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Role of the basal ganglia in switching a planned response

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Abstract

The ability to perform an appropriate response in the presence of competing alternatives is a critical facet of human behavioral control. This is especially important if a response is prepared for execution but then has to be changed suddenly. A popular hypothesis of basal ganglia (BG) function suggests that its direct and indirect pathways could provide a neural mechanism to rapidly switch from one planned response to an alternative. However, if one response is more dominant or 'automatic' than the other, the BG might have a different role depending on switch direction. We built upon the pro- and antisaccade tasks, two models of automatic and voluntary behavior, respectively, and investigated whether the BG are important for switching any planned response in general, or if they are more important for switching from a more automatic response to a response that is more difficult to perform. Subjects prepared either a pro- or antisaccade but then had to switch it unexpectedly on a subset of trials. The results revealed increased striatal activation for switching from a pro- to an antisaccade but this did not occur for switching from an anti- to a prosaccade. This activation pattern depended on the relative difficulty in switching, and it was distinct from frontal eye fields, an area shown to be more active for antisaccade trials than for prosaccade trials. This suggests that the BG are important for compensating for differences in response difficulty, facilitating the rapid switching of one response for another.

Introduction

The ability to choose an appropriate response when competing alternatives exist is a critical facet of behavioral control. Think of a football (soccer) player in defense who needs to rapidly change her planned response if she is 'tricked' by an offensive player's fake movement. To do this effectively requires effort, as an initial response is already in preparation for execution. We recently modeled this situation using a variant of the pro- and antisaccade paradigm (Cameron *et al.*, 2007). Subjects were instructed to prepare a prosaccade (look towards) or antisaccade (look away) to a peripheral stimulus that appeared on a visual screen (Hallett, 1978). Unpredictably, in a subset of trials, the subjects were required to switch their planned response when the instruction changed suddenly. This resulted in response time and error rate 'switch costs', corresponding to response reconfiguration processes that commenced after the initial response was in preparation and took time to complete (Cameron *et al.*, 2007). Several of these task-switching experiments across trials have been conducted previously (e.g. Jersild, 1927; Allport *et al.*, 1994; Rogers & Monsell, 1995; Monchi *et al.*, 2001; Cools *et al.*, 2004; Isoda & Hikosaka, 2008). However, we suggest that the method of Cameron *et al.* (2007), in which the switch occurs within a trial, is a better model of the neural mechanisms required to change a response in preparation.

We showed in Cameron *et al.* (2007) that switch costs resulted when subjects prepared either a pro- or antisaccade to a stimulus, and then had to switch it to the alternative. Switch costs did not result if the instruction changed before the peripheral stimulus was presented, suggesting that a response was required to be in preparation for these behavioral costs to occur. What was most interesting was that switching from the more difficult antisaccade to the more 'automatic' (or dominant) prosaccade produced switch costs that were similar to those when subjects switched in the opposite direction. This finding was intriguing, as the basal ganglia (BG) are associated with suppressing the visually triggered prosaccade on antisaccade trials in the oculomotor field (Briand *et al.*, 1999; Munoz & Everling, 2004; Chan *et al.*, 2005; Peltsch *et al.*, 2008). Thus, it would be predicted that switching from an anti- to a prosaccade should be a relatively simple process, void of BG control as no prosaccade needs to be suppressed. Alternatively, switch costs when switching to a prosaccade are sensible if one considers that the indirect pathway of the BG might be important for suppressing any competing response and the direct pathway might be important for disinhibiting the desired

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response (Mink, 1996; Nambu, 2004), even if it is highly automatic. From this, we hypothesized that similar switch costs should be accompanied by similar activation patterns in the caudate nucleus (CN), the area of the BG that receives competing pro- and antisaccade response signals (Alexander *et al.*, 1986; Hikosaka *et al.*, 2000) that would undergo a selection process by the direct and indirect pathways.

However, our results show, in a first experiment, that correctly switching from a pro- to an antisaccade resulted in greater CN activation but that this did not occur for switching from anti to pro. When subjects failed to switch to an antisaccade, the CN activation pattern differed, suggesting a correlate between CN activation and successfully switching to an antisaccade. In a second experiment, we confirmed that the greater striatal activation for switching from a pro- to an antisaccade was due to response difficultly. We suggest that, rather than acting as a general selector between competing response signals (Mink, 1996; Nambu, 2004), the BG have a particular role in boosting weaker response signals to over-ride dominant response signals.

Materials and methods

All experiments were approved by the Research and Ethics Board of Queen's University, and adhered to the principles of the Canadian Tri-council Policy Statement on Ethical Conduct for Research Involving Humans and the principles of the Declaration of Helsinki (1964). Subjects were recruited from the Queen's University community, and gave their written and informed consent.

Experiment 1

The goal of the first experiment was to determine if the BG are involved in switching a planned response in general or if they are differentially involved in switching from automatic to more difficult behavior.

Subjects

Ten subjects (age 22–28 years) participated in a two-session experiment at the Queen's University magnetic resonance imaging facility, each session being 1.5–2 h in duration. Nine subjects had normal or corrected-to-normal vision and the 10th subject verified that she could distinguish the stimuli without her glasses. All were right-handed and five were male. Subjects did not report any history of neurological or psychiatric disorders, or color blindness.

Paradigm

Subjects lay supine in the scanner and viewed visual stimuli back-projected onto a screen located at the head-end of the scanner. A mirror attached to the head coil and angled at approximately 45° allowed them to view the screen. Subjects were presented with a text screen informing them to prepare for the onset of each experimental run containing 16 trials.

The timings of stimuli are shown in Fig. 1A. Each trial began with a blue cross ('neutral cross', 0.5 ° of visual angle) at the center for 3 s that did not convey any instruction other than to fixate. The cross then changed to a green (instructing a prosaccade) or red (instructing an antisaccade) cross of the same size and luminance. We chose these colors explicitly to take advantage of the familiarity from traffic signals. This did not require participants to learn unfamiliar rules that might confound the interpretation of erroneous responses. The green or red crosses were present for 3 s. Next, a peripheral stimulus (blue circle, 0.5° of visual angle) pseudorandomly appeared at 5.5 ° to the left or right and was also present for 3 s. Subjects were instructed to execute a prosaccade (look towards) to the stimulus or an antisaccade (look away) from the stimulus based on the instruction (pro or anti). In 50% of the trials, the red or green cross changed to the opposite color at 100 ms (25% of total trials) or 200 ms (25% of total trials) after the peripheral stimulus appeared. Previous work (Cameron *et al.*, 2007) demonstrated that these times are within a critical time period for producing switch costs, suggesting that one response was prepared and then changed subsequently (Nakamura *et al.*, 2005). Subjects were told to obey the new instruction, to be as quick and as accurate as possible and, if they executed the wrong response, to correct themselves. Subjects were asked to hold their gaze at the target position until the peripheral stimulus disappeared and, simultaneously, a blue 'neutral X' appeared at the center to redirect their fixation. This 'neutral X' was present for 12 s to allow the hemodynamic response to return to baseline. Each trial was 21 s in duration. Subjects performed 12 runs (divided over two separate sessions of six runs each) of 16 trials: four non-switch antisaccade trials ('anti'), four non-switch prosaccade trials ('pro'), four anti- to prosaccade switch trials ('anti2pro', two with a 100 ms switch time and two with a 200 ms switch time) and four pro-to-antisaccade switch trials ('pro2anti', two with a 100 ms switch time and two with a 200 ms switch time). The trials were presented in a pseudorandom order by creating four distinct pseudorandom trial sequences prior to the experiment. Subjects received these sequences in random order, such that identical sequences could not precede one another, and subjects were not given more than two of each sequence on a given day. Subjects were given one run of practice in front of a computer monitor on each day and eye movements were not recorded during this practice run.

Our goal was to test whether differential functional magnetic resonance imaging activation would result despite similar switching behavior. Thus, our approach was to utilize data only from the subjects ($N = 7$) who showed similar switch costs for switching to the pro- or antisaccade (Fig. 1B and C). Therefore, three of the 10 subjects were removed from further analysis because they produced > 75% errors on pro2anti switch trials. These three subjects demonstrated a large behavioral bias to the prosaccade response, emphasizing the differences in response automaticity. However, their deficit in switching to the antisaccade confounded our interpretation of BG activation; we were interested specifically in examining whether differential BG activation would result depending on switch direction, despite similar switching behavior. If this occurred, it would suggest that the BG have a role in mediating one response over the other. Individual data from all 10 subjects are shown in supporting information, Fig. S1.

Eye tracking and visual display

Visual stimuli were generated using E-PRIME software (Psychology Software Tools Inc., Pittsburgh, PA, USA) running on a PC, and an NEC LT265 DLP video projector (Tokyo, Japan) was used to back-project the image onto a custom-built screen. The projector had a refresh rate of 60 Hz and a resolution of 1024 × 768. Eye tracking was conducted using an ISCAN ETL-400 camera (Burlington, MA, USA) running DQW software v1.10X and sampling the eye position at 120 Hz. The camera was positioned next to the screen, approximately 50 cm from the bore of the magnet to view the right eye of the subject in the mirror. An infrared fiber-optic illuminator was fixed to the head coil prior to the subject entering the bore of the scanner. This illuminated the subject's right eye from an angle of approximately 45° below the eye. Prior to the first functional scan, calibration of the eye tracker was conducted using a nine-point calibration routine, with the nine points covering the maximum available visual field on the screen (approximately 16° in width).

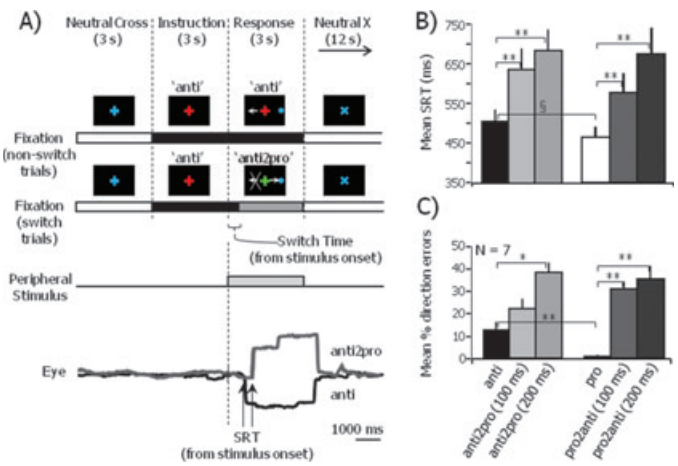

FIG. 1. Experimental stimuli and behavior in Experiment 1. (A) A blue cross ('neutral cross') was illuminated for 3 s and, subsequently, a green or red cross ('instruction') was illuminated for 3 s, instructing a pro or anti response, respectively (shown: anti). The peripheral stimulus then appeared pseudo-randomly to the left or right for 3 s and subjects were told to execute the appropriate response ('response'). However, on 50% of the trials ('switch trials'), the red or green cross switched to the opposite color (shown: anti2pro) at 100 or 200 ms after the peripheral stimulus had appeared, requiring the subjects to switch their response. A neutral fixation stimulus ('neutral X') appeared at the center for 12 s to end the trial. A sample of an eye trace from a single subject comparing a correct anti trial with a correct anti2pro trial for an identical peripheral stimulus location is shown. (B) Mean SRT for correctly performed trials. Left group compares anti trials with anti2pro trials where the instruction switched at 100 or 200 ms after stimulus onset. Right group compares pro trials with pro2anti trials. Asterisks indicate significant differences between comparisons indicated by square brackets (paired *t*-test, Bonferroni corrected for multiple comparisons, $*P < 0.025$, $**P < 0.01$, $^{\S}P = 0.025$). (C) Same conditions as in B but for mean percentage direction errors. Greater SRT and percentage direction errors on switch trials indicate 'switch costs'.

Functional magnetic resonance imaging parameters

All magnetic resonance imaging scans were conducted with a Siemens 3T Magnetom Trio system (Erlangen, Germany), with a 12-channel receive-only head coil, using methods based on blood oxygen-level-dependent (BOLD) contrast (Ogawa *et al.*, 1990; Kwong *et al.*, 1992). High-resolution anatomical images were collected with a T1-weighted MPRAGE sequence, with an anterior/posterior phase-encoding direction. The voxel size was 1 mm in all three directions. The field of view was 256 × 256 mm and the matrix size was 256 × 256. The flip angle was 9°, the echo time was 2.2 ms and the repetition time (TR) was 1760 ms.

Functional scans were collected using a T2*-weighted echo-planar imaging sequence, with slices acquired in the transverse orientation, and with an anterior/posterior phase-encoding direction. Each volume contained 11 slices of 3.3 mm isovoxels (3.3-mm-thick slices), centered by the operator in the transverse plane to include the entire head and body of the CN identified from the anatomical images. We specifically focused on the CN, the main input stage of the BG, using the highest temporal resolution possible (TR, 750 ms) to image the entire structure. This afforded us the ability to examine in greater detail the time-courses of the BOLD activation patterns in the CN for each response type. The field of view was 211 × 211 mm and the matrix size was 64 × 64. The flip angle was 56 ° and the echo time was 30 ms (in order to optimize for the sensitivity of the BOLD contrast). A saturation band was used and applied across the subject's eyes to prevent motion artifacts from the eye movements. On the first trial of every run, the neutral cross was present for a total of 4.5 s, allowing an additional 1.5 s (2 TRs) to achieve steady-state longitudinal magnetization.

Statistical methods

Behavioral data were analysed using custom programs in MATLAB 7.4 (The MathWorks Inc., Natick, MA, USA). The saccade reaction time

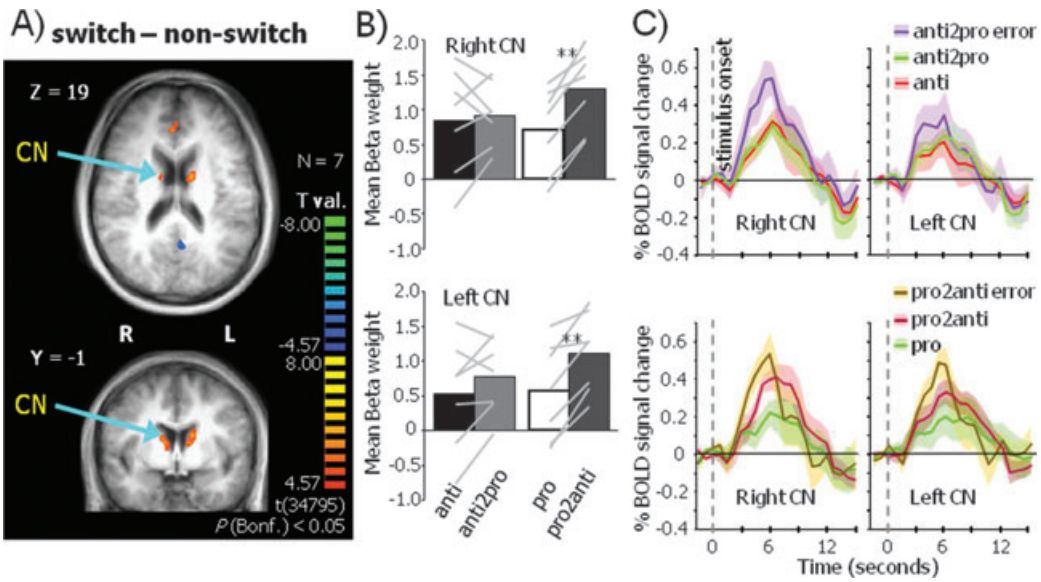

FIG. 2. CN activation during the 'response' period for switch and non-switch trials in Experiment 1. (A) Group contrast map comparing switch trials (pro + anti) with non-switch trials (anti2pro + pro2anti) [Bonferroni corrected at $P < 0.05$ ($T = |4.57|$), cluster-size corrected at $P < 0.05$]. Greater BOLD activation for switch trials relative to non-switch trials ('hot' colors) was found in the CN. Talairach locations of the Y and Z planes are indicated in the figure, and coordinates of peak activation locations for the given contrasts can be found in supporting Table S1. (B) Mean beta weight values for correctly executed trials of the four response types of interest from the CN clusters in A ($N = 7$ subjects). Individual subject data are superimposed as gray lines ($**P < 0.01$, paired *t*-test between correct trials sharing identical preparatory periods). (C) BOLD signal time-courses grouped by trials sharing identical preparatory periods. Solid lines represent the mean percentage BOLD signal change from the seven subjects. Shaded areas represent the SEM (between subjects). Time-courses are aligned on stimulus onset, with the baseline averaged from the last three time-points during the 'instruction' period.

(SRT) was defined as the first saccade away from fixation after stimulus onset, when the velocity exceeded the mean + 3 × the SD of the background velocity. Direction errors were those in which the first saccade was against that of the final instruction. SRTs of < 90 ms were considered anticipatory (Munoz *et al.*, 1998) and were excluded from behavioral analysis; however, these rarely occurred (< 1.5% for any subject). Errors in which subjects failed to fixate the instruction, failed to maintain fixation (measured by saccades in any direction during the fixation period), failed to initiate a saccade or executed multiple saccades during the response period were also removed from behavioral analysis but modeled separately as 'null trials' in the functional magnetic resonance imaging analysis (see below). Direction errors were only analysed if the subject corrected the error (failure to correct errors occurred < 5% of the time for any subject and these trials were also placed in the null category). The percentage of direction errors was calculated by dividing the errors by the total number of valid trials. Finally, entire runs were excluded if the subject had more than 25% of their trials removed for any of the above reasons or if successful eye tracking was not possible. This occurred once for 2/7 subjects and three times for 1/7 subjects. In total, all subjects provided between 9 and 12 functional runs, and no subject had more than 19% of their trials excluded from further analysis for any given run that was included.

Paired *t*-tests (non-directional) were conducted to compare mean SRTs and mean percentage of direction errors across subjects between anti and pro trials, anti and anti2pro trials, and pro and pro2anti trials at each switch time. Left and right target responses were combined to increase statistical power. *P* values were corrected for multiple comparisons (Bonferroni, $P < 0.05$).

Analysis of the functional brain data was conducted using BrainVoyager 1.9 (Maastricht, the Netherlands). Functional images were first pre-processed to remove motion artifacts and linear drift (high pass filtered at 3 cycles/time-course, motion corrected by aligning the images of the time series to the first volume in the series, and corrected for slice timing differences by means of a sinc interpolation). The first two volumes were removed from analysis in order to include only data obtained with a steady-state longitudinal magnetization.

Each subject's high-resolution anatomical scan was transformed into Talairach coordinates (Talairach & Tournoux, 1988) by first using cubic spline interpolation to align the anatomical images into the anterior commissure-posterior commissure (AC-PC) plane and then using trilinear interpolation to transform the anatomical images into Talairach coordinates. An average of all of the subject's individual anatomical images in Talairach coordinates was computed to create a reference volume on which to overlay the functional volumes in Figs 2–4 and 6–10.

The events of interest were modeled with boxcar predictors with a width of the 3 s 'response' period (Fig. 1A), convolved with BrainVoyager's canonical (2 gamma) hemodynamic response function to map the BOLD response time locked to the onset of the visual stimulus, and spanning into the 12 s period ('neutral X') following the response period. A total of eight predictors for the response period were created based on: instruction (switch or non-switch), response (pro- or antisaccade) and performance (correct direction or erroneous direction that was subsequently corrected). For our main analyses, the 100 and 200 ms switch time trials were combined. However, we performed a *post-hoc* analysis whereby the 100 and 200 ms switch times were separated, and all error trials were grouped together under a separate predictor. This was conducted to explore whether there was a difference in CN activation for switch trials that were less difficult (100 ms switch time) and more difficult (200 ms) (Fig. 3F–H). Note that the execution of two saccades during the 'response' period (erroneous switch trials) was contrasted to the execution of one saccade during the 'response' period (correct non-switch trials), as erroneous trials were only included if subjects corrected the error (Figs 4, 8 and 10). However, as this occurs for both erroneous switch trial types, any differences in BOLD activation patterns between the two erroneous switch trial types cannot be attributed to the execution of a second saccade. In addition, the initial 'instruction' period was also modeled with separate predictors (pro, green; anti, red). Finally, all 'null trials' plus trials in which tracking was lost, trials in which the subject made multiple eye movements, failed to correct an error (5%) or 'uncorrected' a correct response (< 2%) were modeled with a separate 'null predictor' in the response period. This was done so that trials that could not be classified as a correct trial or corrected error were still modeled so as not to affect the calculation of the BOLD signal change from baseline.

Group analysis was conducted using a fixed-effects general linear model (GLM) with separate subject predictors, Bonferroni corrected for multiple comparisons at $P < 0.05$ and cluster-size corrected at $P < 0.05$ (yielding a cluster threshold of eight contiguous voxels, as estimated using BrainVoyager's Cluster-level Statistical Threshold Estimator at 1000 iterations). Paired *t*-tests (non-directional) were conducted using MATLAB 7.4 on the beta weight values (GLM parameter estimates) for comparisons described in the Results and figure legends. We specifically compared the BOLD signal time-courses for non-switch and switch trials that shared a common preparatory period (e.g. pro, pro2anti, pro2anti error), allowing us to be certain that differences in CN activation did not relate to differences in the preparatory periods. BOLD signal time-courses were aligned to the onset of the peripheral stimulus, and the baseline was averaged from the final three time-points (including the time-point at stimulus onset) of the 'instruction' period.

Experiment 2

A second experiment was conducted to control for the difference in switching difficulty between pro- and antisaccades. The paradigm and stimuli remained identical to Experiment 1 but the switch times were staircased by ± 50 ms based on performance (described below in the Paradigm and functional magnetic resonance imaging parameters section) to converge on 50% accuracy for switching either response. This manipulation made switching to a pro- or antisaccade similar in difficulty but did not affect the nature of the responses executed (e.g. visually directed prosaccade and internally guided antisaccade). The frontal eye fields (FEFs) were scanned along with the CN as they constitute an area that has shown greater BOLD activation for generating an antisaccade relative to generating a prosaccade (Connolly *et al.*, 2002; Curtis & D'Esposito, 2003; Ford *et al.*, 2005; Brown *et al.*, 2007) and thus FEF activation could be compared with CN activation, which is hypothesized to reflect a response switching mechanism rather than an antisaccade generation mechanism.

Subjects

Eleven different subjects (to avoid confounds from previous experience with 100 and 200 ms switch times) (five male, age 22–30 years) were recruited. All subjects were right handed and reported no history of neurological or psychiatric disorders or color blindness.

Paradigm and functional magnetic resonance imaging parameters

The FEF was scanned in conjunction with the CN, using 16 slices of 3.3 mm isovoxels tilted between the transverse and coronal plane to center on the FEF, and include the head and body of the CN. Subjects

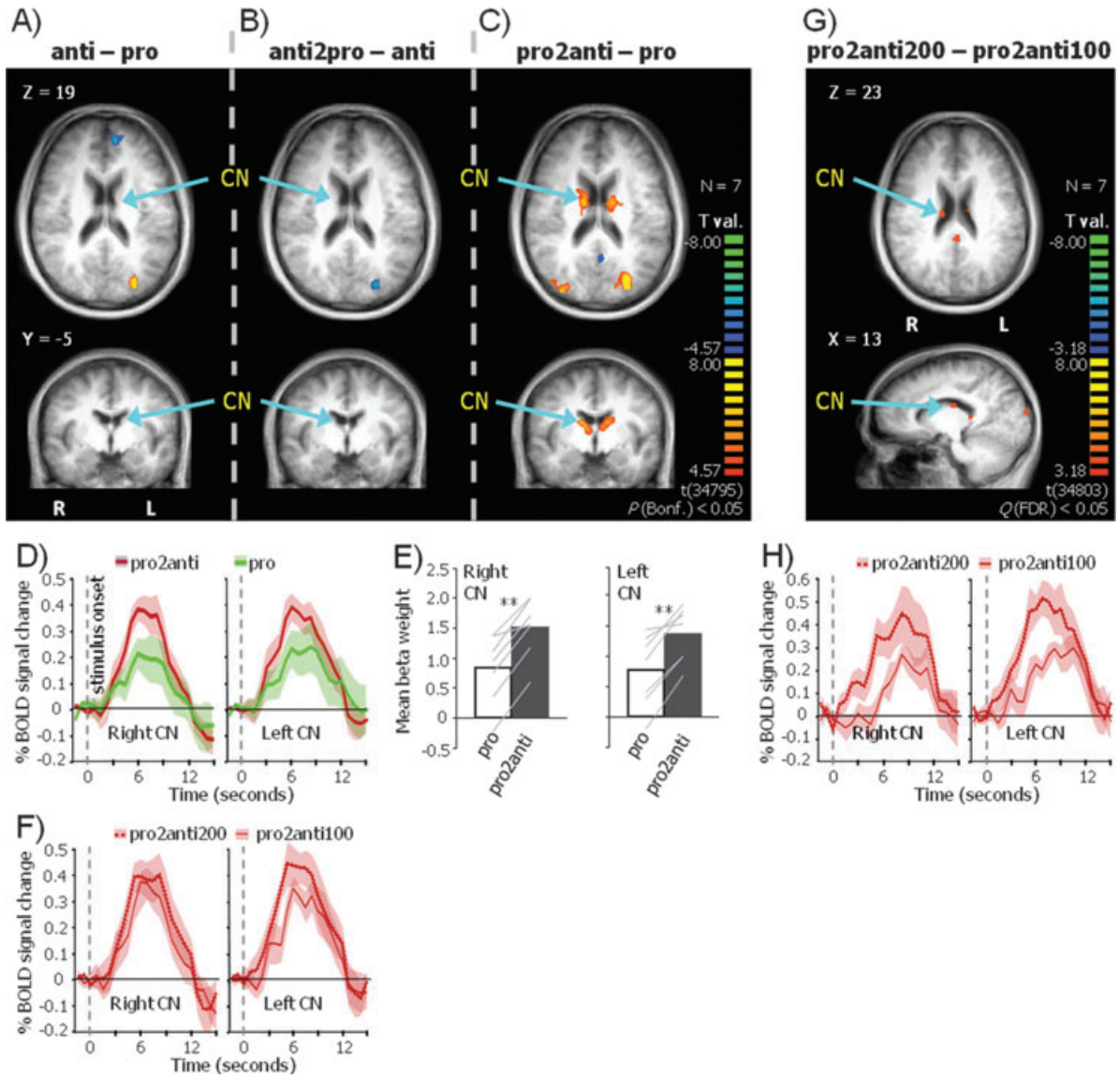

FIG. 3. CN activation during the 'response' period for correct trials in Experiment 1. (A) Group contrast map comparing anti trials with pro trials [Bonferroni corrected at $P < 0.05$ ($T = |4.57|$), cluster-size corrected at $P < 0.05$]. Greater BOLD activation for anti trials relative to pro trials ('hot' colors) was not found in the CN and nor was greater BOLD activation for pro trials relative to anti trials ('cold' colors). (B) Contrast comparing anti2pro trials with anti trials. Greater BOLD activation for anti2pro trials did not result in the CN. (C) Contrast comparing pro2anti trials with pro trials. Greater activation was found bilaterally in the CN for pro2anti switch trials. (D) BOLD signal time-courses aligned on stimulus onset for the CN clusters in C. Solid lines represent the mean BOLD signal change from the seven subjects. Shaded areas represent the SEM (between subjects). (E) Mean beta weight values from the seven subjects for the CN clusters in C (**$P < 0.01$, paired t-test. (F) BOLD signal time-courses for pro2anti 100 ms and pro2anti 200 ms switch trials from the CN clusters in C. (G) Group contrast map comparing pro2anti 100 ms with pro2anti 200 ms switch trials [corrected for multiple comparisons (false discovery rate) at $Q < 0.05$, cluster-size corrected at $P < 0.05$]. Greater activation was found in the CN for pro2anti 200 ms switch trials. (H) BOLD signal time-courses for pro2anti 100 ms and pro2anti 200 ms switch trials from the CN clusters in G.

first performed a task consisting of blocks of anti- and prosaccades contrasted with periods of fixation in order to locate the FEF using the Siemens NEURO3D software, whereby a GLM contrast of saccades minus fixation was conducted.

For the main experiment, the TR was 1 s (due to the greater number of slices) and the flip angle was 62 ° (Ernst angle) to optimize the signal-to-noise ratio for a TR of 1 s. The initial instruction of the first trial was presented for 5 s (additional two TRs) to allow the longitudinal magnetization to reach a steady state. All other scanning parameters remained the same as in Experiment 1.

The initial switch time was 200 ms after stimulus onset for both switch trial types but this increased by 50 ms if the given switch trial was executed correctly or decreased by 50 ms if the given switch trial was executed incorrectly. Switch times were allowed to staircase to a minimum of 50 ms and to a maximum of 500 ms after stimulus onset. If on a given run the subject executed all switch trials incorrectly, or executed all switch trials correctly, they were provided with verbal feedback to improve accuracy, or improve speed, respectively. These runs were then excluded from analysis because the switch time could not be reliably close to the subject's performance threshold. In addition, we were only interested in subjects for who no more than 60% errors and no fewer than 40% errors on either switch trial were achieved. As shown in Fig. 5A, seven subjects produced this behavior and thus four

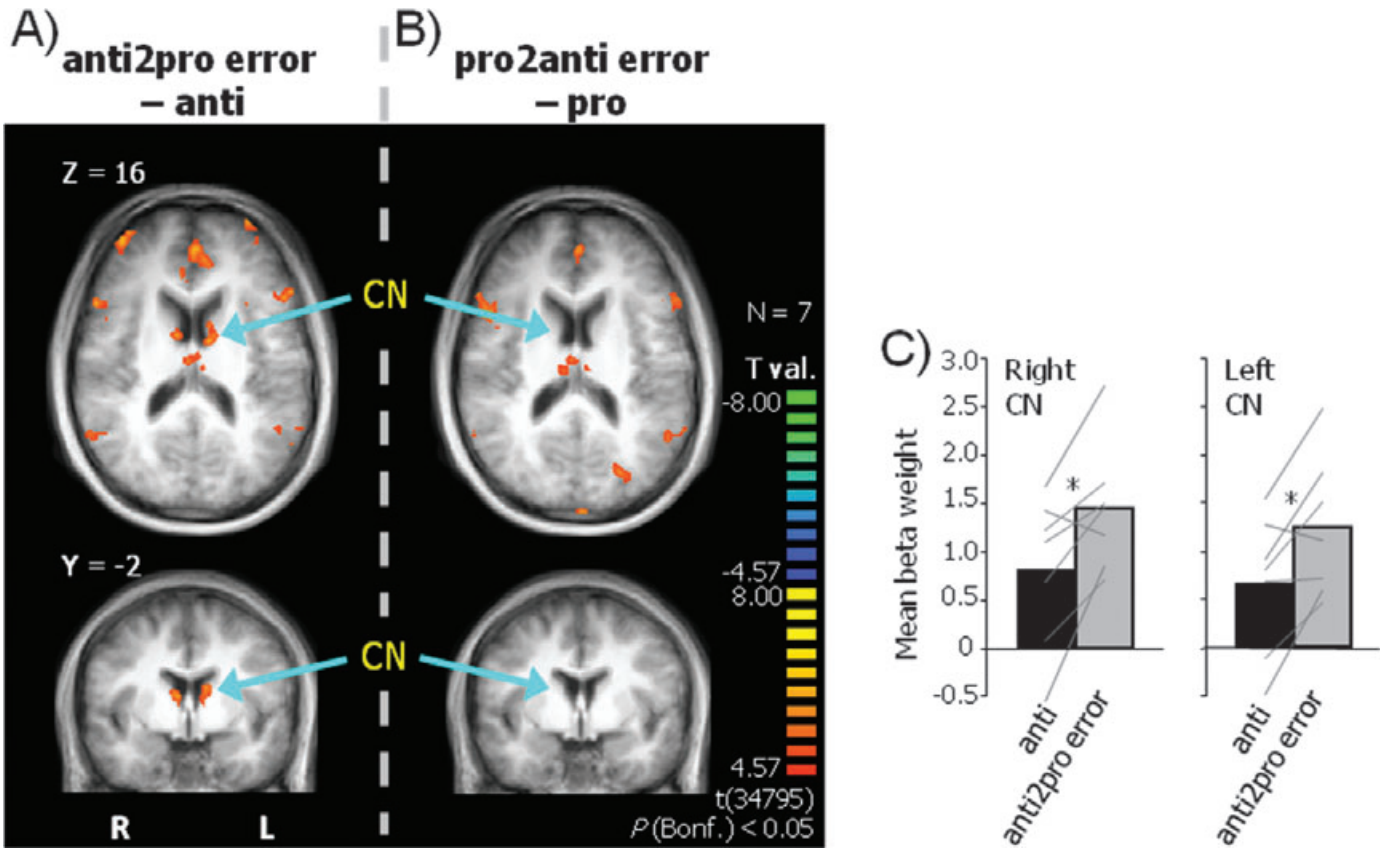

FIG. 4. CN activation during the 'response' period for erroneous switch trials in Experiment 1. (A) Group contrast map comparing anti2pro error trials (executed an antisaccade then corrected to a prosaccade) with correct anti trials (Bonferroni and cluster-size corrected at $P < 0.05$). Significantly greater BOLD activation resulted in the CN for anti2pro error trials relative to anti trials. (B) Contrast comparing pro2anti error trials with pro trials. Greater BOLD activation did not result for pro2anti error trials relative to pro trials in the CN. (C) Mean beta weight values for the CN clusters in A (*$P < 0.05$, paired *t*-test).

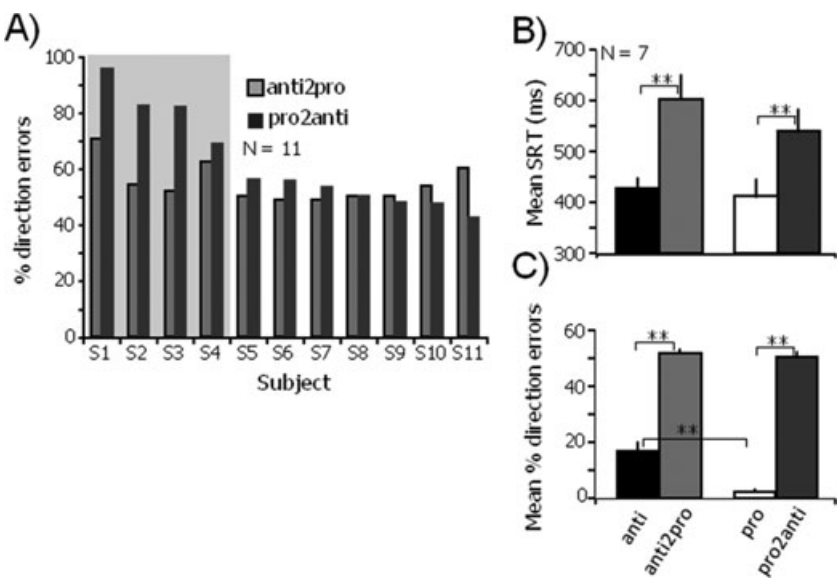

FIG. 5. Behavior in Experiment 2. (A) Percentage direction errors across individual subjects. Subjects S1–S4 were removed from further analysis for failure to produce switch trial error rates between 40 and 60%. (B) Mean SRT for correct trials. (C) Mean percentage direction errors. Asterisks indicate significant differences between comparisons indicated by square brackets (paired *t*-test, Bonferroni corrected for multiple comparisons, **$P < 0.01$).

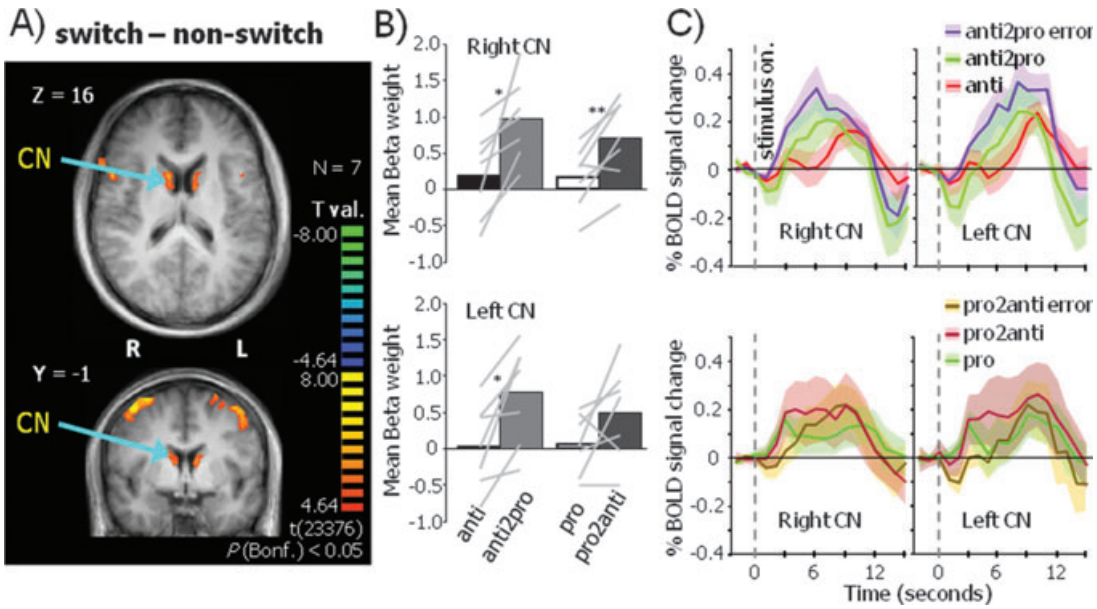

FIG. 6. CN activation during the 'response' period for switch and non-switch trials in Experiment 2. (A) Group contrast map comparing switch trials with non-switch trials [Bonferroni corrected at $P < 0.05$ ($T = |4.64|$), cluster-size corrected at $P < 0.05$]. Greater BOLD activation for switch trials relative to non-switch trials was found in the CN. (B) Mean beta weight values for correctly executed trials of the four response types of interest from the CN clusters in A ($N = 7$ subjects, $^*P < 0.05$, $^{**}P < 0.01$, paired t-test). (C) BOLD signal time-courses from the CN clusters in A grouped by trials sharing the identical preparatory periods.

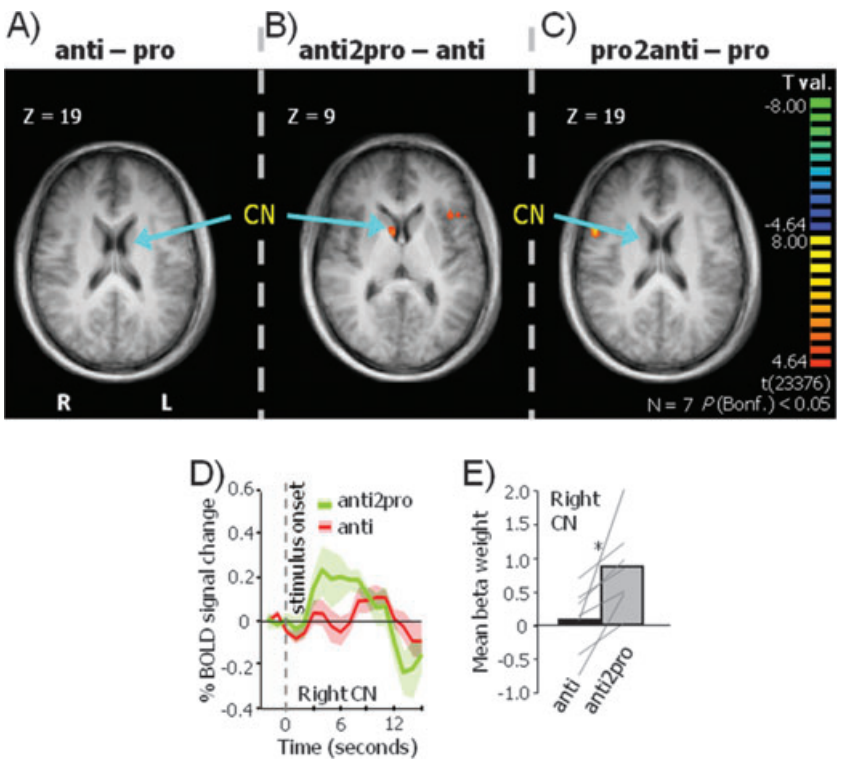

FIG. 7. CN activation during the 'response' period for correct trials in Experiment 2. (A) Group contrast map comparing correct anti trials with correct pro trials [Bonferroni corrected at $P < 0.05$ ($T = |4.64|$), cluster-size corrected at $P < 0.05$]. Greater BOLD activation for anti trials relative to pro trials was not found in the CN. (B) Contrast comparing anti2pro trials with anti trials. Greater BOLD activation for anti2pro trials resulted in the right CN. (C) Contrast comparing pro2anti trials with pro trials. Greater BOLD activation for pro2anti trials was not found in the CN. (D) BOLD signal time-courses for the right CN cluster in B. (E) Mean beta weight values for the CN cluster in B ($^*P < 0.05$, paired t-test).

subjects were excluded from further analysis for failure to perform to criterion (Fig. 5A and supporting Fig. S3). Performance of the removed subjects could not be reliably close to their threshold for switching successfully. As such, their behavior confounded our interpretation of CN BOLD activation that was hypothesized to relate to switching difficulty. In the end, six of the remaining seven

subjects participated on both days of the experiment, each providing a total of 9–12 runs (9 for one subject, 10 for one subject and 11 for two subjects due to runs being excluded for reasons listed previously). The seventh subject was only available for one session and contributed five viable runs.

Subjects were given one run of practice outside the magnet prior to each session, with the switch times set at 100 and 200 ms as in Experiment 1.

Statistical methods

A fixed-effects GLM with separate subject predictors was conducted, Bonferroni corrected for multiple comparisons at $P < 0.05$ and cluster-size corrected at $P < 0.05$ (yielding a cluster threshold of seven contiguous voxels). All other analysis methods remained identical to Experiment 1.

Results

Experiment 1

Behavior

All subjects produced switch costs in either switch direction: SRTs were greater on switch trials than on non-switch trials and subjects often failed to switch successfully (Fig. 1B and C, supporting Fig. S1). For the seven subjects used in further analysis, antisaccades were more difficult to perform than prosaccades, despite similar switching behavior. Non-switch antisaccades ('anti' trials) were slower than non-switch prosaccade ('pro' trials) ($t_6 = 2.96$, $P = 0.025$, corrected for multiple comparisons) (Fig. 1B) and error rates were greater for anti trials than for pro trials ($t_6 = 4.14$, $P < 0.01$, corrected) (Fig. 1C).

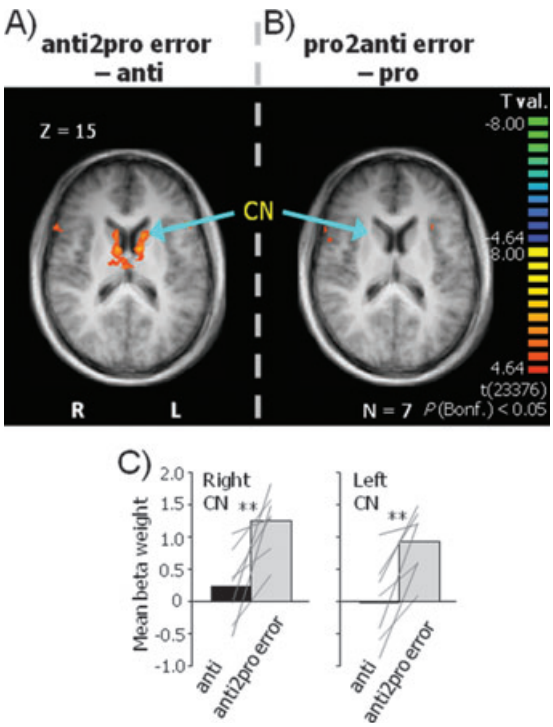

FIG. 8. CN activation during the 'response' period for erroneous switch trials in Experiment 2. (A) Group contrast map comparing anti2pro error trials with correct anti trials (Bonferroni and cluster-size corrected at $P < 0.05$). Greater BOLD activation resulted in the CN for anti2pro error trials relative to anti trials. (B) Contrast comparing pro2anti error trials relative to pro trials. Greater BOLD activation was not found in the CN for pro2anti error trials. (C) Mean beta weight values from the seven subjects for the CN clusters identified by the contrast in A (**$P < 0.01$, paired *t*-test).

Functional magnetic resonance imaging

The initial contrast that was conducted examined whether greater BOLD activation resulted in the CN for switch trials compared with non-switch trials. Correct anti and pro trials were pooled into non-switch trials and subtracted from correct anti2pro and pro2anti trials that were pooled into switch trials. Group activation maps from the GLM of the 'response' period (Fig. 1A) are shown in Fig. 2A, demonstrating that switch trials resulted in greater CN activation than non-switch trials ($T = 4.57$, $P < 0.05$, corrected for multiple comparisons). Our *a-priori* interest was to identify if switching from anti to pro and/or pro to anti resulted in greater CN activation. Thus, we extracted the mean beta weight values across subjects for the four response types (Fig. 2B). Switching from pro to anti (comparison between pro2anti and pro trials) resulted in significantly greater BOLD activation (right CN: $t_6 = 7.02$, $P < 0.001$; left CN: $t_6 = 4.95$, $P < 0.01$) but switching from anti to pro did not (comparison between anti2pro and anti trials) (right CN: $t_6 = 0.34$, $P = 0.75$; left CN: $t_6 = 1.55$, $P = 0.17$). In order to further understand the nature of these contrasts, we extracted the mean percentage BOLD signal changes across subjects for the four correct trial types, as well as for the erroneous switch trials (Fig. 2C), and grouped the trials according to identical preparatory periods. [It has been shown previously with BOLD functional magnetic resonance imaging that frontal areas critical to antisaccade generation show differences in activation upon antisaccade instruction (Connolly *et al.*, 2002, 2005; DeSouza *et al.*, 2003). Thus, it was important to account for any possible effects in CN activation that might relate to differences in preparatory set, rather than to response switching.] On pro2anti trials, the activation profile was greater than on pro trials, whereas on anti2pro trials the activation profile showed little difference from anti trials (Fig. 2C). Interestingly, the activation profiles on erroneous anti2pro and pro2anti trials increased initially relative to the correct trials, with pro2anti error trial activation rising sharply to a peak but then blunting in comparison to the correct pro2anti trials.

Subsequently, we performed separate GLMs comparing anti and anti2pro trials, and pro and pro2anti trials. These contrasts are more justified, as the contrast maps compare trials that have identical preparatory conditions. However, we also directly contrasted anti to pro trials, to confirm the trend shown in Fig. 2B that performing a non-switch antisaccade did not result in greater BG activation relative to a prosaccade in the current experiment. Contrast maps are shown in Fig. 3A–C, demonstrating that only pro2anti trials resulted in greater BOLD activation relative to pro trials (Fig. 3C) ($P < 0.05$, corrected for multiple comparisons). Figure 3D shows the mean BOLD signal time-courses from this contrast. A distinctly greater percentage BOLD signal change for pro2anti trials compared with pro trials is evident. This effect was significant across subjects (right CN: $t_6 = 7.59$, $P < 0.001$; left CN: $t_6 = 5.64$, $P < 0.01$) (Fig. 3E). A region of interest analysis of the CN was conducted (see supporting Fig. S2). This analysis consisted of a GLM but did not utilize a contrast map to define a region; rather, the left and right CN were defined anatomically. The results also showed that pro2anti trials were significantly greater in activation relative to pro trials in the right CN (right CN: $t_6 = 3.64$, $P < 0.05$; left CN: $t_6 = 1.40$, $P = 0.21$) but that anti trials were not greater than pro trials (right CN: $t_6 = -0.017$, $P = 0.92$; left CN: $t_6 = -1.47$, $P = 0.19$). This confirmed that failure to find an increased activation for anti2pro trials relative to

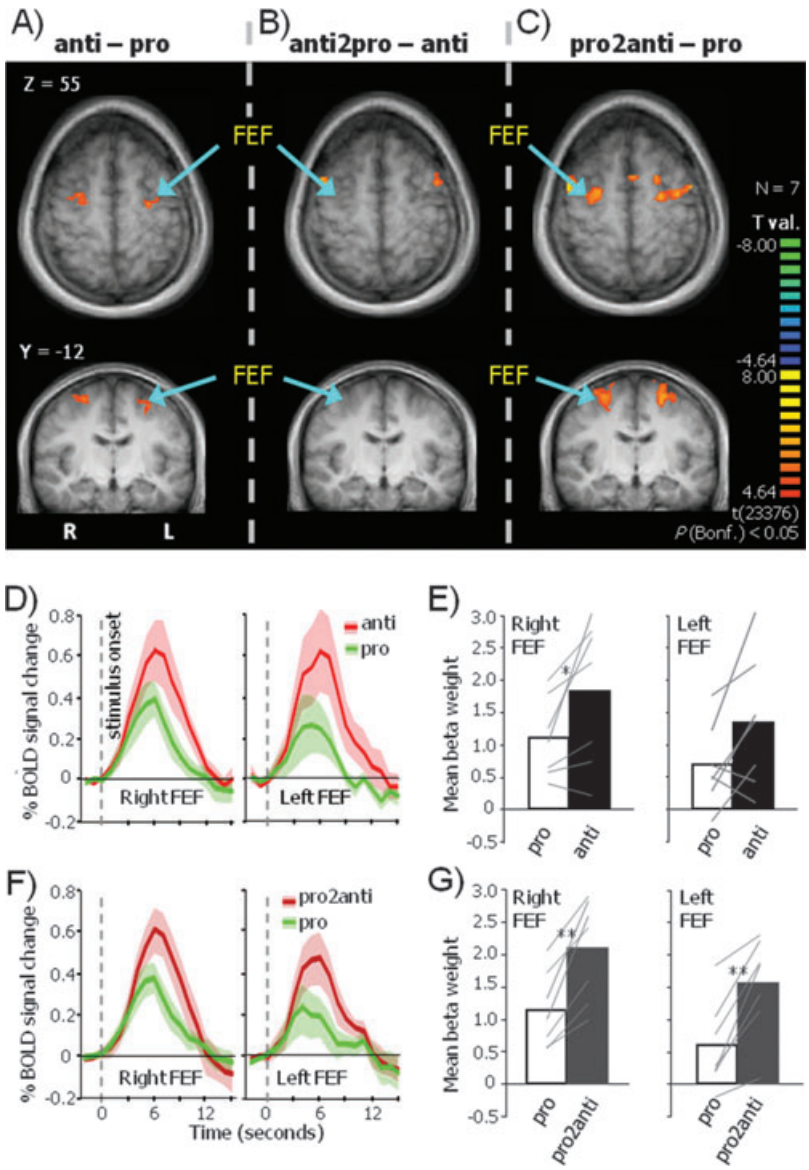

FIG. 9. FEF activation during the 'response' period for correct trials in Experiment 2. (A) Group contrast map comparing correct anti trials with correct pro trials (Bonferroni and cluster-size corrected at $P < 0.05$). Greater BOLD activation for anti trials relative to pro trials was found in the FEF bilaterally. (B) Contrast comparing anti2pro trials with anti trials. Greater BOLD activation for anti2pro trials did not result in the FEF. (C) Contrast comparing pro2anti trials with pro trials. Greater BOLD activation for pro2anti trials was found in the FEF bilaterally. (D) BOLD signal time-courses for the FEF clusters in A. (E) Mean beta weight values for the FEF clusters in A (*$P < 0.05$, paired *t*-test). (F) BOLD signal time-courses for the FEF clusters in C. (G) Mean beta weight values for the FEF clusters in C (**$P < 0.01$).

anti trials (Fig. 3B) cannot be attributed to greater activation for anti trials relative to pro trials.

Next, we performed a separate GLM analysis in which the 100 and 200 ms switch trials were not pooled, to examine whether there was a difference in switching from a pro- to an antisaccade at 100 or 200 ms post-stimulus onset. Figure 3F illustrates the mean BOLD signal time-course from pro2anti switch trials from the CN clusters in Fig. 3C. It is evident that the BOLD response is greater on pro2anti trials at the 200 ms switch time than at the 100 ms switch time. Next, we directly contrasted pro2anti 200 ms to pro2anti 100 ms switch trials. Figure 3G and H shows that, in bilateral regions of the dorsal CN, pro2anti 200 ms switch time trials resulted in significantly greater BOLD activation than pro2anti 100 ms switch time trials. To correct for multiple contrasts, the less conservative false discovery rate method was used (Fig. 3G) ($Q < 0.05$).

Finally, we analysed erroneous switch trials to evaluate whether BG activation is critical to mediating this switching behavior. We directly contrasted erroneous responses on switch trials to correctly executed non-switch trials. Figure 4A and C demonstrates that greater CN activation occurred during erroneous anti2pro trials (corrected by a prosaccade) relative to correct anti trials (mean beta values: right CN: $t_6 = 3.48$, $P < 0.05$; left CN: $t_6 = 3.32$, $P < 0.05$). The contrast of pro2anti error trials to pro trials did not result in significantly greater activation in the CN (Fig. 4B).

In summary, similar switch costs were found in both directions, indicating that the initially instructed response was prepared and there were costs to switching it (Cameron *et al.*, 2007). However, increased CN activation occurred only for switching correctly from a pro- to an antisaccade. Thus, the differential activation for switch direction may

result from a greater demand on BG processes to switch from a more automatic response to a more difficult response. Experiment 2 was conducted subsequently to test whether the differences in CN activation depended on the fact that subjects elicited a visually directed saccade in one condition and an internally guided saccade in the other. We staircased the switch times based on performance (see Materials and methods), equalizing for the difference in switching difficulty. If the CN activation pattern changed relative to Experiment 1, it would dissociate the influence of switching difficulty from the execution of a visually driven or an internally guided saccade.

Experiment 2

Behavior

As shown in Fig. 5A, seven of 11 subjects demonstrated error rates on switch trials of between 40 and 60%, allowing us to examine behavior when the switch direction was similar in difficulty. For these seven subjects, anti trials were not statistically slower than pro trials ($t_6 = 0.79$, $P = 0.46$) (Fig. 5B); however, there was still evidence of prosaccade dominance, as error rates were greater on anti trials compared with pro trials ($t_6 = 4.38$, $P < 0.01$, corrected) (Fig. 5C). Subjects produced significant error rate and SRT switch costs (all $t_6 > 4.99$, $P < 0.01$) (Fig. 5B and C). Reaction times of erroneous saccades on switch trials are shown in supporting Fig. S3. As a result of the staircasing procedure, the average switch time of the instruction for pro2anti trials was 193 ms and the average switch time for anti2pro trials was slightly slower at 205 ms (across subjects), suggesting that switching difficulty was equalized. However, these values were not significantly different from one another ($t_6 = 0.61$, $P = 0.56$).

Functional magnetic resonance imaging

Switch trials resulted in greater CN activation relative to non-switch trials (Fig. 6A). Figure 6B and C shows that anti2pro trials resulted in greater activation than anti trials (right CN: $t_6 = 3.54$, $P < 0.05$; left CN: $t_6 = 3.65$, $P < 0.\ 05$) and pro2anti trials resulted in greater activation relative to pro trials in the right CN (right CN: $t_6 = 4.06$, $P < 0.01$; left CN: $t_6 = 1.77$, $P = 0.16$). Different BOLD signal time-courses resulted between anti2pro error and pro2anti error trials (Fig. 6C); anti2pro error trials resulted in a noticeably greater increase in percentage BOLD signal change relative to both correct anti2pro and anti trials but BOLD activation for pro2anti error trials was delayed in onset.

Separate GLM contrasts of anti to pro trials revealed no greater activation for either response in the CN (Fig. 7A), as in Experiment 1. Contrasting anti2pro trials to anti trials revealed greater activation in the right CN (Fig. 7B, D and E) that was significant across the subjects' mean beta weight values ($t_6 = 3.62$, $P < 0.05$). However, contrasting pro2anti trials to pro trials revealed no increased activation in the CN (Fig. 7C). Analysis of erroneous responses showed greater activation for erroneous anti2pro trials compared with correct anti trials (Fig. 8A and C) (right CN: $t_6 = 3.94$, $P < 0.01$; left CN: $t_6 = 4.67$, $P < 0.\ 01$) but did not show greater activation for erroneous pro2anti trials compared with correct pro trials (Fig. 8B).

An anatomical region of interest analysis of correct trials was conducted on the CN as in Experiment 1. The region of interest analysis showed that the comparison of anti2pro to anti trials revealed greater activation for anti2pro trials in both the right and left CN (right CN: $t_6 = 2.29$, $P < 0.05$; left CN: $t_6 = 3.10$, $P < 0.\ 05$), and the comparison of pro2anti to pro trials revealed greater activation for pro2anti in the right CN ($t_6 = 2.88$, $P < 0.05$) (supporting Fig. S4).

Finally, the FEF were analysed in a similar fashion to the CN, in order to examine a region hypothesized to have a greater role in antisaccade generation, rather than in task switching. In brief, imaging data from the FEF (Figs 9 and 10) demonstrate that performing an antisaccade (either on an anti, pro2anti or pro2anti error trial) resulted in greater activation relative to performing a prosaccade. However, performing an anti2pro or anti2pro error trial did not result in greater activation relative to performing an anti trial. This pattern of activation mirrors previous saccade studies of the FEF in antisaccade generation (Connolly *et al.*, 2002; Curtis & D'Esposito, 2003; Ford *et al.*, 2005; Brown *et al.*, 2007) and, most importantly, is distinct from activation in the CN (which did not show greater activation for anti trials relative to pro trials).

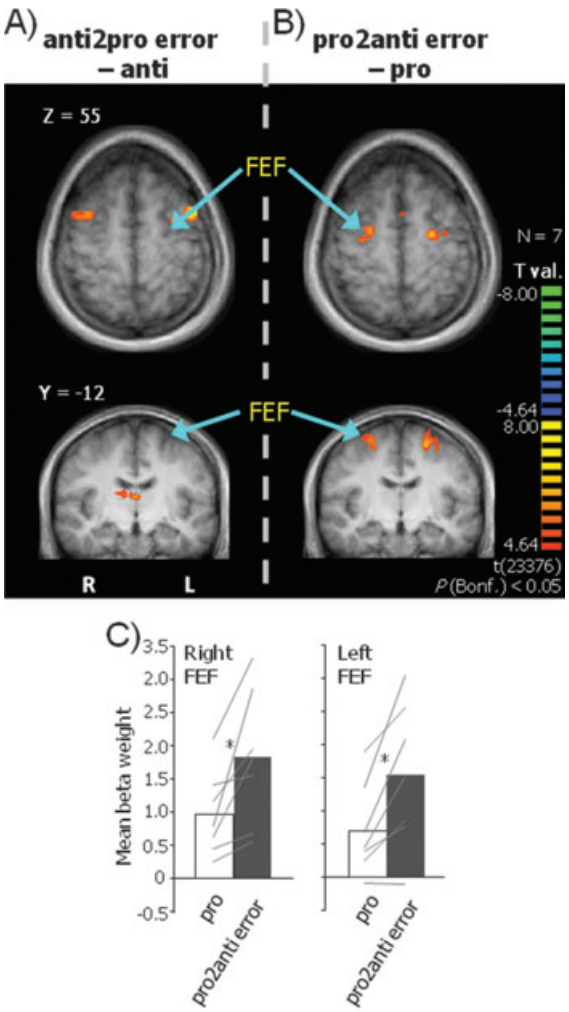

FIG. 10. FEF activation during the 'response' period for erroneous switch trials in Experiment 2. (A) Group contrast map comparing anti2pro error trials with anti trials (Bonferroni and cluster-size corrected at $P < 0.05$). Greater BOLD activation in the FEF did not result for anti2pro error trials relative to anti trials. (B) Contrast comparing pro2anti error trials relative to pro trials. Greater BOLD activation was found in the FEF for pro2anti error trials. (C) Mean beta weight values for the FEF clusters in A (*$P < 0.05$, paired *t*-test).

Discussion

We showed in both experiments that the BG are involved in switching a planned response, as CN BOLD activation was greater on switch trials compared with non-switch trials. However, we suggest that the

BG are more important for switching from an automatic or dominant response to a non-dominant response, as greater activation resulted only for switching to the antisaccade in Experiment 1 (Figs 2 and 3), despite similar switching behavior (Fig. 1B and C). Importantly, this increase in activation correlated to switch time difficulty (Fig. 3F–H). We then showed in Experiment 2 that the CN activation patterns on switch trials changed when differences in switching difficulty were equalized. Therefore, CN activation did not correspond to a general response switching mechanism (Mink, 1996; Nambu, 2004). We suggest instead that the CN activation related to switching difficulty, implying that the BG have a specific role in over-riding a dominant action with an alternative action.

Prosaccades are more automatic and easier to perform than antisaccades, in terms of habituation and demand on attentional and cognitive resources (MacLeod, 1991; Dafoe *et al.*, 2007; Ettinger *et al.*, 2008). Antisaccades also require suppression mechanisms against responding automatically (Everling *et al.*, 1998; Everling & Munoz, 2000), preventing the execution of a visually driven saccade to the stimulus. This suppression mechanism has been interpreted to drive the greater BOLD activation seen in the FEF for antisaccades relative to prosaccades (Connolly *et al.*, 2002), which fits with our findings of greater FEF activation when executing an antisaccade relative to a prosaccade (Fig. 9). Note that the FEF were consistently more active for antisaccades compared with prosaccades, even when a corrective antisaccade was made following an erroneous prosaccade (Fig. 10B and C). This suggests that the FEF activation related to the underlying differences between visually directed saccades and internally guided saccades, and several previous imaging studies have shown greater activation in the FEF for antisaccades relative to prosaccades (O'Driscoll *et al.*, 1995; Sweeney *et al.*, 1996; Curtis & D'Esposito, 2003; DeSouza *et al.*, 2003; Connolly *et al.*, 2005; Ford *et al.*, 2005; Miller *et al.*, 2005; Brown *et al.*, 2006, 2007). Because we did not observe greater CN activation for anti trials relative to pro trials (Figs 3A and 7A, supporting Figs S2 and S4), CN activation cannot be attributed to these same processes. This finding is also supported by the fact that, in Experiment 2, the switch time manipulation did not change the actual responses elicited but the CN activation patterns changed (compare Figs 2 and 3 with Figs 6 and 7).

We propose that CN activation is driven, at least in part, by mechanisms similar to the Stroop task, in which subjects must perform an unusual response under interference from a dominant and more automatic response (e.g. respond with the color of the font that is incongruent with the word that is written). Models of the Stroop effect posit that the dominant response exerts the greatest interference (MacLeod, 1991) and it has been shown that performing the less dominant responses results in greater CN activation (Peterson *et al.*, 2002). In our study, the greatest interference resulted on a pro2anti trial whereby the dominant prosaccade is explicitly instructed to be planned. This would explain why there was not greater activation on anti relative to pro trials, as the pro response was not explicitly instructed to be planned. Under the proposed framework, switching to an antisaccade requires subjects to instantly over-ride a more automatic response, and this is more difficult to accomplish. Conversely, switching to a prosaccade is in the direction of a more automatic response that is easier to perform. The staircasing method of Experiment 2 only yielded a significant increase in anti2pro trials relative to anti trials at the contrast level in the right CN (Fig. 7A–C). However, it can be seen in Fig. 6 that activation was greater on anti2pro relative to anti trials, as well as on pro2anti relative to pro trials. Thus, the largest effect of the staircasing method appears to be increasing the difficulty of switching from anti2pro, making it similar in difficulty to switching from pro2anti. Experiment 1 did not result in increased anti2pro activation, suggesting that, with fixed switch times, the switching difficulty was asymmetric.

Examination of erroneous switch trials provides valuable insight into the underlying mechanisms. In both experiments, greater CN activation was seen for erroneous anti2pro trials relative to correct anti trials. In this situation, the antisaccade response overcame any interference from the more automatic prosaccade, as it was executed despite the change in instruction. Thus, increased CN activation might result if the corrective prosaccade needs to overcome response-system inhibition (e.g. suppression against eliciting a saccade to the stimulus) that had biased the response system against its execution during the initial antisaccade instruction (Vink *et al.*, 2005; Barton *et al.*, 2006; Woodward *et al.*, 2006; Manoach *et al.*, 2007). In contrast, in both Experiments 1 and 2, erroneous pro2anti trials (that were subsequently corrected with an antisaccade) did not result in greater CN activation relative to correct pro trials (Figs 4 and 8), measured by group contrasts. Note, however, that the BOLD activation profiles in Figs 2 and 6 (derived from the contrast of switch minus non-switch) showed that, in Experiment 1, a sharp increase in BOLD activation for pro2anti error trials occurred initially but then blunted in comparison to correct pro2anti trials. In Experiment 2, the BOLD activation pattern on pro2anti error trials was delayed in onset and did not result in greater activation relative to correct pro2anti trials. Together, these different activation patterns between pro2anti and pro2anti error trials suggest that switching successfully to the antisaccade is a process that is mediated, at least in part, by the BG. However, the differences in pro2anti error activation patterns across the experiments might also be reconciled by a response-system inhibition hypothesis; we cannot discount the possibility that, during the pro instruction in Experiment 1, subjects adopted a 'wait-and-see' strategy given that switch times were predicted within 200 ms, effectively inhibiting the response system against eliciting the programmed prosaccade. The result was an increase in BOLD activation when the volitional, non-dominant antisaccade was executed, even if a prosaccade was executed in error first. On a correct non-switch prosaccade trial, the subjects 'released' the programmed response, resulting in less BOLD activation. We hypothesize that, in Experiment 2, no wait-and-see strategy could be employed and no response-system inhibition was imposed on the pro instruction. This resulted in the reduced BOLD activation on correct pro2anti and pro2anti error trials relative to Experiment 1 but still contained an effect of task switching, driving greater BOLD activation on correct pro2anti trials relative to pro trials (Fig. 6C).

So what neural networks might produce the BOLD activation seen in the CN? The dorsal CN receives overlapping projections from the FEF and dorsolateral prefrontal cortex (Alexander *et al.*, 1986; Cui *et al.*, 2003; Gerardin *et al.*, 2003), and several studies have implicated the dorsolateral prefrontal cortex in voluntary saccade control (Guitton *et al.*, 1985; Everling & Desouza, 2005; Pierrot-Deseilligny *et al.*, 2005; Brown *et al.*, 2007; Ettinger *et al.*, 2008). Thus, CN activation could be driven in part by processes related to rule representation and attentional set, and in all by processes related to instantly selecting the appropriate response signals from the FEF (Redgrave *et al.*, 1999; Hikosaka *et al.*, 2000; Monchi *et al.*, 2001; Peterson *et al.*, 2002; Cools *et al.*, 2004). Future studies should try to dissociate these components, in particular investigating whether the CN activation is related to cancellation or reprogramming mechanisms. However, cancellation processes alone should not produce the activation patterns seen on erroneous switch trials. Secondly, cancellation should be a fast-acting process, possibly mediated by a 'hyper-direct' pathway

from the cortex to the subthalamic nucleus, bypassing the CN and exciting the substantia nigra pars reticulata, resulting in increased inhibitory output of the BG against responding (Mink, 1996; Aron & Poldrack, 2006; Isoda & Hikosaka, 2008). A reprogramming explanation suggests that we are measuring increased activation for amplifying weaker or previously inhibited response signals. Thus, we propose that greater CN activation is related to switching to a most effortful response on a given trial, i.e. an antisaccade when a prosaccade is more automatic or either response if the response system was biased against its execution.

Conclusions

The BG have been implicated in the inhibition of inappropriate response signals and the disinhibition of appropriate response signals pertaining to a desired action; however, it has not been tested previously how the BG are involved in switching from one response in preparation to another instantly. Here, we have demonstrated that differences in response difficulty resulted in differential CN activation for switching. When we controlled for the difference in response difficulty, CN activation changed. Therefore, we suggest that the BG are important for effectively switching planned behavior by over-riding biases in the response system towards a particular action. This mechanism is necessary should a more dominant behavior become inappropriate and a new course of action be needed immediately.

Supporting Information

Additional supporting information may be found in the online version of this article:

Fig. S1. Behavior of subjects in Experiment 1.

Fig. S2. CN region of interest analysis in Experiment 1.

Fig. S3. Behavior of subjects in Experiment 2.

Fig. S4. CN region of interest analysis in Experiment 2.

Table S1. Talairach coordinates of peak activations in the CN and FEF from the contrast maps in Figs 2–4 and 6–10.

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Abbreviations

AC-PC, anterior commissure-posterior commissure; anti, non-switch antisaccade trial; anti2pro error, erroneous anti- to prosaccade switch trial; anti2pro, anti- to prosaccade switch trial; BG, basal ganglia; BOLD, blood oxygen level dependent; CN, caudate nucleus; FEF, frontal eye fields; GLM, general linear model; pro, non-switch prosaccade trial; pro2anti error, erroneous pro- to antisaccade switch trial; pro2anti, pro- to antisaccade switch trial; SRT, saccade reaction time; TR, repetition time.

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