Fronto-striatal Contribution to Lexical Set-Shifting

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Fronto-striatal circuits in set-shifting have been examined in neuroimaging studies using the Wisconsin Card Sorting Task (WCST) that requires changing the classification rule for cards containing visual stimuli that differ in color, shape, and number. The present study examined whether this fronto-striatal contribution to the planning and execution of set-shifts is similar in a modified sorting task in which lexical rules are applied to word stimuli. Young healthy adults were scanned with functional magnetic resonance imaging while performing the newly developed lexical version of the WCST: the Wisconsin Word Sorting Task. Significant activation was found in a cortico-striatal loop that includes area 47/12 of the ventrolateral prefrontal cortex (PFC), and the caudate nucleus during the planning of a set-shift, and in another that includes the posterior PFC and the putamen during the execution of a set-shift. However, in the present lexical task, additional activation peaks were observed in area 45 of the ventrolateral PFC area during both matching periods. These results provide evidence that the functional contributions of the various fronto-striatal loops are not dependent on the modality of the information to be manipulated but rather on the specific executive processes required.

Keywords: fMRI, language rules, lexical processing, prefrontal cortex, set-shifting, striatum

Introduction

Basal ganglia have traditionally been associated with the control of movement. Projections from the output nuclei innervate the ventrolateral thalamus projecting exclusively upon the primary motor cortex and the supplementary motor area (Kemp and Powell 1971). Subsequently, it has been proposed that a topographical organization exists between parts of the cortex and the striatum, giving rise to the parallel cortico-striatal loops, as proposed by Alexander et al. (1986). In accordance with this model, it has been shown recently that different parts of the striatum are involved in separate sensorimotor, limbic, and cognitive information processing (Middleton and Strick 2002). Notably, the caudate nucleus and the lateral prefrontal cortex (PFC) have been associated with cognitive functions (Levy et al. 1997) and the putamen and motor/premotor cortex in the execution of movement (Alexander et al. 1986). Based on these studies, fiber tracking using diffusion tensor imaging sequences has provided anatomical evidence that this parallel organization of cortico-striatal loops previously described in monkeys also exist in humans (Bar-Gad and Bergman 2001; Haber 2003).

Inside the basal ganglia, the caudate nucleus is thought to play a greater role in executive processes, while the putamen has been traditionally associated with more motor related activities. Recently, Monchi et al. (2006) have suggested that the caudate nucleus and the putamen are particularly important in the planning and execution of self-generated novel actions, respectively. In the language domain, the putamen has been shown to be involved when speaking a second language (Klein et al. 1994) and the caudate nucleus when a shift occurs from listening to a very familiar language to a less familiar one (Abutalebi et al. 2007). Using functional magnetic resonance imaging (fMRI), Monchi et al. (2001) reported the involvement of 2 different cortico-striatal loops during the performance of the Wisconsin Card Sorting Task (WCST), a task traditionally used to measure cognitive flexibility, via the provision of feedback (positive or negative). During the reception of negative feedback, which indicates the need to plan a set-shift, significant activation was observed in area 47/12 of the midventrolateral PFC, the caudate nucleus, and the thalamus, while matching after negative feedback (i.e., the execution of a set-shift) involved the posterior frontal cortex and the putamen. These results were replicated in a more recent study by Nagano-Saito et al. (2008). However, the functional involvement of fronto-striatal regions in set-shifting has never been explored in the context of lexical stimuli with normal participants.

The involvement of basal ganglia in language and executive functions has also been investigated in patient populations. For example, patients with Parkinson's disease (PD) or Huntington's disease (HD) exhibit cognitive decline dominated by executive processes deficits such as planning and set-shifting impairments (Owen et al. 1996; Dubois and Pillon 1997). Language impairments have also been reported in the form of syntax deficits (Lieberman et al. 1990, 1992; Natsopoulos et al. 1993; Grossman 1999), that is, the ability to find or apply rules whereby words or other elements of sentence structure are combined to form grammatical sentences. Furthermore, studies in patients with HD have suggested that the role of the striatum in language lies in rule and lexical processing (Teichmann et al. 2008). Based on another study with PD and HD patients, Longworth et al. (2005) proposed that the striatum plays a restricted non–language-specific inhibitory role in the late stages of language processing. Finally, it has been proposed that impaired sentence comprehension in PD may reflect an inability to shift cognitive sets (Lieberman 2002).

So far, the involvement of fronto-striatal structures in executive processes such as set-shifting has mostly been investigated in the context of visual stimuli, like images or objects. However, a recent study has investigated the role of the striatum in global executive processes in the context of words, such as the study of Ali et al. (2010), and suggested that the left caudate nucleus may have a specific role in suppressing irrelevant words.

The aim of the present study was to investigate the role of different prefrontal and striatal regions when performing a set-shifting task with lexical rules using fMRI. We hypothesized that fronto-striatal areas contribute to the same executive processes, regardless of whether they are applied to language rules or not. In order to test the role of these regions in language-related processing, we developed a lexical version of our original visual object–based WCST fMRI protocol. The principles governing the task, such as rule application and set-shifting, were the same as those in the original WCST, but the stimuli used in the present task were lexical. We predicted that the new verbal version of the task would reveal a pattern of fronto-striatal activity related to set-shifting similar to the one observed in the original version of the WCST (Monchi et al. 2001; Nagano-Saito et al. 2008), that is, a cognitive cortico-striatal loop involving the midventrolateral PFC (area 47/12), caudate nucleus, and the thalamus during the planning of a set-shift and a more motor one involving the posterior PFC and the putamen during the execution of a set-shift.

Materials and Methods

Subjects

Fourteen healthy right-handed individuals, native French speaking from Quebec (8 females, 6 males; mean age, 26 years; standard deviation [SD] 2.29; range, 22-31 years), participated in this study after giving informed consent. None of them had any history of neurological or psychiatric disorder. The study was approved by the research ethics committee of the Regroupement Neuroimagerie Québec (CMER-RNQ). This committee follows the guidelines of the Tri-Council Policy Statement of Canada, the civil code of Quebec, the Declaration of Helsinki, and the code of Nuremberg.

Cognitive Task

The newly developed Wisconsin Word Sorting Task (WWST) is a lexical analog of the computerized WCST used by Monchi et al. (2001). In order to achieve this goal, a strict correspondence was established between the verbal stimuli of the current version and the stimuli of the original WCST, as well as the rules and the number of exemplars (Fig. 1). Specifically, the 3 classification rules of the original task (i.e., classification according to color, shape, and number of visual stimuli) were replaced by 3 lexical ones: 1 semantic and 2 phonological rules that consisted of syllable onset and syllable rhyme. In the new task, subjects had to classify words according to 1 of 3 rules discovered by trial and error using feedback provided at the end of each trial. Throughout the experiment, 4 reference words were presented in a row at the top of the screen. On each trial, the subject was required to match a new word, presented in the center of the computer screen and below the reference words, to 1 of the 4 reference words but was not told which one of the 3 lexical rules (i.e., semantic, syllable onset, and syllable rhyme) to use (Fig. 2). The selection was indicated by pressing the appropriate button of a magnetic resonance imaging

compatible response box held with the right hand by the participant: The left button, associated with the index finger, moved a cursor under the reference card from left to right, and pressing the right button, corresponding to the middle finger, confirmed the selection. On each trial, participants had to find the proper classification rule and apply it based on feedback following each selection. A change in the screen brightness indicated to the subject whether the answer was correct (bright screen) or incorrect (dark screen). After 6 consecutive correct trials, the rule changed without warning, and the subject had to discover the new rule of classification. As in the original WCST, there were 4 matching possibilities for each one of the categories; 4 semantic categories: transportation, animals, objects, and vegetables; 4 phonological onset syllables: "ba," "a," "ca," and "poi"; 4 phonological rhyme syllables: "au," "é," "an," and "on." Here are a few examples of such matching: Stimulus word "POIGNÉE" (handle) requiring semantic matching → answer "CADRAN" (clock), that is, from the object category; Stimulus word "POIGNÉE" requiring phonological matching based on the onset syllable → answer "POIVRON" (pepper "poi"); Match "POIGNÉE" phonologically based on the rhyme syllable → answer "ARAIGNÉE" (spider, "é").

The words were all chosen to be concrete according to the concreteness scale of Bonin et al. (2003) and to have the same phonological syllabic structure according to the French lexical database *lexique 3* (New et al. 2001) (http://www.lexique.org/). Word length ranged from 4 to 9 letters; the number of syllables ranged from 2 to 3. Choosing broad categories was essential in order to achieve an exact correspondence with the constraints of the original WCST. This included controlling for the number of stimulus words that share more than one attribute with a given response card. For example, the words *barreau* and *bateau* share the same onset and rhyme syllables. Words were selected out of over 135 000 words contained in the French lexical database *lexique 3* (New et al. 2001). We selected the onset and rhyme syllable in which there were the most words. From this selection, we matched the words that shared the same onset and rhyme syllables, and from this last selection, we finally chose the words that shared the same semantic category. Other criterions are also important in a lexical task such as the frequency of the words, the imagery value, and the number of phonological and orthographic neighbors (Bonin et al. 2003). While we did control for some of these factors, a perfect compliance with all these latter constraints was not possible. However, since the participants were fully trained on the task prior to scanning, the possible confounding factors arising from such a design were minimized in our study.

The same types of trials that were identified for the WCST version of Monchi et al. (2001) were defined for the present lexical analog. In the
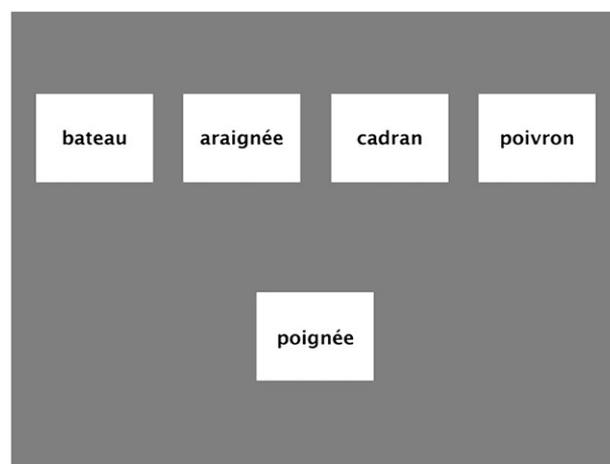
Figure 2. An example of a typical trial of the WWST. In this example, the participant is presented with the word *poignée* (handle) as a test stimulus. Matching according to semantics would require selection of the word *cadran* (frame), according to rhyme syllable would require selection of the word *araignée* (spider), and according to onset syllable the word *poivron* (pepper).

Wisconsin Card Sorting Task			
3 Rules	Colors	Shapes	Numbers
4 Attributes	Red, Green, Yellow, Blue	Triangle, Star, Cross, Circle	One, Two, Three, Four

Wisconsin Word Sorting Task			
3 Rules	Semantic	Syllable Onset	Syllable Rhyme
4 Attributes	Transportation, Animals, Objets, Vegetables	Ba, A, Ca, Poi	O, E, An, On

Figure 1. Schematic diagram of the rule and attribute correspondence between the WCST and the WWST.

WWST, 2 types of trial occur: those following negative feedback, requiring a set-shift, and those following positive feedback, requiring the maintenance of the current rule of classification. Two distinct temporal periods could also be distinguished within each trial: receiving feedback, when the subject has to use the information provided to choose whether to maintain or change the rule for classification, and matching following feedback, when the participant executes the response based on the chosen rule (matching according to a new rule or matching according to the same rule as in the previous trial). Thus, 4 different stages of the task can be defined: event 1, receiving negative feedback, which indicates to the participant "the need to plan a set-shift (i.e. to choose a different rule than the one used for the last trial)"; event 2, matching following negative feedback, where the participant "executes the set-shift (i.e. to perform the first match according to the new chosen rule)"; event 3, receiving positive feedback, which indicates to the participant "the need to maintain the same rule as in the previous trial"; event 4, matching following positive feedback, where the participant "performs a match according to the same rule as in the previous trial." A control condition was added in which the test word was 1 of the 4 reference words, and a participant was required to match the test word to its reference twin. In this condition, 2 other event periods were defined: event 5, control feedback, where the brightness of the screen does not change, and event 6, control matching, which required selecting the card identical to the test cards among the reference cards.

The participants took part in one fMRI session. Each scanning session contained 4 functional runs; each run was made up of 4 blocks of the task. Each block consisted of 3 experimental conditions (corresponding to each one of the 3 rules) and one control condition presented in a pseudorandom fashion. Before the scanning session began, subjects were fully trained on the task using a personal computer. They practiced until they performed the tasks with less than 2% of perseverative errors, that is, incorrect and repetitive use of the same classification rule after negative feedback (excluding the first trial of a new rule), and set-loss errors, that is, incorrect classification after having applied the proper rule at least 3 times. This optimal level of performance was reached within 5 blocks of the task by all participants. Prior to training, participants were also familiarized with the word list in order to verify that they knew the words and could match each word according to the various categories. During the scanning period, the computer screen was projected onto a mirror in the magnetic resonance imaging (MRI) scanner.

Data Acquisition
The participants were scanned using a 3-T Siemens Trio Magnetom MRI scanner at the Unité de Neuroimagerie Fonctionnelle du Centre de Gériatrie de l'Université de Montréal. The scanning session consisted of a 7-min T_1 3D gradient echo sequence with 1 mm^3 resolution, followed by 4 series of echoplanar T_2*-weighted functional acquisitions with prospective motion correction. Each functional series contained 210 acquisitions repeated every 2.5 s. Each frame contained 36 slices of 3.5 mm each placed along the anterior commissure/posterior commissure with a matrix size 64 × 64 pixels, isotropic kernel 3.5 × 3.5 × 3.5 mm^3, Flip Angle 90°, and time echo 30 ms.

Data Analysis
Data analysis was performed using the fmristat software developed by Worsley et al. (2002) (http://www.math.mcgill.ca/keith/fmristat/), in the same manner as in our earlier WCST studies (Monchi et al. 2001, 2004). The first 3 frames of each run were discarded. Images from each run were first realigned to the fourth frame for motion correction and smoothed using a 6-mm full-width at half-maximum 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 2 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 square residuals, after a bias correction for correlation induced by the linear model. The autocorrelation parameter was first regularized by

spatial smoothing and was then 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 were then spatially normalized by nonlinear transformation into the standard proportional stereotaxic space of Talairach and Tournoux (1988) using the MNI305 brain as an approximation via the algorithm of Collins et al. (1994). 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 mixed-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 (Worsley et al. 2002; Worsley 2005). Statistical maps were thresholded at $P < 0.05$ corrected for multiple comparisons using the minimum between a Bonferroni correction and random field theory for all peaks. Predicted peaks that appeared in our previous studies with the traditional WCST (Monchi et al. 2001, 2004) are also reported at $P < 0.0001$ noncorrected and indicated by an asterisk (*) in the tables and in the text.

Four contrasts for statistical analysis were generated by subtracting the appropriate control period trials from the experimental event periods: 1) receiving negative feedback minus control feedback, indicating that a shift is required; 2) matching after negative feedback minus control matching, which is the execution of the first match after the set-shift; 3) receiving positive feedback minus control feedback, indicating that the current matching criterion must continue to be used; 4) matching after positive feedback minus control matching, which is the execution of a match according to the current criterion. Finally, to better dissociate the 2 fronto-striatal loops, we performed another 4 interactions: 5) receiving negative feedback (event 1) versus receiving positive feedback (event 3); 6) matching after negative feedback (event 2) versus matching after positive feedback (event 4); 7) (receiving negative feedback [event 1] minus receiving positive feedback [event 3]) versus (matching after negative feedback [event 2] minus matching after positive feedback [event 4]); and its reverse 8) (matching after negative feedback [event 2] minus matching after positive feedback [event 4]) versus (receiving negative feedback [event 1] minus receiving positive feedback [event 3]).

Results

In the new task, subjects had to classify words according to 1 of 3 lexical rules: semantic, syllable onset, and syllable rhyme. On each trial, the subject was required to match a new word to 1 of 4 reference words but was not told which 1 of the 3 rules to use. The rules had to be discovered by trial and error.

Behavioral Data
All 14 participants completed 64 conditions (4 runs, 16 conditions per run). Behavioral data (errors and reaction times) were analyzed using SPSS 15.0 for Windows. Errors were divided into perseverative errors (0.06%), set-loss errors (2.38%), that is, incorrect classifications after shifts in condition (when the participant wrongly changed rule after having applied it correctly at least 3 times), and negative feedback related to searching for the correct sorting rule by trial and error (13.42%). Note that the latter errors were not considered errors because participants could not know the new classification rule on the first attempt after a set-shift. Response times were analyzed for the different matching periods. For the control matching condition (event 5), the average reaction time was 1285.5 ms (SD: 154.44), for the positive matching (event 3) 1627.70 ms (SD: 182.68), and for negative matching (event 1) 1990.35 ms (SD: 186.95).
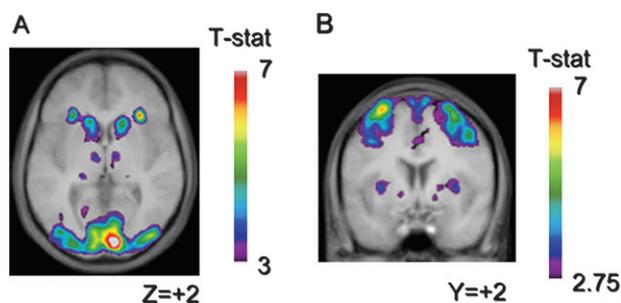
fMRI Data

We compared the average blood oxygen level–dependent (BOLD) signal obtained during the matching and feedback periods of trials requiring semantic, onset syllable, and rhyme syllable rules combined with that obtained during the corresponding periods in the control trials. As predicted, the results showed the involvement of 2 sets of regions associated with 2 different cortico-striatal loops during the performance of the WWST: one involving the midventrolateral PFC (area 47/12), the caudate nucleus, and the thalamus during the planning of a set-shift (Fig. 3A) and another involving the posterior PFC and the putamen during the execution of a set-shift (see Tables 4–6 and Fig. 3B).

Receiving Negative Feedback

When receiving negative feedback (event 2) was compared with control feedback (event 6) (Table 1), significantly increased activity was observed, bilaterally, in the frontopolar cortex (area 10), the middorsolateral PFC (areas 46 and 9/46, with the peak in the right hemisphere only being significant at a value of $P < 0.0001$ uncorrected), the midventrolateral PFC (area 47/12), the supplementary motor area (SMA) (area 6), the posterior temporal cortex (area 37), the posterior parietal cortex (area 7), the lateral premotor cortex (area 6), and the occipital region (areas 17, 18, and 19). There was also significant increased activity, in the left hemisphere, the posterior frontal cortex (at the junction of areas 6, 8, and 44), the anterior cingulate cortex (area 32), and the posterior cingulate cortex (area 31). Subcortically, significantly increased activity was observed, bilaterally, in the caudate nucleus, the mediodorsal thalamus, in a cluster covering the red nucleus and the subthalamic nucleus, and in the substantia nigra in the right hemisphere only.

Matching After Negative Feedback

Comparing the BOLD signal during matching after negative feedback (event 1) with control matching (event 5) (Table 2) revealed significant bilateral activation in the frontopolar cortex (area 10), the middorsolateral PFC (areas 46 and 9/46), the posterior PFC (at the junction of areas 6 and 8), in 2 regions of the midventrolateral PFC (area 47/12 and area 45), lateral premotor cortex (area 6), supplementary motor area (area 6), posterior parietal cortex (areas 7 and 40), and in the occipital region (areas 18 and 19). There were also significant increases in activity in the right anterior cingulate cortex (area 32), right temporal cortex (area 37), and the right occipital cortex (area 17).

Receiving Positive Feedback

When comparing positive feedback (event 4) with control feedback (event 6), significantly increased activity was observed bilaterally in the occipital cortex (areas 17, 18, and 19).

Table 1

Receiving negative feedback (event 1) minus control feedback (event 5)

Anatomical area	Stereotaxic coordinates				
	x	y	z	t-values	Cluster size
Frontopolar cortex (area 10)					
Left	−38	54	14	4.13	1344
Right	34	60	12	3.85	648
Anterior cingulate cortex (area 32)					
Left	−8	34	26	3.88	5000
Midventrolateral PFC (area 47/12)					
Left	−30	26	−2	6.04	>10 000
Right	32	26	0	6.49	4503
Middorsolateral PFC (46 and 9/46)					
Left	−52	26	30	4.44	4105
Right	52	24	36	3.58*	312
Medial premotor cortex (SMA) (area 6)					
Left	−4	14	54	4.86	5000
Right	8	16	50	4.39	5000
Posterior frontal cortex (junction of areas 6, 8, and 44)					
Left	−48	6	38	6.46	4204
Left	−36	18	26	4.86	4204
Lateral premotor cortex (area 6)					
Left	−50	0	54	4.39	4145
Left	−40	0	40	4.16	4145
Temporal cortex (area 37)					
Left	−44	−64	−8	6.19	>10 000
Right	32	−62	−12	5.77	>10 000
Posterior cingulate cortex (area 31)					
Left	−20	−64	6	3.88	>10 000
Posterior parietal cortex (area 7)					
Left	−24	−74	40	4.98	>10 000
Right	24	−76	46	4.82	>10 000
Occipital cortex (area 17)					
Left	−10	−94	0	6.34	>10 000
Right	10	−92	4	8.53	>10 000
Occipital cortex (area 18)					
Left	−12	−80	−12	7.13	>10 000
Left	−40	−80	−2	5.54	>10 000
Right	12	−82	−8	7.19	>10 000
Occipital cortex (area 19)					
Left	−26	−86	22	6.4	>10 000
Left	−26	−74	38	4.96	>10 000
Right	22	−86	26	4.88	>10 000
Right	42	−64	−8	6.2	>10 000
Mediodorsal thalamus					
Left	−8	−14	8	4.79	>10 000
Right	8	−11	3	3.99	>10 000
Caudate nucleus (head)					
Left	−14	22	−2	6.3	>10 000
Right	16	20	0	6.11	4400
Red nucleus					
Left	−4	−28	−4	5.79	>10 000
Right	6	−24	−4	5.72	>10 000
Substancia nigra					
Right	6	−16	−12	5.52	>10 000
Subthalamic Nucleus					
Left	−6	−14	0	4.75	>10 000
Right	8	−12	−4	5.01	>10 000

Figure 3. Location of the cortico-striatal peaks. Functional activity difference superimposed on the anatomical MRI, which is the average of the T_1 acquisitions of the 14 participants transformed into the Montreal Neurological Institute standard proportional stereotaxic space. (A) Horizontal section through area 47/12 of the midventrolateral PFC, caudate nucleus, and thalamus peaks at Z = +2 mm. The peaks shown here were observed during receiving negative feedback compared with control feedback (Table 1) but similar peaks were also observed in receiving negative feedback compared with positive feedback (Tables 5 and 7). (B) Coronal section through the putamen and premotor peaks located at Y = +2 mm. These peaks occurred in the matching following negative versus matching following positive feedback (Tables 6 and 7).

There was also a significant increase in activity in the left inferior temporal cortex (area 37) and in a cluster covering the right red nucleus and substantia nigra (Table 3).

Table 2

Matching after negative feedback (event 2) minus control matching (event 6)

Anatomical area	Stereotaxic coordinates				
	x	y	z	t-values	Cluster size
Frontopolar cortex (area 10)					
Left	−36	56	16	5.16	>10 000
Right	30	56	18	5.19	>10 000
Middorsolateral PFC (46 and 9/46)					
Left	−48	28	32	4.74	>10 000
Right	42	36	26	5.26	>10 000
Anterior cingulate cortex (area 32)					
Right	10	30	28	5.69	>10 000
Midventrolateral PFC (area 47/12)					
Left	−30	28	6	7.12	>10 000
Right	34	28	0	5.27	>10 000
Midventrolateral PFC (area 45)					
Left	−44	28	16	4.58	>10 000
Right	56	16	10	3.63	4448
Medial premotor cortex (SMA) (area 6)					
Left	−6	−4	68	4.52	>10 000
Right	2	−4	68	4.52	>10 000
Posterior PFC (junction of areas 6, 8, and 44)					
Left	−50	6	44	5	>10 000
Left (area 44)	−50	14	16	3.85	>10 000
Right	46	20	42	4.17	>10 000
Lateral premotor cortex (area 6)					
Left	−44	2	40	5.34	>10 000
Left	−28	0	5	5.26	>10 000
Right	28	0	52	6.92	>10 000
Inferior parietal cortex (40)					
Left	−36	−48	42	6.38	>10 000
Right	44	−46	46	5.12	>10 000
Temporal cortex (area 37)					
Right	56	−60	−24	4.99	4002
Posterior parietal cortex (area 7)					
Left	−28	−62	44	6.95	>10 000
Left	−32	−66	58	4.89	>10 000
Right	30	−58	54	7.48	>10 000
Precuneus (area 7)					
Left	−12	−68	50	5.2	>10 000
Left	−2	−90	44	4.72	>10 000
Right	2	−72	52	7.01	>10 000
Occipital cortex (area 18)					
Right	30	−92	−10	5.11	4100
Occipital cortex (area 19)					
Left	−6	−88	38	4.19	>10 000
Right	2	−80	28	3.75	>10 000
Occipital cortex (area 17)					
Right	12	−94	−8	4.06	4089

Table 3

Receiving positive feedback (event 3) minus control feedback (event 5)

Anatomical area	Stereotaxic coordinates				
	x	y	z	t-values	Cluster size
Inferior temporal cortex (area 37)					
Left	−44	−64	−6	5.06	>10 000
Occipital cortex (area 17)					
Left	−10	−82	4	5.29	>10 000
Right	10	−74	10	5.79	>10 000
Occipital cortex (area 18)					
Left	−12	−80	−12	5.64	>10 000
Left	−28	−88	10	5.44	>10 000
Right	14	−80	−10	6.88	>10 000
Right	16	−94	18	5.04	>10 000
Occipital cortex (area 19)					
Left	−30	−68	−12	4.52	>10 000
Left	−16	−92	28	4.98	>10 000
Right	30	−64	−10	4.79	>10 000
Red nucleus					
Right	4	−24	−6	5.72	1904
Substantia nigra					
Right	6	−14	−8	4.6	1904

Matching After Positive Feedback

When matching after positive feedback (event 3) was compared with control matching (event 5, Table 4), significantly increased activity was observed, bilaterally, in the middorsolateral PFC (areas 46 and 9/46, with the peak in the right hemisphere only being significant at a value of $P < 0.0001$ uncorrected), the supplementary motor area (area 6), the lateral premotor cortex (area 6), the posterior parietal cortex (areas 40 and 7), and the precuneus (area 7). Four unilateral peaks were detected, namely the right occipital cortex (areas 17 and 18), the left ventrolateral prefrontal cortex (VLPFC) (area 45 and area 47/12), the left posterior PFC (intersection of areas 6, 8, and 44), and the right frontopolar cortex (area 10).

Receiving Negative Feedback Relative versus Receiving Positive Feedback

In order to examine areas specifically involved in planning a set-shift in the context of the WWST, the activity related to receiving positive feedback (event 2) was subtracted from that related to receiving negative feedback (event 4). The BOLD signal was significantly greater bilaterally in the midventrolateral PFC (area 47/12), the caudate nucleus, and the thalamus. Other significant activation was also found bilaterally in the frontopolar cortex (area 10), the middorsolateral PFC (areas 46 and 9/46), the premotor cortex (area 6), the supplementary motor area (area 6), the inferior frontal sulcus (at the junction of areas 6, 8, and 44), the posterior parietal cortex (areas 7 and

Table 4

Matching after positive feedback (event 4) minus control matching (event 6)

Anatomical area	Stereotaxic coordinates				
	x	y	z	t-values	Cluster size
Frontopolar cortex (area 10)					
Right	24	54	16	4.27	1120
Right	28	44	20	3.65	1120
Middorsolateral PFC (46 and 9/46)					
Left	−44	30	16	4.66	3005
Left	−48	26	30	4.2	3005
Right	44	34	28	3.56*	312
Midventrolateral PFC (area 45)					
Left	−46	28	18	4.37	9760
Midventrolateral PFC (area 47)					
Left	−30	28	6	5.87	9760
Medial premotor cortex (SMA) (area 6)					
Left	−4	14	52	6.82	>10 000
Right	8	14	50	5.07	>10 000
Posterior PFC					
Left (junction of areas 6, 8, and 44)	−36	12	30	3.84	3001
Left (areas 6 and 8)	−50	6	44	4.77	3001
Lateral premotor cortex (area 6)					
Left	−28	2	56	5.31	1264
Right	26	0	50	5.39	>10 000
Inferior parietal cortex (area 40)					
Left	−32	−50	42	4.57	>10 000
Right	40	−58	42	3.78	>10 000
Posterior parietal cortex (area 7)					
Left	−28	−62	42	6.22	>10 000
Left	−38	−52	54	5.4	>10 000
Right	30	−60	56	4.87	>10 000
Precuneus (area 7)					
Left	−4	−78	44	4.78	>10 000
Right	2	−80	42	4.63	>10 000
Occipital cortex (area 18)					
Right	30	−90	−10	3.94	912
Occipital cortex (area 17)					
Right	12	−96	−8	3.21	912

40), the inferior temporal cortex (area 37), the occipital cortex (areas 17, 18, and 19), and in the left anterior cingulate cortex (area 32, Table 5).

Matching After Negative Feedback versus Matching After Positive

In order to understand the regional brain activity differentiating the 2 matching periods, we also contrasted the average BOLD signal during matching after negative feedback with that during matching after positive feedback (Table 6). The results revealed significant increased activity bilaterally in the posterior PFC (at the junction of areas 6 and 8) and the putamen (only at a significance level of $P < 0.0001$ uncorrected). Significant activation was also observed bilaterally in the frontopolar cortex (area 10), the lateral premotor cortex (area 6), the inferior and posterior parietal cortex (areas 40 and 7), the middorsolateral PFC (areas 46 and 9/46), the

midventrolateral PFC (area 47/12), the anterior cingulate cortex (area 32), in the right hemisphere of area 45 of the midventrolateral PFC, and the right middle temporal cortex (area 21).

Receiving Negative Feedback minus Receiving Positive Feedback versus Matching After Negative Feedback minus Matching After Positive

When performing the interaction corresponding to planning a set-shift versus executing a set-shift, significantly greater activity was observed in the right hemisphere in the ventrolateral PFC (area 47/12) and the caudate nucleus (only at a significance level of $P < 0.0001$ uncorrected) and in the left hemisphere in the dorsolateral PFC (areas 46 and 9/46, only at a significance level of $P < 0.0001$ uncorrected), the lateral premotor cortex (area 6), and in the occipital cortex (area 19) (Table 7). In the reverse interaction corresponding to planning of a set-shift versus executing one, significant activation was found in the left hemisphere in the frontopolar cortex (area 10), the anterior cingulate cortex (area 32), and the middle temporal cortex (area 21) and in the right hemisphere in the dorsolateral PFC (area 9), the ventrolateral PFC (area 45), the

Table 5
Receiving negative feedback (event 1) minus receiving positive feedback (event 3)

Anatomical area	Stereotaxic coordinates				
	x	y	z	t-values	Cluster size
Frontopolar cortex (area 10)					
Left	−32	52	12	4.22	1656
Right	34	58	12	4.46	4176
Middorsolateral PFC (46 and 9/46)					
Left	−48	24	30	5.14	>10 000
Right	48	26	34	4.48	>10 000
Midventrolateral PFC (47/12)					
Left	−30	26	−2	6.71	>10 000
Right	32	26	2	7.42	>10 000
Anterior cingulate cortex (area 32)					
Left	−8	32	26	5.6	>10 000
Medial premotor cortex (SMA) (area 6)					
Left	−4	14	52	7.29	>10 000
Right	8	16	48	6.23	>10 000
Posterior PFC (areas 6, 8, and 44)					
Left	−40	6	28	5.65	>10 000
Right	42	4	34	6.13	>10 000
Lateral premotor cortex (area 6)					
Left	−44	2	40	6.93	>10 000
Inferior parietal cortex (area 40)					
Left	−38	−46	46	3.88	>10 000
Right	36	−46	42	4.73	>10 000
Posterior parietal cortex (area 7)					
Left	−28	−48	44	4.48	>10 000
Right	30	−52	42	4.41	>10 000
Inferior temporal cortex (area 37)					
Left	−48	−60	−14	7.04	>10 000
Right	50	−60	−12	5.66	>10 000
Precuneus (area 7)					
Left	−6	−66	52	4.78	>10 000
Right	8	−64	52	4.38	>10 000
Occipital cortex (area 17)					
Left	−14	−96	−2	6.39	>10 000
Right	−2	−90	0	4.3	>10 000
Occipital cortex (area 18)					
Left	−34	−86	12	6.97	>10 000
Right	14	−98	10	5.7	>10 000
Occipital cortex (area 19)					
Left	−28	−78	28	6.75	>10 000
Right	32	−78	30	5.72	>10 000
Caudate nucleus					
Left	−10	14	4	5.78	>10 000
Right	14	14	2	6.61	>10 000
Thalamus					
Left	−8	−16	10	5.52	>10 000
Right	10	−12	8	5.47	>10 000
Red nucleus					
Left	−6	−24	−2	5.48	>10 000
Right	6	−24	−2	5.64	>10 000

Table 6
Matching after negative feedback (event 2) minus matching after positive (event 4)

Anatomical area	Stereotaxic coordinates				
	x	y	z	t-values	Cluster size
Frontopolar cortex (area 10)					
Left	−34	58	14	6.88	>10 000
Right	30	60	0	6.38	>10 000
Middorsolateral PFC					
Left (areas 46 and 9/46)	−36	44	24	4.35	>10 000
Right (areas 46 and 9/46)	40	48	24	5.09	>10 000
Left (area 9)	−42	28	36	6.01	>10 000
Right (area 9)	44	34	40	5.64	>10 000
Anterior cingulate cortex (area 32)					
Left (area 32)	−4	42	20	5.42	>10 000
Right (area 32)	2	34	18	4.64	>10 000
Supplementary motor area (area 6)					
Left	−2	28	42	8.17	>10 000
Right	2	30	44	8.66	>10 000
Posterior PFC					
Right (junction of areas 6, 8, and 44)	42	12	38	6.5	>10 000
Midventrolateral PFC (area 47/12)					
Left	−44	18	−6	4.9	5360
Right	46	18	−8	5.44	>10 000
Midventrolatreal PFC (area 45)					
Right	54	20	16	4.12	>5000
Lateral premotor cortex (area 6)					
Left	−18	10	74	4.18	>10 000
Right	30	8	62	4.97	>10 000
Middle temporal cortex (area 21)					
Right	66	−34	0	4.7	2984
Posterior parietal cortex (area 40)					
Left	−42	−54	44	6.48	>10 000
Right	48	−46	48	8.18	>10 000
Posterior parietal cortex (area 7)					
Left	−32	−64	48	5.96	>10 000
Right	36	−60	54	6.92	>10 000
Precuneus (area 7)					
Left	−8	−78	58	4.96	>10 000
Right	4	−72	52	7.03	>10 000
Occipital cortex (area 18)					
Left	−20	−92	6	4.08	>10 000
Occipital cortex (area 17)					
Left	18	−96	−10	4.07	>10 000
Putamen					
Left	−30	6	6	3.44*	152
Right	34	2	2	4.26	>5000

medial PFC (area 8), the supplementary motor area (area 6), and bilaterally in the posterior parietal cortex (area 40) and the putamen (Table 8).

Table 7

(Receiving negative feedback − receiving positive feedback) − (matching after negative feedback − matching after positive feedback)

Anatomical area	Stereotaxic coordinates				
	x	y	z	t-values	Cluster size
Midventrolateral PFC (area 47/12)					
Right	34	24	10	4.15	216
Middorsolateral PFC (9/46)					
Left	−46	26	30	3.73	176
Posterior PFC (areas 6 and 8)					
Left	−38	16	24	3.63	184
Left	−48	4	44	4.54	1256
Temporal cortex (area 37)					
Right	44	−72	0	3.65	240
Occipital cortex (area 19)					
Left	−28	−80	30	4.68	1872
Right	34	−74	32	3.57	192
Occipital cortex (area 17)					
Left	−12	−96	0	4.13	272
Caudate nucleus					
Right	12	18	6	3.61*	56

Table 8

(Matching after negative feedback − matching after positive feedback) − (receiving negative feedback − receiving positive feedback)

Anatomical area	Stereotaxic coordinates				
	x	y	z	t-values	Cluster size
Frontopolar cortex (area 10)					
Left	−2	62	−8	5.46	9872
Dorsolateral PFC (area 9)					
Right	16	60	34	5.03	2792
Anterior cingulate cortex (area 32)					
Left	−2	50	−4	6.15	9872
Medial PFC (area 8)					
Right	16	52	44	4.53	2792
VLPFC (area 45)					
Right	50	36	0	4.22	1656
Supplementary motor area (area 6)					
Right	4	36	62	3.89	1712
Middle temporal cortex (area 21)					
Left	−46	−8	−28	4.42	832
Posterior parietal cortex (area 40)					
Left	−50	−58	46	4.93	5512
Right	54	−46	44	4.33	1464
Putamen					
Left	−30	2	6	4.31	1464
Right	32	−14	6	4.75	2536

Table 9

Frontal and basal ganglia activation during the lexical WWST

	Receiving negative feedback	Matching after negative feedback	Receiving positive feedback	Matching after positive feedback	Receiving negative versus receiving positive	Matching after negative versus matching after positive
DLPFC	B	B	—	B	B	B
VLPFC (47/12)	B	B	—	L	B	B
VLPFC (45)	—	B	—	L	—	R
PPFC	L	B	—	L	B	B
ACC	L	R	—	—	L	B
Caudate	B	—	—	—	B	—
Putamen	—	—	—	—	—	B

The first 4 boxes represent the presence of significant increased activity relative to the appropriate control condition. B, bilateral; R, right; L, left; DLPFC, dorsolateral prefrontal cortex; PPFC, posterior prefrontal cortex; ACC, anterior cingulate cortex.

Discussion

Cortico-striatal Activity

The primary purpose of this study was to investigate the involvement of the striatum (caudate nucleus and the putamen) and the different subdivisions of the PFC in rule selection and execution when lexical stimuli are used. As predicted, 2 sets of cortico-striatal regions showed significant activation during the performance of the present lexical version of the task: one involving the ventrolateral PFC, the caudate nucleus, and the thalamus (Tables 5 and 9) during the planning of a set-shift and another involving the posterior PFC and the putamen during the execution of a set-shift (Tables 6 and 9). Indeed, receiving negative feedback compared with control feedback and also with receiving positive feedback, namely the comparisons that examine the planning of a set-shift, showed bilateral increase of activity in the caudate nucleus, the mediodorsal thalamus, and in area 47/12 of the ventrolateral PFC. This finding is consistent with previous studies that revealed greater involvement of these structures during the planning of novel actions (Lewis et al. 2004; Monchi et al. 2006) and during the planning of a set-shift using the traditional version of the WCST (Monchi et al. 2001). Furthermore, during the execution of a set-shift, which is shown in the contrast matching after negative feedback (event 2) versus matching after positive feedback (event 6), there was significant activation bilaterally in the posterior PFC (at the junction of areas 6 and 8), the putamen, and the thalamus. These areas are part of the "motor" fronto-striatal loop as defined by Alexander et al. (1986). This activity was also found when matching according to a new rule in the traditional card version of the WCST (Monchi et al. 2001) and shows that the posterior PFC and the putamen are involved in the execution of a set-shift, regardless of whether visual or language rules are used to guide the execution. The present study, therefore, provides further support that the putamen is specifically involved in matching according to a new rule and not according to an on-going one (Monchi et al. 2006). In agreement with the present results, other studies using language have also supported the involvement of the fronto-striatal regions in executive processes. First of all, lesion studies in bilinguals have indicated that damage to subcortical structures results in pathological language switching (Perani and Abutalebi 2005). Furthermore, focal lesions of the left caudate nucleus have shown a selective deficit of controlled syntactic processes (Friederici et al. 2003; Kotz et al. 2003).

Prefrontal Activity

Significant activity was found in the dorsolateral PFC during receiving negative feedback versus control feedback but not when comparing receiving positive feedback versus control feedback (areas 9 and 46, Fig. 4A and Table 7). In monkeys, lesions confined to the middorsolateral prefrontal cortical region that covers areas 46, 9, and 9/46 impair severely the monitoring of stimuli or events within working memory but not the maintenance of information per se (Petrides 1991, 1995, 2000). The involvement of the dorsolateral PFC in the monitoring (tracking) of information in humans has been supported by numerous functional neuroimaging studies across many sensory modalities, including language (Petrides 2005). In the case of the classical pictographic version of the WCST,
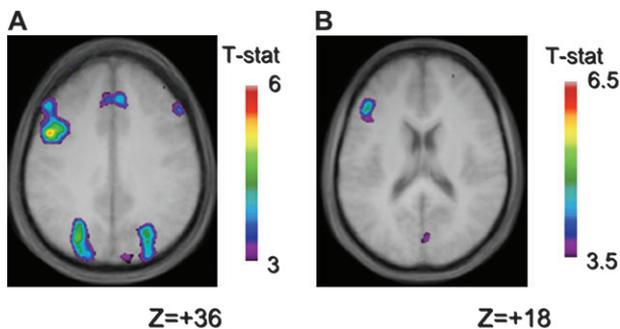
Figure 4. Location of the prefrontal peaks in the present study that differed from the pictogram version of the WCST. The anatomical MRI shown in (*A*) and (*B*) is the average of the T_1 acquisitions of the 14 participants transformed into stereotaxic space. (*A*) Horizontal section through the middorsolateral PFC peaks located at $Z = +36$. The peaks shown here are for receiving negative feedback versus control feedback. In the present lexical study (WWST), such a peak only occurred during receiving negative feedback but not during receiving positive feedback (Table 7), as in our previous studies with the pictographic version of the WCST. (*B*) Horizontal section through area 45 of the midventrolateral PFC peak located at $Z = +18$ mm. The peak shown here in the left hemisphere was obtained from the comparison matching following positive feedback versus control matching (Tables 4 and 7); a similar bilateral peak was also observed from the comparison matching following negative feedback versus control matching (Tables 6 and 7). No such peak was observed in our previous studies with the pictographic WCST.

significant activation of the dorsolateral PFC was observed during both feedback periods, both positive and negative. We had proposed that this involvement of the dorsolateral PFC was required to track the rule (color, shape, or number) that was previously selected in order to choose the rule for the next match (Monchi et al. 2001; Nagano-Saito et al. 2008). After training, positive feedback indicates that the same rule should be applied, while negative feedback promotes the use of a different rule for classification. We have recently provided further evidence for this functional role of the dorsolateral PFC by showing that performance on the WCST is impaired when stimulating with transcranial magnetic stimulation the dorsolateral PFC during the feedback periods but not during the matching ones (Ko et al. 2008). However, in the present study using the WWST, significant activation of the dorsolateral PFC is observed only during the negative feedback periods but not the positive ones. We postulate that visual rules (color, shapes, and number) are intrinsic to the stimulus while lexical ones (semantic, rhymes, and attack) require more abstraction, and therefore, the visual ones are more likely to interfere with each other. Thus, the monitoring process may be taxed to a greater extent when maintaining set in the task with visual rules than in the lexical one, which would explain the difference in dorsolateral PFC activity observed between the 2 tasks (WCST and WWST) during positive feedback in comparison with control feedback. Indeed, this interpretation is in agreement with the study of MacDonald et al. (2000) who showed that dorsolateral PFC is more engaged for color naming than for word reading, suggesting a role in monitoring. The authors also proposed that the dorsolateral PFC would be more implicated when a rule needs to be maintained in a situation in which a strong response tendency must be overridden.

Similarly to our results with the traditional WCST (Monchi et al. 2001; Nagano-Saito et al. 2008), patterns of activity in area 47/12 of the ventrolateral PFC were observed bilaterally during both receiving and matching negative feedback, namely the comparison examining the planning and execution of a set-

shift. It has been proposed that this prefrontal area is involved in the active comparison and retrieval of stimuli from memory according to a rule and that this area is not modulated by stimulus type (Petrides 2005). Evidence in favor of this proposal has been obtained both from functional neuroimaging studies (Petrides 2005) and, more recently, from single neuron recording in the macaque monkey (Cadoret and Petrides 2007). In the WCST or the current WWST, this process occurs after receiving a negative feedback. At this point, the participant needs to retrieve the possible available rules to perform a set-shift. This result is consistent with the other neuroimaging studies on the functional role of the PFC (Duncan and Owen 2000; Bunge 2004; Dove et al. 2008). Furthermore, in the monkey, lesions confined to the inferior prefrontal convexity lead to an impairment in shifting from a previously relevant rule to a new response mode (Iversen and Mishkin 1970). This region of the PFC described in the monkey is architectonically and topographically comparable with the VLPFC of the human brain as described by Petrides and Pandya (2002). Interestingly, analysis of cortico-cortical connection patterns in area 47/12 of the ventrolateral PFC in the monkey has shown that it is predominantly connected with the rostral inferotemporal cortex, namely the visual association cortex (Petrides and Pandya 2002). This anatomical evidence helps explain why area 47/12 is observed during the matching periods of both the WCST (Nagano-Saito et al. 2008) and the WWST.

One of the major difference with respect to the activation patterns of the PFC between our previous studies on the WCST and the current study on the WWST is linked to area 45 of the ventrolateral PFC. Indeed, in the current study, significant activation was observed in area 45 of the left ventrolateral PFC during both matching periods (Fig. 4*B* and Table 9). Interestingly, this activation was not observed in either of the 2 previous studies using the classic visual rule–based version of the task (Monchi et al. 2001; Nagano-Saito et al. 2008). Area 45 is predominantly connected with auditory association cortex of the superior temporal gyrus and multimodal cortex of the superior temporal sulcus. In both WCST and WWST, matching requires comparing visual and semantic attributes while only the WWST requires the comparison of phonological and auditory attributes. Consistent with this notion, functional neuroimaging of phonological processing has been more often associated with significant activation in area 45 of the ventrolateral PFC (Fiez 1997; Gitelman et al. 2005), while recent fMRI studies of verbal retrieval mechanisms have observed a specific involvement of area 47/12 in semantic retrieval (Bunge et al. 2003; Nagel et al. 2008), and a transcranial magnetic stimulation study has shown that disruption of region 47/12 specifically impairs semantic but not phonological processing (Devlin et al. 2003). Furthermore, many authors indicate that ventrolateral PFC is involved in tasks that required semantic selection (Thompson-Schill et al. 1997; Crosson et al. 2001; Tremblay and Gracco 2006; Nagel et al. 2008) or semantic access (Wagner et al. 2001; Devlin et al. 2003); however, the exact localization within the ventrolateral PFC is not always clear within these studies.

Recent studies by Badre et al. (2005, 2007) have proposed a 2-process model of mnemonic control supported by 2 subregions of the ventrolateral PFC, the anterior ventrolateral PFC (BA 47/12) and the midventrolateral PFC (BA 45). In one of these studies (Badre et al. 2005), the authors varied "selection

demands" by manipulating the associative strength and other features between the cue and the target. The results have shown that the involvement of anterior VLPFC (area 47/12) decreases with increasing associative strength between stimuli specifically. While the activity of mid-VLPFC (area 45) also increased with decreasing associative strength, it also increased with incongruence and judgment specificity (i.e., according to a specific feature as opposed to a global judgment). The authors proposed that area 45 plays a more global role in control retrieval especially as competition increases among the items. In our case, the matching period in the WWST is more analogous to the weak association strength than in the matching period in the WCST because visual features in the WCST had strong association and consequently the demand on controlled retrieval is lower for the WCST than for the WWST. Furthermore, visual rules (color, shapes, and number) are intrinsic to the stimulus while lexical ones (semantic, rhymes, and attack) require more abstraction, and therefore, matching according to a specific feature or rule induces more competition in the WWST than in the WCST and requires more controlled retrieval. These latter interpretations are in accordance with the fact that no significant activity was found in area 45 in any of the matching periods (matching following positive or negative feedback) of the WCST (Monchi et al. 2001; Nagano-Saito et al. 2008) while it was found in the present study using the WWST in both matching periods and more specifically within the (matching after negative feedback versus matching after positive feedback) minus (receiving negative feedback versus receiving positive feedback) interaction (Table 8).

Conclusion

The present study shows that the involvement of the fronto-striatal regions in executive processes seems to remain the same regardless of the nature of the stimulus material, visual nonverbal or verbal. Furthermore, patterns of PFC activation in the WWST indicate recruitment of additional regions that relate to the specific nature of the material to be processed (such as area 45 for the lexical stimuli) but do not support different roles of these regions across sensory modalities. Moreover, the present investigation is consistent with the case studies of Pickett et al. (1998) and Longworth et al. (2005) where patients with bilateral lesions in the caudate nucleus as well as in the putamen were impaired in understanding distinctions in meaning conveyed by syntax in English sentences, as well as in the ability to shift from different cognitive sets. Similarly, Lieberman et al. (2005) reported an increase of error rates in comprehending syntax and set-shifting resulting from an hypoxic injury to the globus pallidus induced by high altitude (Mount Everest climbers). Finally, the present study provides further support to the proposal that the cortico-striatal regions that regulate language comprehension also regulate many aspects of behavior such as motor control and abstract reasoning (Lieberman 2002). Indeed, Longworth et al. (2005) have proposed that patients with lesions to the basal ganglia may reflect impairment of a function that is not specific to language but that is involved in language comprehension and production.

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