Objective: Recent studies of functional brain imaging have shown the involvement of the basal ganglia in executive processes such as planning and set-shifting. However, the specific contributions of the striatum in those processes remain unknown. This study aimed to test the hypothesis that the caudate nucleus is primarily involved in the preparation of a novel action and not in set-shifting per se.

Methods: In the present event-related functional magnetic resonance imaging (fMRI) study, a new task was developed that permitted, for the first time, to distinguish between shifts in classification when the rule is implicitly given by the task from shifts that require cognitive comparison and planning.

Results: Significantly increased activity in the caudate nucleus and the putamen was observed only in conditions in which cognitive planning was required to perform a set-shift, whereas significant activation was seen in the subthalamic nucleus (another region of the basal ganglia) in all shifting conditions whether or not planning was required.

Interpretation: We suggest that the caudate nucleus and the putamen are particularly important, respectively, in the planning and the execution of a self-generated novel action, whereas the subthalamic nucleus may be required when a new motor program is solicited independently of the choice of strategy.

Abnormalities of the basal ganglia (BG) have been described in many neurological disorders such as Parkinson’s disease, and thus it is important to gain a greater understanding of the functional role of the different nuclei of the BG in the healthy brain in order to reveal the neural origins of the cognitive and motor deficits observed in those disorders. Traditionally thought to be associated with the control of movement and motor learning, BG has been shown by neuropsychological studies in patients with Parkinson’s and Huntington’s disease to contribute to a variety of executive functions, including planning and set-shifting (ie, the ability to alter our mode of response in the face of changing circumstances). Among the different BG nuclei, the caudate nucleus has been shown to play a greater role in executive processes, whereas other structures such as the putamen and subthalamic nucleus have traditionally been associated with more motor-related activities. However, there is evidence that the role of the putamen may not be directly linked to the movement itself, but rather to the condition under which it is made, whereas the subthalamic nucleus may exert a specific influence on the BG output related to the control of movement. Hence, whereas the evidence accumulated to date suggests that the various nuclei of the BG may have different functional roles, their distinct contribution to the planning and execution of action remains unknown.

Recently, functional magnetic resonance imaging (fMRI) has been used routinely to investigate the neural substrates of various cognitive functions in normal subjects as well as patients with neurological or psychiatric disorders. In the earlier fMRI studies, it was difficult to make fine distinctions in cognitive processing and to distinguish between small neural structures, especially subcortical ones. However, recent methodological advances both in the type of acquisition sequences and in data analysis has made it possible to study the involvement of subcortical structures, such as the different parts of the BG, in specific cognitive conditions.

In a previous event-related fMRI study of the Wisconsin Card-Sorting Task in young healthy adults, we observed significant activation in the caudate nucleus specifically when subjects received negative feedback (ie, when a set-shift was required). While the involvement of the caudate nucleus in set-shifting has also been confirmed in other neuroimaging studies, there is still no evidence up to now of whether the...
Fig 1. The different conditions of the Montreal Card-Sorting Task. (A) An example of the cue card that appears for 3.5 seconds at the beginning of a block of retrieval trials. In this example, the cue card contains two red circles. (B) An example of two consecutive retrieval trials without shift. Because the color red is the only attribute shared by the test card and the cue on both trials, matching must be based on color. Note that the location of the response on subsequent trials is the same, resulting in the same finger being used to perform the matching response. In this and the other examples (C, D, E), the orange line under one of the reference cards indicates the selected response. (C) An example of two consecutive retrieval trials with shift. Left: the test card contains four red stars and hence shares the color attribute with the cue card (containing two red circles, shown in A). Right: on the subsequent trial, the test card now shares a different attribute with the cue card (in this example “number”). Thus, a shift in classification category occurs requiring a novel response. Note also that, in this condition, the location of the response necessarily changes and a different finger has to be used. (D) An example of two consecutive trials in the continuous shift condition. Left: the only reference card that shares an attribute with the test card is the second one, and therefore the second reference card has to be selected according to color. Right: in the subsequent trial, a test card containing one pink square is shown. The first reference card must now be selected because it is the only one that shares an attribute with the test card (number), and therefore a shift in classification occurs. Thus, in this condition, a continuous shift occurs guided implicitly by the only shared attribute between the test card and one of the reference cards. Note that the location of the response is always changing and therefore requires the use of a different finger. (E) An example of a control trial. The test card always matches exactly one of the reference cards and the subject simply must select the twin reference card.

Caudate nucleus is most important for the execution of the shift per se or rather for its planning (ie, the cognitive decision to shift). Here, a new card-sorting task was developed called the Montreal Card-Sorting Task that allowed us to dissociate between these two aspects of set-shifting. Using fMRI in young healthy adults, we tested the hypothesis that the caudate nucleus is primarily involved in the preparation of a novel action and not in the execution of set-shifting per se. A mixed-design protocol was used in which trials occurred within blocks but were reconstructed and analyzed in an event-related manner.

Subjects and Methods
Subjects
Ten right-handed healthy subjects (mean age, 23.4 years; range, 18–31; five males, five females) participated in this study. Subjects had no previous personal or family history of neurological or psychiatric disorders and were not taking any prescribed medication at the time of scanning. Handedness was assessed by the Edinburgh Handedness Inventory.18 All subjects gave informed consent to the protocol, which was reviewed and approved by the Research and Ethics Committees of the Montreal Neurological Institute.

Cognitive Task
In the Montreal Card-Sorting Task used here, four reference cards were on display in a row at the top of a computer screen in all trials. These reference cards displayed one red triangle, two green stars, three yellow crosses, and four blue circles, respectively (Fig 1). On each classification trial, a new test card was presented in the middle of the screen below the reference cards, and the subject had to match the test card to one of the four reference cards. This was done by pressing one of four buttons with the right hand, using one of four fingers, each one corresponding to one of the reference cards. The match of each test card to one of the reference cards was determined by a classification rule that differed across experimental conditions. On each trial, as soon as the subject responded, a period of 2.3 seconds followed when the screen became bright if the response was correct and dark if the response was incorrect. This period only served as feedback and was not useful for the correct execution of the subsequent trial. No incentives (financial reward or other) were provided or suggested to the subjects for the accuracy of their performance. The duration of each trial varied according to the subject’s reaction time during the matching, hence providing the asynchrony between stimulus presentation and frame acquisition required for event-related acquisition.

There were four different experimental conditions in this experiment: (1) retrieval without shift; (2) retrieval with shift; (3) continuous shift; and (4) control. Trials in the continuous shift and the control conditions occurred in different blocks presented in a random order. The retrieval without shift and retrieval with shift trials were interleaved within the same blocks.

In the retrieval blocks (see Fig 1A–C), a series of classification trials were preceded by the brief presentation of a single cue card containing one to four objects that consisted of
one of four shapes in one of four possible colors for a period of 3.5 seconds (see Fig 1A). This was then followed by a blank period of 3.5 seconds. The cue card did not reappear and had to be remembered throughout the series of classification trials. On every trial, a new test card that shared a single attribute (color, shape, or number) with the cue card held in memory was presented underneath the reference cards (see Fig 1B, C). The subject had to select one of the four reference cards based on this attribute. For instance, if the test card and the cue card shared the color red (as in the example shown in Fig 1B), a match to the reference card that has red in it was required. There were two types of classification trials in the retrieval blocks: trials without shift, and trials with shift. Trials without shift (see Fig 1B) occurred when the test cards on two or more consecutive trials shared the same attribute with the cue card. In the example shown in Figure 1B, a different red test card is presented on consecutive trials so that a match to the reference card that has red in it was required on each of these trials. On the other hand, trials with shift (see Fig 1C) occurred when the test cards on two consecutive trials did not share the same attribute with the cue card. In the example shown in Figure 1C, a trial where the only shared attribute between the cue card and the test card is the color (both cards are red) was followed by a trial in which the only shared attribute between the cue card and the test card is number (both cards contain two objects). Hence a “shift” was required from classification according to color to classification according to number. Three shift trials occurred within each retrieval block of trials. Shifts in classification occurred randomly after 2, 3, 4, or 5 consecutive classifications in a row using the same criterion, the total number of trials per block being variable. In the retrieval with shift condition, an active comparison needed to be performed between the cue and the test cards to execute the shift. Also, in this condition, the correct reference card on subsequent trials was located at different positions, requiring the use of a different finger on each trial. In contrast, in the retrieval without shift condition, the correct reference card on subsequent trials was located in the same position, hence requiring the same finger movement.

In the continuous shift condition (see Fig 1D), no cue card was presented. Each test card contained only one attribute shared with a single reference card, and thus there was only one possible response based on this attribute. In this condition, test cards were presented so that shifts in classification occurred on each new trial in a random order. In the example shown in Figure 1D, a trial was presented in which the test card shared an attribute only with the first reference card (the color green) followed by a trial in which the test card shared an attribute only with the first reference card (one object). Twelve trials occurred within each block of the continuous shift condition. Unlike the retrieval with shift condition, no active planning or comparison was needed to execute the shift because the new rule for classification was implicitly given by the task. Note also that, in this condition, the correct reference card on subsequent trials was located at different positions, requiring the use of a different finger on each trial.

In the control condition, the test card on each trial was a replica of one of the four reference cards (see Fig 1E), and the subject was required only to match the test card to its twin within the four reference cards. Twelve trials occurred within each block of the control condition.

Subjects performed six retrieval blocks including both shift and nonshift trials, as well as three blocks of the continuous shift and control conditions per run. Before scanning, subjects were trained on the task using a personal computer. During this training session, all subjects performed four series of six retrieval and three continuous shift and control conditions.

**Functional Magnetic Resonance Imaging Scanning**

Subjects were scanned using a 1.5-Tesla Siemens Sonata MRI scanner at the McConnell Brain Imaging Centre. Each scanning session began with a T1-weighted three-dimensional volume acquisition for anatomical localization, followed by acquisitions of echo planar T2*-weighted images with BOLD contrast. Functional images were acquired in six runs containing 200 volumes each acquired every 2.5 seconds (TE, 50 milliseconds; FA, 90 degrees). Volumes contained 24 slices, voxel size 4.7 × 4.7 × 4.7 mm³.

**Data Analysis**

The methods for data analysis were the same as in our previous studies[^12] and made use of the fMRistrat software developed by Worsley and colleagues.[^20] The first three frames in each run were discarded because the BOLD signal does not reliably reach steady state during those frames. Images from each run then were realigned to the fourth frame for motion correction and smoothed using a 6mm full-width half-maximum (FWHM) isotropic Gaussian kernel. The statistical analysis of the fMRI data was based on a linear model with correlated errors. The design matrix of the linear model was first convolved with a difference of two gamma hemodynamic response functions timed to coincide with the acquisition of each slice. The correlation structure was modeled as an autoregressive process. At each voxel, the autocorrelation parameter was estimated from the least squares residuals, after a bias correction for correlation induced by the linear model. The autocorrelation parameter was first regularized by spatial smoothing and then was used to “whiten” the data and the design matrix. The linear model was reestimated using least squares on the whitened data to produce estimates of effects and their standard errors. The resulting effects and standard effect files then were spatially normalized by nonlinear transformation into the standard proportional stereotaxic space of Talairach and Tournoux[^21] using the algorithm of Collins and colleagues.[^22] Anatomical images were also normalized to the Talairach space using the same transformation. In a second step, runs, sessions, and subjects were combined using a mixed-effects linear model for the data taken from the previous analysis. A random-effects analysis was performed by first estimating the ratio of the random-effects variance to the fixed-effects variance, and then regularizing this ratio by spatial smoothing with a Gaussian filter. The amount of smoothing was chosen to achieve 110 effective degrees of freedom.[^20,23] Statistical maps were thresholded at p value less than 0.05 corrected for multiple comparisons for all peaks and at p value less than 0.001 uncorrected for predicted peaks within the BG.

Error trials were not considered in the fMRI analysis be-
cause the error rate was very low during scanning (below 3% across all conditions for all subjects). Furthermore, the trial following an error trial in the retrieval condition was also removed because it cannot be classified into any of the two categories (with shift, without shift). Activity during the matching period (from the moment a new test card is presented to the moment a response is made) on each trial of the four conditions (retrieval without shift, retrieval with shift, continuous shift, and control) was combined to generate the following six contrasts for statistical analysis: (1) retrieval without shift minus control; (2) retrieval with shift minus control; (3) continuous shift minus control; (4) retrieval with shift minus retrieval without shift; (5) retrieval with shift minus continuous shift; (6) continuous shift versus retrieval without shift.

We predicted that the caudate nucleus would be particularly involved in the retrieval with shift, that is, the condition requiring active planning to perform a shift in classification, but not in the continuous shift nor the retrieval without shift conditions in which no such planning is required.

Results
Significantly increased cortical activity was found in all subtractions described above and these were in agreement with our results previously reported using fMRI during the performance of the Wisconsin Card-Sorting Task.12 Because the present fMRI protocol was specifically designed to study BG involvement in executive processes, only the subcortical peaks are reported and discussed here.

As predicted, there was a significant increase in activity in the right caudate nucleus (1) when the retrieval with shift was compared with the control condition, (2) when the retrieval with shift was compared with the retrieval without shift condition, and (3) when the retrieval with shift was compared with the continuous shift condition (Table, Fig 2A–C).

Significant activation was also observed in the left putamen when retrieval with shift was compared with retrieval without shift (Figs 2B and 3A) and also in the globus pallidus when the continuous shift was compared with the retrieval without shift condition (see Table).

In addition, there was significant activity in the region of the brain that encompasses the subthalamic nucleus. Although with the fMRI resolution used here it may be difficult to determine with certainty whether the observed increases in activity in this region are actually focused in the subthalamic nucleus, the coordinates of the activity clusters observed coincided well with the delimitation of this nucleus in the Talairach and Tournoux atlas. In the subthalamic nucleus, sig-

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A significant increase in activity was observed, bilaterally when the retrieval with shift was compared with the retrieval without shift condition, and, in the left side only, when the continuous shift was compared with the retrieval without shift condition (see Table). For the retrieval with shift minus the retrieval without shift subtraction, the cluster of significant voxels for this region lay in the left side of the brain between X = -16 to
-7, Y = -30 to -20, and Z = -14 to 0 (Fig 3A), and in the right side of the brain between X = 11 to 15, Y = -23 to -18, and Z = -8 to -2 (see Fig 3A). For the continuous shift minus the retrieval without shift subtraction, the cluster of significant voxels for this region lay in the left side of the brain between X = -19 to -7, Y = -26 to -18, and Z = -14 to -6 (see Fig 3B).

Finally, significantly increased activity was observed in the thalamus, bilaterally, when the retrieval with shift was compared with the retrieval without shift condition, and in the right thalamus when the continuous shift was compared with the retrieval without shift condition (see Table). Note that no other subcortical region reached significance, even at a low level of significance of p value less than 0.01 uncorrected in any of the subtractions.

Discussion
These results show that the caudate nucleus is specifically involved in the active planning of a novel action. Increased activity in the caudate nucleus in this experiment cannot be attributed to the short-term retention in memory of the cue card because significant activation in this structure was observed when comparing the retrieval with shift to the retrieval without shift conditions (both conditions having identical short-term memory requirements) and not when comparing the retrieval without shift to the control condition (even though the retrieval condition had a short-term memory requirement and the control did not). This finding is consistent with the fMRI study of Lewis and colleagues14 who suggest that the caudate nucleus is particularly involved in cognitive manipulation, but not in maintenance or retrieval of information within working memory.

In earlier neuroimaging studies that showed the involvement of the caudate nucleus in set-shifting,11–13 the experimental design could not determine whether the caudate nucleus is important in the shift per se or its planning (ie, the cognitive decision to shift). Here, the experimental design was such that it enabled us to distinguish between these possibilities. Indeed, the continuous shift condition, in which the rule is provided implicitly to the subject, permitted us to examine whether the caudate nucleus is involved in the shift per se, or rather in the active planning of the novel action solicited by the task. Importantly, there was no increase in activity during the continuous shift versus the control condition in the caudate nucleus, showing that shifting per se is not the cause of the increase in neostriatal activity in shifting tasks. This conclusion is further supported by the fact that activity in the caudate nucleus was significantly increased both during the re-

Fig 3. Location of the subthalamic nucleus peaks in the various subtractions. The anatomical MRI images shown are the average of the T1 acquisitions of the 10 subjects transformed into stereotaxic space. (A) Location of the bilateral subthalamic nucleus activation in the retrieval with shift versus the retrieval without shift condition. Note also the presence of a peak in the left putamen. Axial sections are shown every 2mm from Talairach coordinate Z = -8 to Z = -2. (B) Location of left subthalamic activation in the continuous shift versus the retrieval without shift condition. Axial sections are shown every 2mm from Talairach coordinate Z = -12 to Z = -6.
retrieval with shift versus the continuous shift condition and during the retrieval with shift versus the control condition. Thus, the significant increase in activity observed in this nucleus in set-shifting must be caused by the active planning of a novel action, and not to the shift per se. This hypothesis is consistent with a previous positron emission tomography study\(^{10}\) in which significantly increased activity in the caudate nucleus was observed only in conditions in which multiple moves had to be planned in advance during the performance of a planning task (ie, the Tower of London).

The significant increase in activity in the putamen in this study when retrieval with shift was compared with retrieval without shift is in agreement with our previous fMRI study of the Wisconsin Card-Sorting task in which significant activity in the putamen was only observed during matching after negative feedback (ie, during the execution of a set-shift), but not during matching following positive feedback (ie, matching using the same rule as previously).\(^{12}\) This study provides further evidence that the putamen is involved in the execution of nonroutine actions. Cunnington and colleagues\(^{24}\) had reported significant activity of the putamen during self-initiated movements, but not during externally triggered alternating movements. Interestingly, in the present study, significant putamen activity was not observed during the continuous shift condition in which the movement to be performed is implicitly given by the task (via the only possible choice of card) and therefore “externally triggered.” Altogether these results indicate that the putamen may play an important role in the execution of an action that is based on a self-determined novel strategy.

The fact that a significant increase in activity was observed only in the left putamen is consistent with the required contralateral motor response.\(^{1,2,25}\) Furthermore, significantly increased activity was only found in the right caudate nucleus and not the left. This seems in agreement with previous positron emission tomography studies reporting that, in Parkinson’s disease, significant decreased dopamine release in the right caudate nucleus only correlated with performance on frontal executive tasks,\(^{26,27}\) and fMRI experiments showing significant increased activity in the right caudate nucleus only during the performance of a cognitive task in healthy adults.\(^{25,28}\) However, other fMRI studies of cognitive functions have also reported bilateral activation of the caudate nucleus,\(^{12,14}\) and bilateral activation of the putamen has also been reported in an fMRI study of finger movements where movements were performed only with the right hand.\(^{24}\)

In sharp contrast with the striatum, increased activity in the subthalamic nucleus was observed when comparing conditions in which the finger used to respond changed on each trial with conditions in which the finger used to respond remained the same (ie, retrieval with shift versus retrieval without shift and continuous shift versus retrieval without shift). These findings indicate that activity in the subthalamic nucleus is not linked to the active planning of an action, but rather to the execution of a new movement (ie, finger movement in this particular study). This finding receives support from previous neurophysiological studies in monkeys and humans showing that a large proportion of neurons in the subthalamic nucleus respond during active and passive limb movements.\(^{3,16,17}\) Indeed, it has been suggested that the subthalamic nucleus exerts a specific influence on the BG output related to the control of movement parameters.\(^{3,16,17}\)

Along with this hypothesis, we suggest that activity in the subthalamic nucleus is less context dependent than in the caudate nucleus and putamen because subthalamic activity was not dependent on the planning of a set-shift, but rather on the execution of a different limb movement.

In conclusion, the present fMRI study enabled us to dissociate between the activity of different BG structures and allowed us to determine the specific functional contribution of the caudate nucleus in planning and set-shifting. We were able to separate the functional roles of the caudate nucleus, the putamen, and the subthalamic nucleus in the preparation and execution of actions. Such functional imaging studies may allow for a better understanding of the pathophysiology of the cognitive and motor deficits in illnesses linked to BG dysfunction, such as Parkinson’s disease.\(^{19}\)

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