training-related increases in DIS and 25814 voxels when testing for decreases. The omnibus p values of $p < 0.1$ consequently corresponded to Z-scores of 3.40 and 3.56, respectively (the classical p value of $p < 0.05$ corresponded to Z-scores of 3.63 and 3.79).

## RESULTS

### *Behavioral Results*

During the first PETscanning session (before training) subjects performed the DIS task giving on average 81% (SD 7%) of correct responses. During the PETscanning after training performance raised to an average of 97% (SD 2%) of correct responses. The individual values are listed in Table II. A two-way ANOVA having as factors the day of scanning (two levels) and the repetition of the task within the days of scanning (four levels) revealed that the increase in performance between days was significant ($F = 83$, $p < 0.0001$). However, there was neither an effect of task repetition within days ($F = 0.4$), nor an interaction between the factors day and repetition ($F = 0.1$). The mean orientation JNDs, which were determined outside the scanner on the days of PETscanning, were respectively on average 10.1° (SD 4.7°) before the training period and 3.7° (SD 2.3°) after the

TABLE II

*Just Noticeable Differences in Orientation and Percentages of Correct Responses During PET Scanning*

| Subjects | Just noticeable difference (°) | | Percentage correct (%) | |
|---|---|---|---|---|
| | Before training | After training | Before training | After training |
| MW | 15.9 | 4.2 | 79 | 96 |
| WK | 14.8 | 8.0 | 71 | 95 |
| LM | 11.8 | 3.3 | 80 | 98 |
| PY | 6.9 | 2.5 | 86 | 98 |
| PP | 6.4 | 1.9 | 90 | 98 |
| CE | 5.0 | 2.3 | 83 | 94 |
| Mean (SD) | 10.1 (± 4.7) | 3.7 (± 2.3) | 81 (± 7) | 97 (± 2) |

training. The individual JNDs in orientation are listed in Table II. A paired *t*-test showed that this improvement in the perceptual abilities of the subjects was significant at $p < 0.005$. Finally, a trend concerning the evolution of the RTs could be obtained by comparing the available RT measurements obtained during the two PETscanning sessions. Thus a paired *t*-test showed that the RTs decreased significantly ($p < 0.05$) from an average of 397.5 ms (SD 29 ms) before the training to 369.5 ms (SD 42 ms) after the training period. The average (± SD) values of the RTs, JNDs and performances are all illustrated in Figure 2.

## *PET Results*

### *Task Effect*

*Orientation Discrimination versus Control* (DIS1- CONT1) and (DIS2-CONT2). The largest cluster showing a task effect of DIS was situated in the cerebellar region. The most significant peak of this activation was situated in the left superior cerebellar cortex, but the cluster to which this peak belonged extended bilaterally over the cerebellar hemispheres and another activation peak was situated in the cerebellar vermis. The same cluster also extended superiorly in the z-axis towards the fusiform gyri and an additional activation peak was observed in the middle part of the right fusiform gyrus. In the frontal lobes, bilateral activation foci were observed in the precentral gyri and in the dorso-lateral parts of the superior frontal gyri. Another activation peak was located in the medial part of the left superior frontal gyrus. Subcortically and outside of the cerebellum, we observed an activation in the medial pulvinar. Table III lists the above-mentioned activations and the same results are presented as surface projections of the Z-map onto an individual MRI in Figure 3. Table III also lists the regions activated when comparing DIS to

TABLE III

*Regions Showing a Significant Task Effect, When Comparing Orientation Discrimination to the Control Task, Independently of the Level of Training (Normal Type), Before Training (Italics) and After Training (Bold)*

| Regions (peak of focus) | Coordinates in Talairach space (x y z mm) | Z-score | | Effect size (% change) | |
|---|---|---|---|---|---|
| | | Before training | After training | Before training | After training |
| Left cerebellar cortex (superior part) | – 26 – 56 – 22 | 7.9 | 5.7 | 9.3 | 4.8 |
| Cerebellar vermis | – 2 – 54 – 14 | 7.8 | 7.3 | 11.7 | 9.1 |
| Right precentral gyrus | 36 – 22 56 | 7.9 | 6.2 | 10.3 | 5.9 |
| Left precentral gyrus | –30 – 18 64 | 7.2 | 5.6 | 7.4 | 5.1 |
| Left superior frontal gyrus (medial part) | – 8 – 2 52 | 7.2 | 6.3 | 7.2 | 6.0 |
| Left superior frontal gyrus (lateral part) | – 14 – 12 68 | 7.0 | 5.2 | 8.1 | 5.4 |
| Right superior frontal gyrus (lateral part) | 20 – 12 56 | 6.2 | 5.3 | 6.8 | 5.6 |
| Right fusiform gyrus | 16 – 52 – 16 | 7.5 | 7.0 | 8.3 | 7.0 |
| *Left fusiform gyrus (posterior part)* | *– 24 – 84 – 20* | *6.2* | *2.5* | *5.5* | *2.0* |
| *Left fusiform gyrus (posterior part)* | *– 26 – 80 – 10* | *6.1* | *1.5* | *6.5* | *1.5* |
| *Right calcarine sulcus* | *14 – 90 4* | *6.1* | *3.7* | *5.9* | *3.3* |
| *Right intraparietal sulcus* | *42 – 40 50* | *6.8* | *4.0* | *6.0* | *3.2* |
| *Left superior parietal gyrus* | *– 28 – 52 64* | *5.0* | *1.3* | *4.0* | *1.0* |
| *Right superior parietal gyrus* | *22 – 62 60* | *4.7* | *1.3* | *3.9* | *1.0* |
| **Right caudate nucleus** | **20 – 10 22** | **1.9** | **6.4** | **1.6** | **6.2** |
| Pulvinar | 0 – 28 2 | 6.3 | 5.3 | 5.9 | 4.8 |

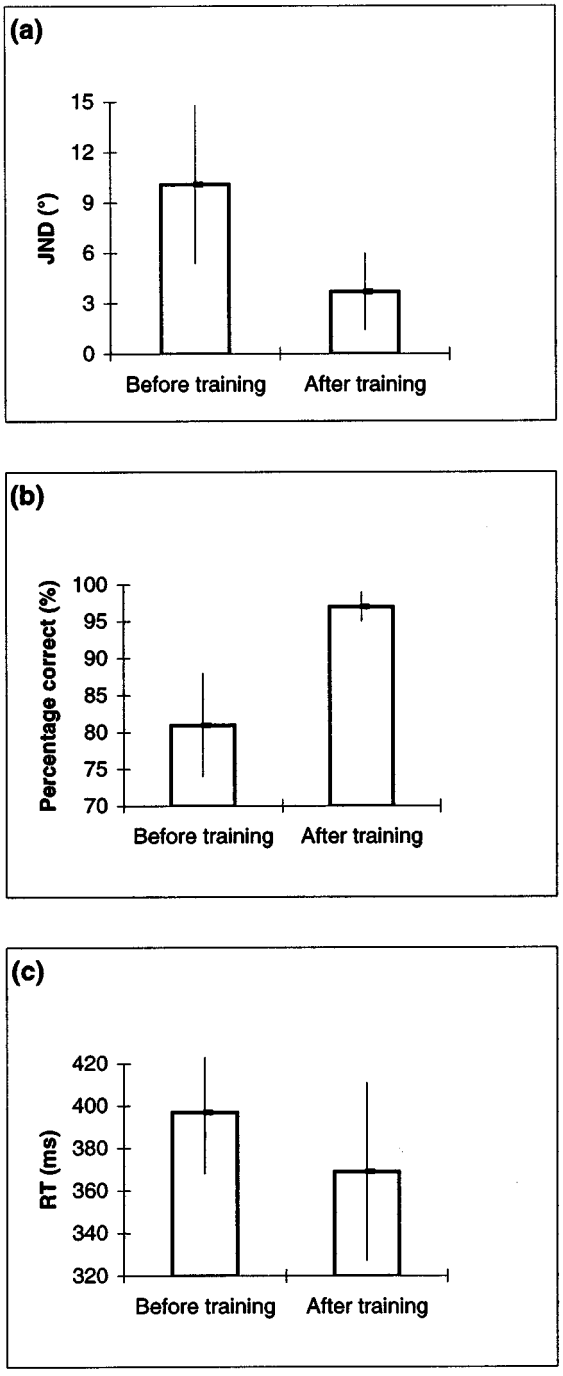


Fig 2 – *Changes in (a) orientation JND (°), (b) response accuracy (%) and in (c) response time (ms) with training. The average of the three behavioral measurements (± SD) before and after the training period are plotted. The response time data are based on only four subjects (cf. Materials and Methods).*

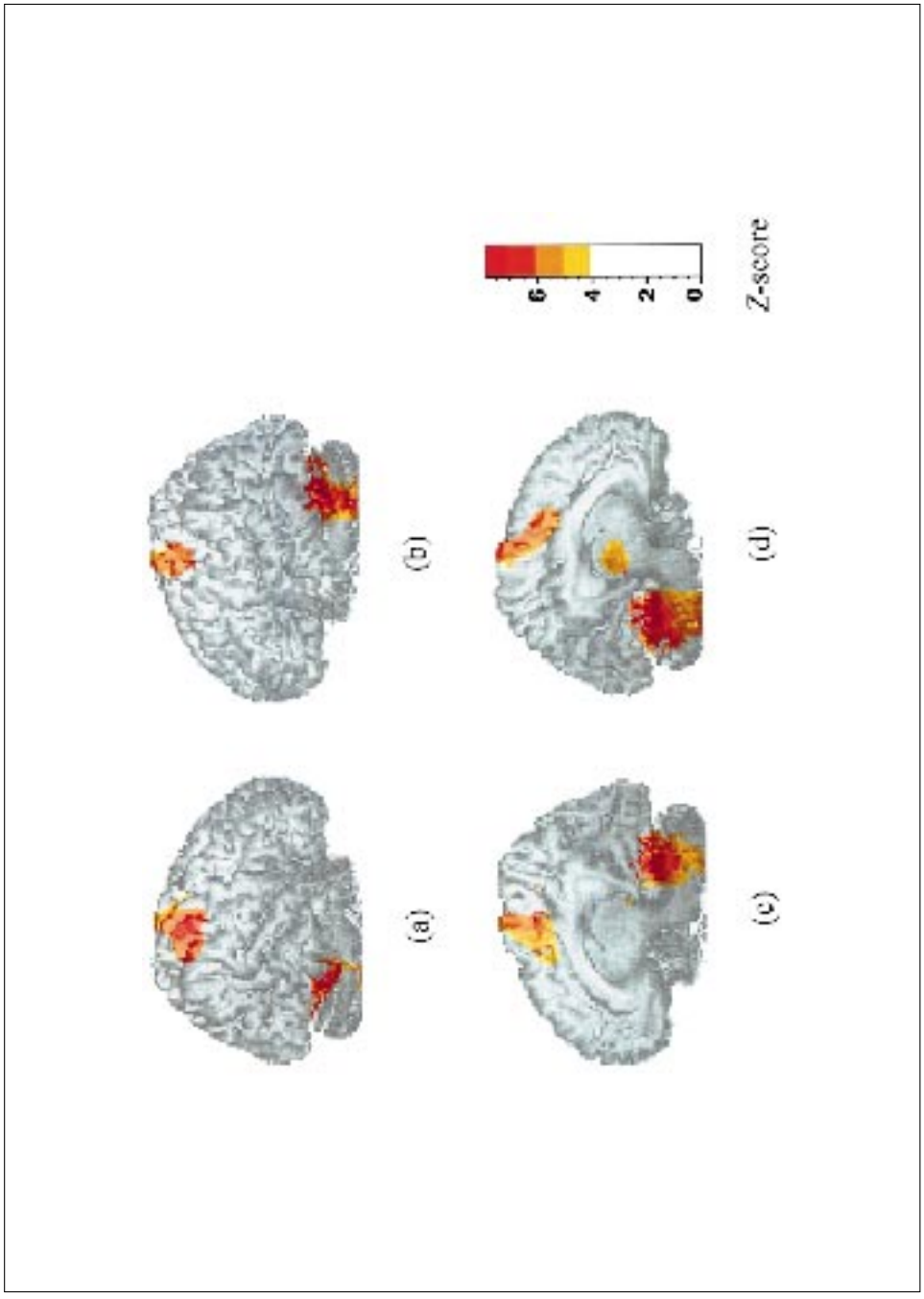


Fig 3 – *Surface projection of the SPM showing regions activated in orientation discrimination compared to control, independently of the effect of training. The illustrated regions reached significance in the two contrasts (DIS1-CONT1) and (DIS2-CONT2). The SPM was projected onto a normalized MRI of one of the subjects. The color scale indicates the level of significance expressed as a Z-score. (a) Right lateral view (b) left lateral view (c) right medial view (d) left medial view.*

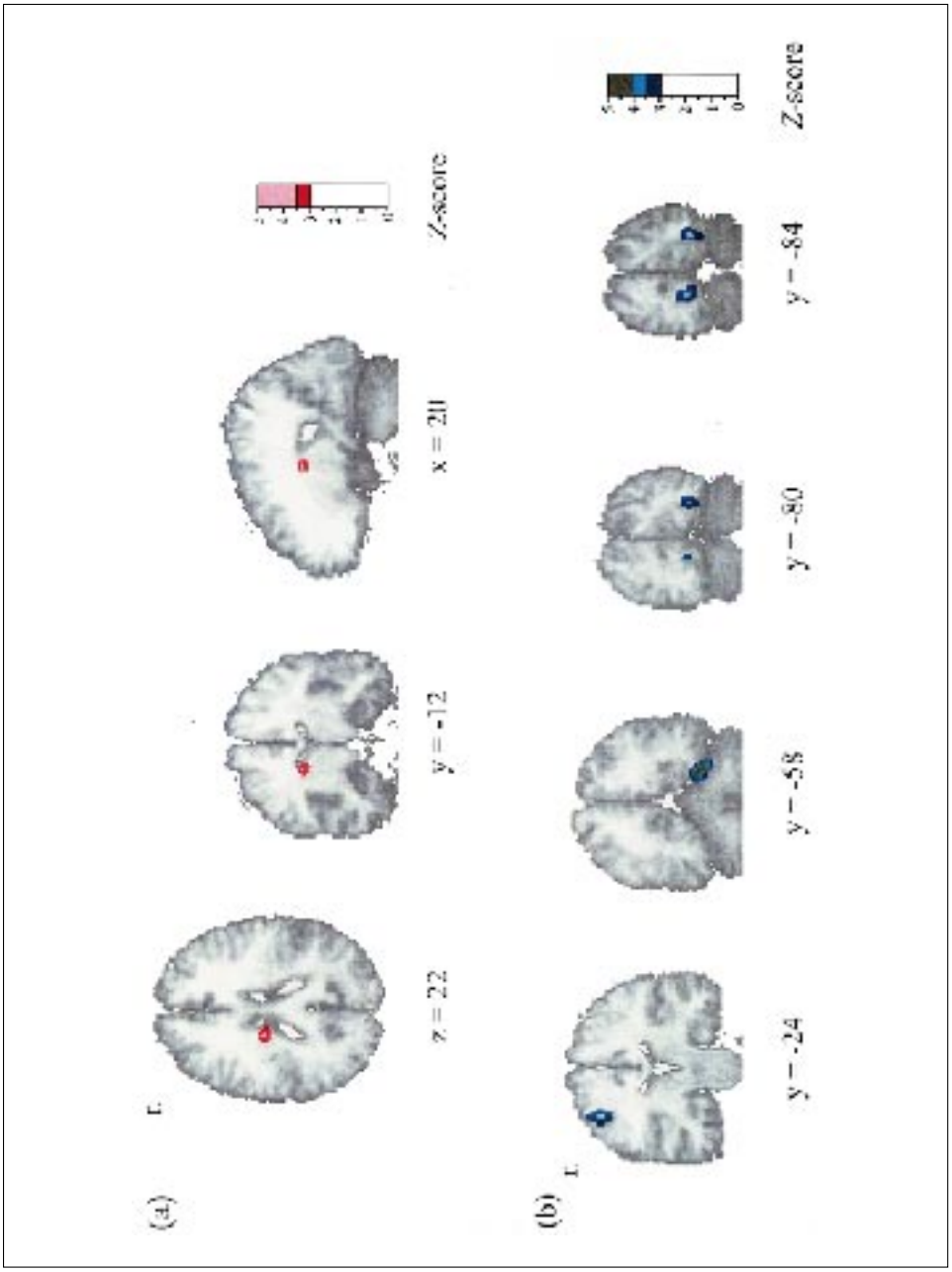


Fig 4 – *Horizontal (a), coronal (a, b) and sagittal (a) sections through the SPMs fused with the summed MRIs of the six subjects: (a) Region showing training-related rCBF increase during orientation discrimination. The region was determined by the contrast [(DIS2-CONT2)-(DIS1-CONT1)], masked with the contrast testing for a significant task effect after training (DIS2-CONT2). (b) Regions showing training-related rCBF decreases during orientation discrimination. These regions were determined by the contrast [(DIS1-CONT1)-(DIS2-CONT2)], masked by the contrast (DIS1-CONT1). The color scale indicates the level of significance expressed as a Z-score. The right hemisphere is on the left side of the image.*

CONT respectively before (in italics) and after (in bold) the training period. These regions are indicated in order to provide complete information concerning the task effect of orientation discrimination at both skill levels.

## *Training Effect*

*Orientation Discrimination After Training > Before Training* (DIS2-CONT2)-(DIS1-CONT1). The only region showing significant activation increases during DIS after the training period was situated in the body of the right caudate nucleus. This region is listed in Table IV and illustrated in Figure 4a as fusions of the concerned MRI sections with the *Z*-map of interest. Figure 5 represents the activity profile of the mean adjusted rCBF of the peak of this activation.

TABLE IV

*Regions Showing an Effect of Training (Activation Increase) and a rCBF Increase During Orientation Discrimination Relative to Control After the Training Period*

| Regions (peak of focus) | Coordinates in Talairach space (x y z mm) | | | Z-score | P value | Effect size (% change) |
|---|---|---|---|---|---|---|
| Right caudate nucleus | 20 | – 12 | 22 | 3.8 | 0.03 | 4.8 |

*Orientation Discrimination Before Training > After Training* (DIS1-CONT1)-(DIS2-CONT2). The most significant cluster, resulting from the comparison testing for activation decreases during DIS following the training period, encompassed both the left middle fusiform gyrus and the superior part of the left cerebellar cortex. The peak of this cluster lay just between these two structures, a location which is most probably the result of the large filter which was used to smooth the data (15 mm). When projected into the individual MRIs,

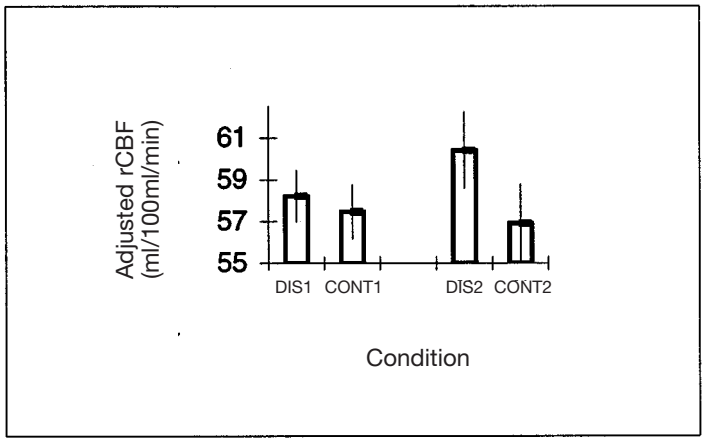


Fig 5 – *Activity profile of the right caudate nucleus, the region where training induced a significant increase in activation during orientation discrimination. This profile plots the mean adjusted rCBF in DIS and in CONT, before and after the training. Vertical lines indicate the standard deviations.*

the cluster indeed extended consistently (6/6 subjects) over both of the above-mentioned structures. The only activity decrease we observed in the frontal lobes was situated in the right central sulcus. In the occipital lobes, two bilateral regions in the posterior parts of the fusiform gyri also showed a reduced activity when comparing the activation pattern before and after the training. The two regions were situated at almost identical (y,z) coordinates, but in the x-dimension only the right-sided cluster extended medially and included parts of the lingual gyrus. The above-mentioned regions are listed in Table V and

TABLE V

*Regions Showing an Effect of Training (Activation Decrease) and a rCBF Increase During Orientation Discrimination Relative to Control Before the Training Period*

| Regions (peak of focus) | Coordinates in Talairach space (x y z mm) | | | Z-score | P value | Effect size (% change) |
|---|---|---|---|---|---|---|
| Left superior cerebellar cortex / fusiform gyrus | – 24 | – 58 | – 16 | 4.7 | 0.001 | 5.2 |
| Right precentral gyrus/ postcentral gyrus | 36 | – 24 | 56 | 3.7 | 0.07 | 4.7 |
| Left fusiform gyrus | – 26 | – 80 | – 8 | 3.7 | 0.07 | 5.2 |
| Right lingual gyrus / fusiform gyrus | 18 | – 84 | – 8 | 3.6 | 0.08 | 4.7 |

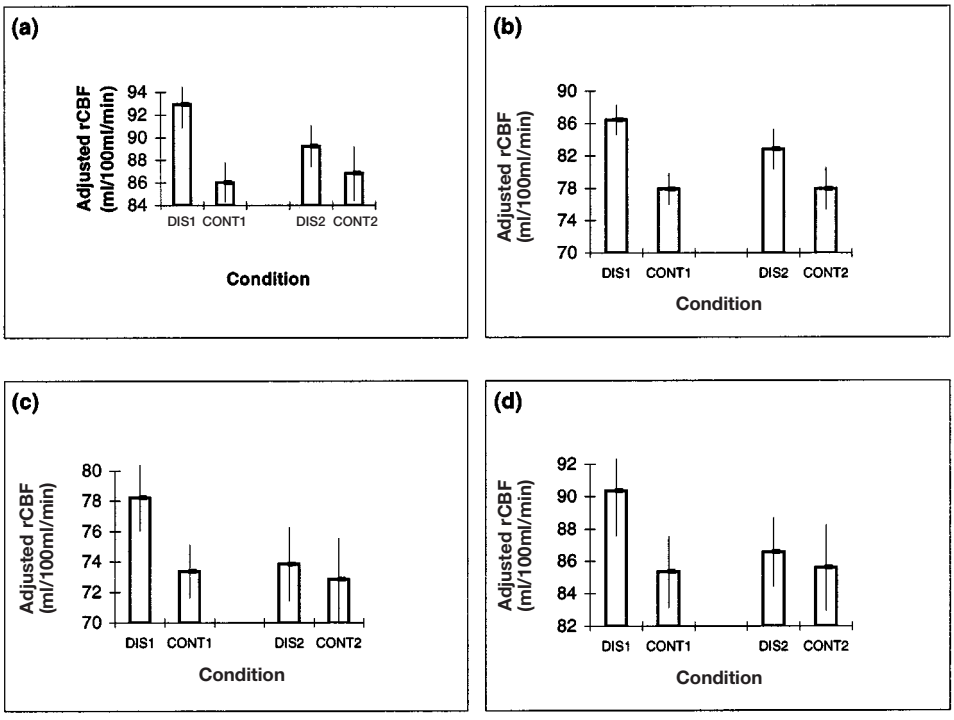


Fig 6 – *Activity profiles of the four regions where training induced a significant decrease in activation during orientation discrimination. These profiles plot the mean adjusted rCBF in DIS and in CONT, before and after the training. Vertical lines indicate the standard deviations. (a) Left superior cerebellar cortex/fusiform gyrus (b) right precentral gyrus/postcentral gyrus (c) left fusiform gyrus (d) right lingual gyrus/fusiform gyrus.*

illustrated in Figure 4b as fusions of the concerned coronal MRI sections with the *Z*-map of interest. Figure 6 represents the activity profiles of the mean adjusted rCBF of the peaks of these activations.

## Discussion

In the present study we investigated the effect of extensive training in orientation discrimination upon the cerebral activation pattern related to this task in naive subjects. Below we will discuss the behavioral and PET results we obtained in the light of the recent research in skill learning.

### *Task Effect*

When DIS was compared to the low-level passive control condition without considering the effect of learning, the activation pattern included posterior visual areas, frontal motor areas as well as parts of the thalamus and the cerebellum. Cerebellar activity changes have been observed in previous studies on orientation discrimination, both when using a passive control condition (Orban, Dupont, Vogels et al., 1997) and when using a control condition requiring the same motor response than in the DIS task (Gulyás and Roland, 1995; Schiltz et al., 1999). The same studies also reported other subcortical activations in relation to grating detection or discrimination. In the frontal lobes the bilateral activations in the precentral gyri corresponded most probably to the primary motor areas (Colebatch, Deiber, Passingham et al., 1991; Sadato, Ibanez, Campbell et al., 1997). The coordinates of the superior frontal regions (situated medially and dorso-laterally) suggested that they correspond respectively to the supplementary motor and the premotor areas (Colebatch et al., 1991). In the present study we expected neuronal activity increases in both primary and premotor movement regions since the DIS task required both the selection of a movement and the execution of the selected plan (Deiber, Passingham, Colebatch et al., 1991). More posteriorly, we observed activity increases related to DIS in the middle part of the right fusiform gyrus, in a region described as area VP by Sereno, Dale, Reppas et al. (1995). In summary, the present results reveal that a simple visual discrimination task activates several subcortical and cortical regions among which direct anatomical connections have been described (Glickstein, May and Mercier, 1985; Saint-Cyr, Ungerleider and Desimone, 1990).

### *Training Effect*

#### *Imaging Training and Learning*

In the present study both the increase in mean response accuracy (15%) and the decrease in mean response time (20 ms) indicated that subjects had acquired skill in DIS during the training phase. Learning was also demonstrated by the decrease in average JND (6°) after the training period which revealed that the subject's ability to discriminate fine orientation differences had improved. When investigating the learning-induced changes in functional neuroanatomy, however,

these very same parameters which behaviorally indicate the presence of learning become confounding factors. Indeed, changes in RT (i.e. in the task-related processing time) or in response accuracy (i.e. in the level of task difficulty and consequently in attentional load) as such are known to modulate neuronal activity (Corbetta, Miezin, Dobmeyer et al., 1990; Grady, Horwitz, Pietrini et al., 1995; Spitzer, Desimone and Morane, 1988; Winstein, Grafton and Pohl, 1997). These behavioral parameters can only be stabilized by gradually modifying and adjusting the task parameters. This procedure avoids the behavior-related confounds, but introduces new task-related confounds. Indeed it has been shown that the manipulation of task parameters (i.e. presentation rate or $\delta$) also affects the neuronal response (Fox and Raichle, 1984; Orban et al., 1997; Schneider, Casey and Noll, 1994). In summary, brain imaging studies on learning either keep the task parameters constant and make the behavioral parameters vary, or the opposite. Both strategies have their interest, since they focus on different aspects of the learning. In this experiment we chose to keep the task parameters (presentation rate and $\delta$) constant. Since we investigated learning in naive subjects this implied that the behavioral performances (RT and accuracy) differed between scanning days. As discussed above, we suggest that in the present case these performance-related changes must be considered as being part of the learning process since they do not result from manipulations of the task parameters but from internal adaptations initiated by practice.

Training equals a certain amount of task repetitions. Here we chose a very high amount of repetitions in order to assure that a significant amount of learning had taken place between the two PET sessions. It would be interesting to follow the training-related changes more closely and determine the precise evolution of neuronal changes as a function of training. Radioprotection norms prevented us from doing so in the present study, but fMRI could provide insights into this question.

Repetition of an experimental task in two different PETscanning sessions might induce neuronal changes that are unrelated to the training and learning which occur between the two sessions. In the present study, the only possible control for such potential effects would be the use of a control group composed of untrained subjects, who perform the discrimination task in two different PETscanning sessions without intermediate training. We did, however, not include such a group in our design because we think that the effect of simple task repetition on the observed rCBF changes is negligible in the present experiment. Indeed training in DIS was so extensive that such an effect should be minor compared to the learning-related effects. Considering the results, this hypothesis was confirmed by the observation that all of the rCBF changes we observed between PET sessions were located within regions well-known to play a role in orientation discrimination (for details and references see below).

### *Training-Related rCBF Increases*

The body of the right caudate nucleus was the only region which was significantly more activated by DIS after the training than before (see Figures 4a and 5). A theory initiated in the sixties proposes that the caudate nucleus

contains functionally differentiated regions whose functions are determined by the cortical areas which innervate them. Concerning visual pattern and object discrimination, a correspondence between function and innervation of the posterior part of the caudate nucleus and the extrastriate and inferotemporal visual areas could indeed be established. On the one hand, Divac, Rosvold and Szwarcbart (1967) showed that the posterior part of the caudate nucleus (i.e. the tail) is implicated in visual pattern discrimination processes. And more recently Levy, Friedman, Davachi et al. (1997) observed that the only region of the caudate nucleus metabolically active during a visual discrimination task (when compared to a sensori-motor control task) was the caudal portion of the right caudate nucleus body. On the other hand, independent anatomical studies have shown that the projections from the visual cortex are densest to the posterior part of the caudate nucleus. Thus it is known that the occipito-parietal cortex projects to the dorsal genu of the caudate nucleus, the prestriate area projects to the posterior genu and the caudal tail and finally, the temporal areas project to the rostral part of the tail (Saint-Cyr et al., 1990; Baizer, Desimone and Ungerleider, 1993; Webster, Bachevalier and Ungerleider, 1993; Yeterian and Pandya, 1995).

The early lesion studies (Battig, Rosvold and Mishkin, 1960; Buerger, Gross and Rocha-Miranda, 1974; Divac et al., 1967) also demonstrated that neostriatal lesions have an effect on the learning of the tasks they investigated. Thus the caudate nucleus appears to play a role both in stable performance and learning of visual discrimination tasks. A role in skill and habit learning is classically assigned to the whole neostriatum. Mishkin, Malamut and Bachevalier (1984) were the first to propose the existence of a cortico-striatal habit system, which they opposed to the associative declarative memory system. This system stores the changing probability that a specific stimulus (or environment) will evoke a specific response. It is the result of reinforcement contingencies which operate in a given situation and require more than one trial. Each successful trial strengthens the habit incrementally. The same ideas were taken up more recently by Salmon and Butters (1995) and White (1997).

Evidence defending the idea that the cortico-striatal system plays an important role in this type of learning comes from lesion studies in animals, patient studies and recently from imaging studies in healthy human adults. In the rat, White and coworkers (McDonald and White, 1993; McDonald and White, 1994; Packard, Hirsh and White, 1989) have dissociated different memory systems among which one cortico-striatal system which is involved in the slow incremental learning of associations between sensory cue and response, but not in memory tasks of spatial relations. In humans it was observed that compared to normal, age-matched control subjects (or Alzheimer and amnesiac patients) persons suffering from Huntington's or Parkinsons's disease are impaired in motor and visuo-motor skill learning (Harrington, Haaland, Yeo et al., 1990; Heindel, Butters and Salmon, 1988; Pascual-Leone, Grafman, Clark et al., 1993; Paulsen, Butters, Salmon et al., 1993; Saint-Cyr, Taylor and Lang, 1988; Willingham and Koroshetz, 1993), visual skill learning (Martone, Butters, Payne et al., 1984) and cognitive skill learning (Butters, Wolfe, Martone et al., 1985; Knowlton, Mangels and Squire, 1996). Concerning imaging studies, none of the

experiments targeting visual skill learning in healthy human adults reported any neostriatal changes (Poldrack, Desmond, Glover et al., 1998; Schiltz et al., 1999; Vaina, Belliveau, Burin de Roziers et al., 1997). Among the visuo-motor studies, the majority of the learning-related changes observed in the neostriatum concerned more ventral and anterior regions than the one in the present study (20, – 12, 22). Thus Krebs, Brashers-Krug, Rauch et al. (1998) reported increased rCBF in the right ventral striatum (15, 6, – 8), when comparing early learning in mechanical device manipulation with motor performance. Grafton, Mazziotta, Presty et al. (1992) and Grafton, Woods and Tyszka (1994) reported rCBF increases in the left putamen (– 28, – 1, – 3 and – 29, – 3, – 4), but only during the second day of rotor pursuit learning. The most consistent neostriatal activity changes are related to the studies in serial reaction time learning. The modulated regions were situated in the putamen at the coordinates (15, 15, – 7) (Grafton, Hazeltine and Yvry, 1995), (10, 11, – 8) (Rauch, Savage, Brown et al., 1995), (19, 9, 13) and (25, 6, 0) (Rauch, Whalen, Savage et al., 1997), (15, 5, – 9) (Doyon, Owen, Petrides et al., 1996). The only study describing changes in the posterior part of the neostriatum is the one by Deiber, Wise, Honda et al. (1997). This experiment reports an activity increase in the left posterior putamen (– 30, – 10, – 8 and – 28, – 4, 4) during learning of conditional evaluation and motor tasks. Among the above-mentioned visuo-motor paradigms, the experimental task in the latter study was the most similar to the present DIS task. Indeed, subjects had to identify a visual stimulus and associate a motor response with the stimulus. The major difference between the two tasks was the fact that in the present study the visual stimuli were more difficult to discriminate. Given both the well-known connections of the caudate nucleus with the visual system and its role in visual discrimination learning we propose that this difference concerning the visual component of the task accounts for the location of the activity increase in the caudate nucleus in the present study as opposed to the putamen in the study by Deiber et al. (1997). Since there are no consistencies between the tasks used (uni- or bimanual) and the laterality of the striatal activation changes reported in the above-mentioned studies, at the present moment we cannot yet propose any explanatory hypotheses concerning the laterality of the learning-induced striatal activation changes.

*Training-Related rCBF Decreases*

The largest region showing significant rCBF decreases with training was situated in the anterior part of the *cerebellar cortex*. These activity decreases are in line with the results of recent imaging studies showing that the cerebellum plays a crucial role in low-level skill learning (Doyon, 1997). Motor, visuo-motor and visual skill learning all seem to implicate the cerebellum. Concerning motor skills, the cerebellum is activated during trial and error learning (Jenkins, Brooks, Nixon et al., 1994; Jueptner, Frith, Brooks et al., 1997) and its activity decreases with training in finger and eye movement sequences (Dejardin, Dubois, Bodart et al., 1998; Friston, Frith, Passingham et al., 1992) and training in maze tracing (van Mier, Tempel, Perlmutter et al., 1998). In visual skill learning cerebellar activity decreases have consistently been observed with all

paradigms (Poldrack et al., 1998; Schiltz et al., 1999; Vaina et al., 1997). The visuo-motor skill learning studies have obtained more controversial results which depend strongly on the paradigm used. Cerebellar activity decreases with practice were observed with studies using rotor pursuit (Grafton et al., 1994) and step-tracking (Flament, Ellerman, Kim et al., 1996) tasks. In these experiments the cerebellum appears to be most active during the phase of implicit learning, which requires the detection and correction of visuo-motor errors. It has been proposed that the cerebellar activity depends on the stage of learning, with massive contributions in early stages (i.e. during learning) which are followed by a significant activity drop once an asymptotic performance level is reached (i.e. during over-learned or automatic performance) (Doyon, 1997; Thach, 1996). Also in the present study cerebellar activity was high while subjects were learning the task whereas after the training the overlearned task induced significantly less activity in the cerebellum.

The most anterior region showing rCBF decreases with training was located in the right *precentral gyrus* and is likely to correspond to the primary motor area (Colebatch et al., 1991; Sadato et al., 1997). It is conceivable that after the training subjects employed less force to push the button with their left, non-dominant hand. Given that the activation strength in the primary motor area is related to the force of movement (Dettmers, Fink, Lemon et al., 1995), this would result in reduced primary motor area activity. Since we did not record electromyograms this must however remain speculation. The present cued motor response was a very simple button-press, which as such did not require any learning for optimal task performance. Thus it is not surprising that we observed rCBF decreases instead of the primary motor area activity increases described by previous motor (Karni et al., 1995; Schlaug, Knorr and Seitz, 1994; Seitz, Roland, Bohm et al., 1990) and visuo-motor (Grafton et al., 1995; Grafton et al., 1992; Grafton et al., 1994) skill learning studies.

In the occipital visual cortex activity decreased bilaterally in the *fusiform gyrus*. On the left side, two peaks were observed. The anterior peak was situated close to V4v as described by Sereno et al. (1995). The coordinates of this region (– 24, – 58, – 16) are just slightly lateral to those of an anterior fusiform region (– 32, – 60, – 20) which showed nonspecific (i.e. not specifically related to the orientation used during training) rCBF decreases following training in DIS in our previous study targeting perceptual learning (Schiltz et al., 1999). The two regions situated on the posterior part of the fusiform gyrus (– 26, – 80, – 8 and 18, – 84, – 8) were quasi symmetrical with respect to the sagital midline, the right cluster extending slightly more medially into the lingual gyrus. These regions were, again, located very closely to regions showing non-specific training effects in the perceptual learning study. With the spatial limitation of PET these activations can only be identified, relatively imprecisely, as the representations of central vision in V1, V2, V3 and/or V4, their peaks being located bilaterally in areas V3 (DeYoe, Carman, Bandettini et al., 1996; Sereno et al., 1995; Shipp, Watson, Frackowiak et al., 1995). It is worth noting that the current fusiform activations are, however, clearly not situated in the regions of the fusiform gyrus which are activated by more complex stimuli like faces (40, – 55, – 10) (Kanwisher, McDermott and Chun, 1997) (– 38 ± 2, – 56 ± 4, – 6

± 2) (Gauthier, Skudlarski, Gore et al., 2000). In summary, although the present study did not allow us to assess directly whether these activity changes are specific for the orientation used during training or not, their locations indicate that they were probably not orientation-specific. The present findings confirm the results we and others obtained in previous studies on visual skill learning (Poldrack et al., 1998; Vaina et al., 1997) which all report activity decreases in the posterior occipital cortex as a consequence of learning. These results strengthen the assumption that visual discrimination learning involves mechanisms resulting in neuronal activity decreases in the visual cortex. The changes induced by low-level visual skill learning thus sharply contrast with the more anterior located fusiform activity increases consistently observed when natural or artificial expertise is acquired in recognition and categorization of higher-level stimuli like faces, greebles or cars (Gauthier, Tarr, Anderson et al., 1999). This difference most probably reflects the fact that expertise is the final stage of high-level visual skill learning, which implicates more complex stimuli (i.e. greebles) and tasks (i.e. categorization at the subordinate level) than the orientation discrimination task used in the current experiment concerning low-level visual skill learning.

In summary, the present PET study showed that extensive training in orientation discrimination induces massive neuronal activity decreases in the regions underlying this skill. The only training-related activity increase we observed was located in the posterior part of the caudate nucleus, confirming the role of this structure in skill learning.

*Acknowledgements*. This work has been supported by the FMRE, the ARC (grant n°95/00-189) and the PAI n°22. The authors are indebted to R. Bausart and B. Georges of the PET Unit in Louvain-la-Neuve (UCL) and to Professor G. Cosnard of the Unité de Radiodiagnostique in Brussels (UCL). We are also indebted to Professor G.A. Orban of the Laboratory of Neuro- en Psychophysiologie (KULeuven) for making available the stimuli and computer programs and providing experienced advice. Finally, we thank A. Ledberg for statistical advice and S. Dubois and E. Olivier for helpful discussions.

## References

AHISSAR, M., and HOCHSTEIN, S. Task difficulty and the specificity of perceptual learning. *Nature, 387:* 401-406, 1997.

BAIZER, J.S., DESIMONE, R., and UNGERLEIDER, L.G. Comparison of subcortical connections of inferior temporal and posterior parietal cortex in monkeys. *Vision Neurosciences 10:* 59-72, 1993.

BATTIG, K., ROSVOLD, H.E., and MISHKIN, M. Comparison of the effects of frontal and caudate lesions on the delayed response and alternation in monkeys. *Journal of Comparative Physiology and Psychology, 53:* 400-404, 1960.

BROOKS, V.B. *The Neural Basis of Motor Control*. Oxford: Oxford University Press, 1986.

BROWN, L.L., SCHNEIDER, J.S., and LIDSKY, T.I. Sensory and cognitive functions of the basal ganglia. *Current Opinions in Neurobiology, 7:* 157-163, 1997.

BUERGER, A.A., GROSS, C.G., and ROCHA-MIRANDA, C.E. Effects of ventral putamen lesions on discrimination learning by monkeys. *Journal of Comparative Physiology and Psychology, 86:* 440-446, 1974.

BUTTERS, N., WOLFE, J., MARTONE, M., GRANHOLM, E., and CERMAK, L.S. Memory disorders associated with Huntington's disease: Verbal recall, verbal recognition and procedural memory. *Neuropsychologia, 23:* 729-743, 1985.

COLEBATCH, J.G., DEIBER, M.P., PASSINGHAM, R.E., FRISTON, K.J., and FRACKOWIAK, R.S. Regional cerebral blood flow during voluntary arm and hand movements in human subjects. *Journal of Neurophysiology, 65:* 1392-1401, 1991.

CORBETTA, M., MIEZIN, F.M., DOBMEYER, S., SHULMAN, G.L., and PETERSEN, S.E. Attentional

modulation of neural processing of shape, color, and velocity in humans. *Science, 248:* 1556-1559, 1990.

DEIBER, M.P., PASSINGHAM, R.E., COLEBATCH, J.G., FRISTON, K.J., NIXON, P.D., and FRACKOWIAK, R.S. Cortical areas and the selection of movement: A study with positron emission tomography. *Experimental Brain Research, 84:* 393-402, 1991.

DEIBER, M.P., WISE, S.P., HONDA, M., CATALAN, M.J., GRAFMAN, J., and HALLETT, M. Frontal and parietal networks for conditional motor learning: A positron emission tomography study. *Journal of Neurophysiology, 78:* 977-991, 1997.

DEJARDIN, S., DUBOIS, S., BODART, J.M., SCHILTZ, C., DELINTE, A., MICHEL, C., ROUCOUX, A., and CROMMELINCK, M. PET study of human voluntary saccadic eye movements in darkness: effect of task repetition on the activation pattern. *European Journal of Neurosciences, 10:* 2328-2336, 1998.

DETTMERS, C., FINK, G.R., LEMON, R.N., STEPHAN, K.M., PASSINGHAM, R.E., SILBERSWEIG, D., HOLMES, A., RIDDING, M.C., BROOKS, D.J., and FRACKOWIAK, R.S. Relation between cerebral activity and force in the motor areas of the human brain. *Journal of Neurophysiology, 74:* 802-815, 1995.

DEYOE, E.A., CARMAN, G.J., BANDETTINI, P., GLICKMAN, S., WIESER, J., COX, R., MILLER, D., and NEITZ, J. Mapping striate and extrastriate visual areas in human cerebral cortex. *Proceedings of the National Academy of Sciences USA, 93:* 2382-2386, 1996.

DIVAC, I., ROSVOLD, H.E., and SZWARCBART, M.K. Behavioral effects of selective ablation of the caudate nucleus. *Journal of Comparative Physiology and Psychology, 63:* 184-190, 1967.

DOYON, J. Skill learning. *International Review of Neurobiology, 41:* 273-294, 1997.

DOYON, J., OWEN, A.M., PETRIDES, M., SZIKLAS, V., and EVANS, A.C. Functional anatomy of visuomotor skill learning in human subjects examined with positron emission tomography. *European Journal of Neurosciences, 8:* 637-648, 1996.

FLAMENT, D., ELLERMAN, J.M., KIM, S.G., UGURBIL, K., and EBNER, T.J. Functional magnetic resonance imaging of cerebellar activation during the learning of a visuomotor dissociation task. *Human Brain Mapping, 4:* 210-226, 1996.

FOX, P.T., and RAICHLE, M.E. Stimulus rate dependence of regional cerebral blood flow in human striate cortex, demonstrated by positron emission tomography. *Journal of Neurophysiology, 51:* 1109-1120, 1984.

FRISTON, K.J. Commentary and opinion: II. Statistical parametric mapping: Ontology and current issues. *Journal of Cerebral Blood Flow and Metabolism, 15:* 361-370, 1995.

FRISTON, K.J., FRITH, C.D., LIDDLE, P.F., DOLAN, R.J., LAMMERTSMA, A.A., and FRACKOWIAK, R.S. The relationship between global and local changes in PET scans. *Journal of Cerebral Blood Flow and Metabolism, 10:* 458-466, 1990.

FRISTON, K.J., FRITH, C.D., PASSINGHAM, R.E., LIDDLE, P.F., and FRACKOWIAK, R.S. Motor practice and neurophysiological adaptation in the cerebellum: A positron tomography study. *Proceedings of the Royal Society London, Series B, Biological Sciences, 248:* 223-228, 1992.

GAUTHIER, I., TARR, M.J., ANDERSON, A.W., SKUDLARSKI, P., and GORE, J.C. Activation of the middle fusiform 'face area' increases with expertise in recognizing novel objects. *Natural Neurosciences, 2:* 568-573, 1999.

GAUTHIER, I., SKUDLARSKI, P., GORE, J.C., and ANDERSON, A.W. Expertise for cars and birds recruits brain areas involved in face recognition. *Natural Neurosciences, 3:* 191-196, 2000.

GESCHEIDER, G.A. *Psychophysics. Methods, Theory and Application (second edition).* Hillsdale, New Jersey: Lawrence Erlbaum Associates, 1985.

GIBSON, E.J. Improvements in perceptual learning judgements as a function of controlled practice of training. *Psychological Bulletin, 50:* 402-431, 1953.

GLICKSTEIN, M., MAY, J.G.d., and MERCIER, B.E. Corticopontine projection in the macaque: The distribution of labelled cortical cells after large injections of horseradish peroxidase in the pontine nuclei. *Journal of Comparative Neurology, 235:* 343-359, 1985.

GRADY, L., HORWITZ, B., PIETRINI, P., MENTIS, M.J., UNGERLEIDER, L.G., RAPOPORT, S.I., and HAXBY, J.V. Effect of task difficulty on cerebral blood flow during perceptual matching of faces. *Human Brain Mapping, 4:* 227-239, 1995.

GRAFTON, S.T., HAZELTINE, E., and IVRY, R. Functional mapping of sequence learning in normal humans. *Journal of Cognitive Neurosciences, 7:* 497-510, 1995.

GRAFTON, S.T., MAZZIOTTA, J.C., PRESTY, S., FRISTON, K.J., FRACKOWIAK, R.S., and PHELPS, M.E. Functional anatomy of human procedural learning determined with regional cerebral blood flow and PET. *Journal of Neurosciences, 12:* 2542-2548, 1992.

GRAFTON, S.T., WOODS, R.P., and TYSZKA, M. Functional imaging of procedural motor learning: Relating cerebral blood flow with individual subject performance. *Human Brain Mapping, 1:* 221-234, 1994.

GULYAS, B., and ROLAND, P. Cortical fields participating in spatial frequency and orientation discrimination: Functional anatomy by positron emission tomography. *Human Brain Mapping, 3:* 133-152, 1995.

HARRINGTON, D.L., HAALAND, K.Y., YEO, R.A., and MARDER, E. Procedural memory in Parkinson's

disease: Impaired motor but not visuoperceptual learning. *Journal of Clinical and Experimental Neuropsychology, 12:* 323-339, 1990.

HEINDEL, W.C., BUTTERS, N, and SALMON, D.P. Impaired learning of a motor skill in patients with Huntington's disease. *Behavioural Neuroscience, 102:* 141-147, 1988.

HONDA, M., DEIBER, M.P., IBANEZ, V., PASCUAL-LEONE, A., ZHUANG, P., and HALLETT, M. Dynamic cortical involvement in implicit and explicit motor sequence learning. A PET study. *Brain, 121:* 2159-2173, 1998.

JENKINS, I.H., BROOKS, D.J., NIXON, P.D., FRACKOWIAK, R.S., and PASSINGHAM, R.E. Motor sequence learning: A study with positron emission tomography. *Journal of Neurosciences, 14:* 3775-3790, 1994.

JUEPTNER, M., FRITH, C.D., BROOKS, D.J., FRACKOWIAK, R.S., and PASSINGHAM, R.E. Anatomy of motor learning. II. Subcortical structures and learning by trial and error. *Journal of Neurophysiology, 77:* 1325-1337, 1997.

KANWISHER, N., MCDERMOTT, J., and CHUN, M.M. The fusiform face area: A module in human extrastriate cortex specialized for face perception. *Journal of Neurosciences, 17:* 4302-4311, 1997.

KARNI, A., and SAGI, D. The time course of learning a visual skill. *Nature, 365:* 250-252, 1993.

KARNI, A., MEYER, G., JEZZARD, P., ADAMS, M.M., TURNER, R., and UNGERLEIDER, L.G. Functional MRI evidence for adult motor cortex plasticity during motor skill learning. *Nature, 377:* 155-158, 1995.

KARNI, A, MEYER, G., REY-HIPOLITO, C., JEZZARD, P., ADAMS, M.M., and TURNER, R. The acquisition of skilled motor performance: Fast and slow experience-driven changes in primary motor cortex. *Proceedings of the National Academy of Sciences USA, 95:* 861-868, 1998.

KINAHAN, P.E., and ROGERS, J.G. Analytic three-dimensional image reconstruction using all detected events. *IEEE Trans Nucl Sci* NS, *36:* 964-968, 1990.

KNOWLTON, B.J., MANGELS, J.A., and SQUIRE, L.R. A neostriatal habit learning system in humans. *Science, 273:* 1399-1402, 1996.

KREBS, H.I., BRASHERS-KRUG, T., RAUCH, S.L., SAVAGE, C.R., HOGAN, N., RUBIN, R.H., FISCHMAN, A.J., and ALPERT, N.M. Robot-aided functional imaging: Application to a motor learning study. *Human Brain Mapping, 6:* 59-72, 1998.

LEVY, R., FRIEDMAN, H.R., DAVACHI, L., and GOLDMAN-RAKIC, P.S. Differential activation of the caudate nucleus in primates performing spatial and nonspatial working memory tasks. *Journal of Neurosciences, 17:* 3870-3882, 1997.

MARTONE, M., BUTTERS, N., PAYNE, M., BECKER, J.T., and SAX, D.S. Dissociations between skill learning and verbal recognition in amnesia and dementia. *Archives of Neurology, 41:* 965-970, 1984.

MAYER, M.J. Practice improves adults' sensitivity to diagonals. *Vision Research, 23:* 547-550, 1983.

MAZZIOTTA, J.C., HUANG, S.C., PHELPS, M.E., CARSON, R.E., MACDONALD, N.S., and MAHONEY, K. A noninvasive positron computed tomography technique using oxygen-15-labeled water for the evaluation of neurobehavioral task batteries. *Journal of Cerebral Blood Flow and Metabolism, 5:* 70-78, 1985.

MCDONALD, R.J., and WHITE, N.M. A triple dissociation of memory systems: Hippocampus, amygdala, and dorsal striatum. *Behavioural Neuroscience, 107:* 3-22, 1993.

MCDONALD, R.J., and WHITE, N.M. Parallel information processing in the water maze: evidence for independent memory systems involving dorsal striatum and hippocampus. *Behavioural Neural Biology, 61:* 260-270, 1994.

MICHEL, C., SIBOMANA, M., BODART, J.M., GRANDIN, C., COPPENS, A., BOL, A., DE VOLDER, A., WARSCOTTE, V., THIRAN, J.P., and MACQ, B. Interactive delineation of brain sulci and their merging into functionnal images. *IEEE Med Imag Conf Record San Francisco*, 1480-1484, 1995.

MILNER, B. *Les Troubles de la Mémoire Accompagnant des Lésions Hippocampiques Bilatérales*. Paris: Centre National de la Recherche Scientifique, 1962.

MISHKIN, M., MALAMUT, B., and BACHEVALIER, J. *Memories and Habits: Two Neural Systems*. New York: Guilford Press, 1984.

OLDFIELD, R.C. The assessment and analysis of handedness: The Edinburgh inventory. *Neuropsychologia, 9:* 97-113, 1971.

ORBAN, G.A., DUPONT, P., VOGELS, R., BORMANS, G., and MORTELMANS, L. Human brain activity related to orientation discrimination tasks. *European Journal of Neurosciences, 9:* 246-259, 1997.

PACKARD, M.G., HIRSH, R., and WHITE, N.M. Differential effects of fornix and caudate nucleus lesions on two radial maze tasks: Evidence for multiple memory systems. *Journal of Neurosciences, 9:* 1465-1472, 1989.

PASCUAL-LEONE, A., GRAFMAN, J., CLARK, K., STEWART, M., MASSAQUOI, S., LOU, J.S., and HALLETT, M. Procedural learning in Parkinson's disease and cerebellar degeneration. *Annals of Neurology, 34:* 594-602, 1993.

PASSINGHAM, R. *The Frontal Lobes and Voluntary Action*. Oxford: Oxford University Press, 1993.

PAULSEN, J.S., BUTTERS, N., SALMON, D.P., HEINDEL, W.C., and SWENSON, M.R. Prism adaptation in Alzheimer's and Huntington's disease. *Neuropsychology, 7:* 73-81, 1993.

PETERSEN, S.E., VAN MIER, H., FIEZ, J.A., and RAICHLE, M.E. The effects of practice on the functional

anatomy of task performance. *Proceedings of the National Academy of Sciences USA, 95:* 853-860, 1998.

PIETRZYCK, U., HERHOLZ, K., FINK, G., JACOBS, A., MIELKE, R., SLANSKY, I., WÜRKER, M., and HEISS, W.D. An interactive technique for three-dimensional image registration: Validation for PET, SPECT, MRI and CT brain studies. *Journal of Nuclear Medicine, 35:* 2011-2018, 1994.

POLAT, U., and SAGI, D. Spatial interactions in human vision: From near to far via experience-dependent cascades of connections *Proceedings of National Academy of Sciences USA, 91:* 1206-1209, 1994.

POLDRACK, R.A., DESMOND, J.E., GLOVER, G.H., and GABRIELI, J.D. The neural basis of visual skill learning: an fMRI study of mirror reading. *Cerebral Cortex, 8:* 1-10, 1998.

RAUCH, S.L., SAVAGE, C.R., BROWN, H.D., CURRAN, T., ALPERT, N.M., KENDRICK, A., FISCHMAN, A.J., and KOSSLYN, S.M. A PET investigation of implicit and explicit sequence learning. *Human Brain Mapping, 3:* 271-286, 1995.

RAUCH, S.L., WHALEN, P.J., SAVAGE, C.R., CURRAN, T., KENDRICK, A., BROWN, H.D., BUSH, G., BREITER, H.C., and ROSEN, B.R. Striatal recruitment during an implicit sequence learning task as measured by functional magnetic resonance imaging. *Human Brain Mapping, 5:* 124-132, 1997.

SADATO, N., IBANEZ, V., CAMPBELL, G., DEIBER, M.P., LE BIHAN, D., and HALLETT, M. Frequency-dependent changes of regional cerebral blood flow during finger movements: Functional MRI compared to PET. *Journal of Cerebral Blood Flow and Metabolism, 17:* 670-679, 1997.

SAINT-CYR, J.A., TAYLOR, A.E., and LANG, A.E. Procedural learning and neostriatal dysfunction in man. *Brain, 111:* 941-959, 1988.

SAINT-CYR, J.A., UNGERLEIDER, L.G., and DESIMONE, R. Organization of visual cortical inputs to the striatum and subsequent outputs to the pallido-nigral complex in the monkey. *Journal of Comparative Neurology, 298:* 129-156, 1990.

SALMON, D.P., and BUTTERS, N. Neurobiology of skill and habit learning. *Current Opinions in Neurobiology, 5:* 184-190, 1995.

SCHILTZ, C., BODART, J.M., DUBOIS, S., DEJARDIN, S., MICHEL, C., ROUCOUX, A., CROMMELINCK, M., and ORBAN, G.A. Neuronal mechanisms of perceptual learning: Changes in human brain activity with training in orientation discrimination. *Neuroimage, 9:* 46-62, 1999.

SCHILTZ, C., BODART, J.M., DUBOIS, S., MICHEL, C., ORBAN, G.A., ROUCOUX, A., and CROMMELINCK, M. The effects of training in a visuo-motor task on the rCBF in the human brain: A PET study. *Neuroimage, 7:* S833, 1998.

SCHLAUG, G., KNORR, U., and SEITZ, R. Inter-subject variability of cerebral activations in acquiring a motor skill: A study with positron emission tomography. *Experimental Brain Research, 98:* 523-534, 1994.

SCHMIDT, R.A. *Motor Control and Learning: A Behavioral Emphasis*. Champaign: Human Kinetics Publishers, 1985.

SCHNEIDER, W., CASEY, B.J., and NOLL, D. Fuctional MRI mapping of stimulus rate effects across visual processing stages. *Human Brain Mapping, 1:* 117-133, 1994.

SCHOUPS, A.A., VOGELS, R., and ORBAN, G.A. Human perceptual learning in identifying the oblique orientation: Retinotopy, orientation specificity and monocularity. *Journal of Physiology (London), 483:* 797-810, 1995.

SEITZ, R.J., ROLAND, E., BOHM, C., GREITZ, T., and STONE-ELANDER, S. Motor learning in man: A positron emission tomographic study. *Neuroreport, 1:* 57-60, 1990.

SERENO, M.I., DALE, A.M., REPPAS, J.B., KWONG, K.K., BELLIVEAU, J.W., BRADY, T.J., ROSEN, B.R., and TOOTELL, R.B. Borders of multiple visual areas in humans revealed by functional magnetic resonance imaging. *Science, 268:* 889-893, 1995.

SHIPP, S., WATSON, J.D., FRACKOWIAK, R.S., and ZEKI, S. Retinotopic maps in human prestriate visual cortex: The demarcation of areas V2 and V3. *Neuroimage, 2:* 125-132, 1995.

SHIU, L.P., and PASHLER, H. Improvement in line orientation discrimination is retinally local but dependent on cognitive set. *Perceptual & Psychophysics, 52:* 582-588, 1992.

SPITZER, H., DESIMONE, R., and MORAN, J. Increased attention enhances both behavioral and neuronal performance. *Science, 240:* 338-340, 1988.

SQUIRE, L.R., KNOWLTON, B., and MUSEN, G. The structure and organization of memory. *Annual Review of Psychology, 44:* 453-495, 1993.

TALAIRACH, J., and TOURNOUX, J. *Coplanar Stereotaxic Atlas of the Human Brain*. Stuttgart: Georg Thieme Verlag, 1988.

THACH, W.T. On the specific role of the cerebellum in motor learning and cognition: Clues from PET activation and lesion studies in man. *Behavioural and Brain Sciences, 19:* 411-431, 1996.

VAINA, L.M., BELLIVEAU, J.M., BURIN DES ROZIERS, E.B., and ZEFFIRO, T. The relationship between cortical activation and psychophysical performance in humans during fast learning of motion discrimination. *Neuroimage, 5:* S137, 1997.

VAN LEHN, K. Cognitive skill acquisition. *Annual Review of Psychology, 47:* 513-539, 1996.

VAN MIER, H., TEMPEL, L.W., PERLMUTTER, J.S., RAICHLE, M.E., and PETERSEN, S.E. Changes in brain activity during motor learning measured with PET: Effects of hand of performance and practice.

*Journal of Neurophysiology, 80:* 2177-2199, 1998.
VOGELS, R., and ORBAN, G.A. The effect of practice on the oblique effect in line orientation judgments. *Vision Research, 25:* 1679-1687, 1985.
VOTAW, J.R. Signal-to-Noise Ratio in Neuro Activation PET Studies. *IEEE Transactions on Medical Imaging, 152:* 197-205, 1996.
WEBSTER, M.J., BACHEVALIER, J., and UNGERLEIDER, L.G. Subcortical connections of inferior temporal areas TE and TEO in macaque monkeys. *Journal of Comparative Neurology, 335:* 73-91, 1993.
WETHERHILL, G.B., and LEWITT, H. Sequential estimation of points on a psychometric function. *British Journal of Mathematics, Statistics and Psychology, 18:* 1-10, 1965.
WHITE, N.M. Mnemonic functions of the basal ganglia. *Current Opinions in Neurobiology, 7:* 164-169, 1997.
WILLINGHAM, D.B., and KOROSHETZ, W.J. Evidence for dissociable motor skills in Huntington's disease patients. *Psychobiology, 21:* 173-182, 1993.
WINSTEIN, C.J., GRAFTON, S.T., and POHL, P.S. Motor task difficulty and brain activity: Investigation of goal-directed reciprocal aiming using positron emission tomography. *Journal of Neurophysiology, 77:* 1581-1594, 1997.
WOODS, R.P., CHERRY, S.R., and MAZZIOTTA, J.C. Rapid automated algorithm for aligning and reslicing PET images. *Journal of Computer Assisted Tomography, 16:* 620-633, 1992.
YETERIAN, E.H., and PANDYA, D.N. Corticostriatal connections of extrastriate visual areas in rhesus monkeys. *Journal of Comparative Neurology, 352:* 436-457, 1995.

Christine Schiltz, Laboratory of Neurophysiology (NEFY), UCL 5449 Av. Hippocrate, 54, B-1200 Brussels (Belgium). E-mail: schiltz@nefy.ucl.ac.be

(*Received 13 July 2000 reviewed 18 September 2000, revised 7 December 2000; accepted 8 December 2000*)