Reduced Basal Ganglia Function When Elderly Switch between Coordinated Movement Patterns

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Structural and neurochemical changes in frontostriatal circuits are thought to underlie age-related behavioral deficits on cognitive tasks. Here, we test the hypothesis that age-related motor switching deficits are associated with reduced basal ganglia (BG) function. Right-handed volunteers (15 Old, and 15 Young) made spatially and temporally coupled bimanual circular motions during event-related FMRI. A visual cue signaled the right hand to Switch or Continue its circling direction. Switching from mirror symmetric to asymmetric (SW»ASYMM) took longer and resulted in more contralateral (left-) hand disruptions than vice versa. These effects were more pronounced in the elderly, showing that the ability to suppress and flexibly adapt motor behavior (agility) declines with age. For both groups, switching activated the BG and a typical network for task-set implementation, including dorsal anterior cingulate cortex/supplementary motor area (pre-SMA, SMA-proper) and anterior insula/inferior frontal gyrus. A region of interest analysis revealed significantly reduced SW»ASYMM activation in bilateral subthalamic nucleus and right globus pallidus, only in the elderly. Age-related behavioral deficits may be related to inefficient recruitment of cortico-BG loops to suppress undesired movements. The elderly may use an alternative strategy to select the required movement pattern as indicated by increased activation of prefrontal cortex.

Keywords: aging, basal ganglia, cognition, motor control, task switching

Introduction

During healthy aging, the ventricles and fissures of the brain expand, with concomitant decreases in gray matter volume and white matter integrity (Good et al. 2001; Resnick et al. 2003; Sullivan and Pfefferbaum 2006). There are also age-related changes in subcortical structures including decreased volume of basal ganglia (BG) nuclei (Gunning-Dixon et al. 1998; Raz et al. 2003), and degradation of the nigrostriatal dopamine system (Volkow et al. 1998; Erixon-Lindroth et al. 2005). Such structural and neurochemical changes in frontostriatal circuits are thought to underlie age-related behavioral deficits on cognitive tasks (Hedden and Gabrieli 2004; Backman et al. 2006).

Switching between responses, requiring both inhibition of primed action and facilitation of alternative action, is an important dimension of executive function that is clearly affected in old individuals (Monsell 2003). We combined task switching, a ubiquitous task in the cognitive literature (Monsell 2003), with bimanual coordination dynamics (Kelso 1995), to investigate age-related differences in "motor" task switching. The literature on bimanual coordination has established that asymmetric interlimb patterns are more difficult to perform than symmetric patterns (Swinnen 2002; Swinnen and Wenderoth 2004). For example, when movement frequency is progressively increased, it is relatively easy to demonstrate instability and

"spontaneous" transitions from asymmetric bimanual circling drawing (e.g., both hands counterclockwise) to an easier symmetric pattern of bimanual circling that involves simultaneous activity of homologous muscles (Semjen et al. 1995; Carson et al. 1997). Although the neural basis of spontaneous phase transitions during frequency stress has been investigated in young adults (Aramaki et al. 2006), a fundamentally different question concerns the neural basis of "intentional" switching between modes of coordination, and across age groups.

Here, we used a task requiring participants to continuously draw bimanual circles, with asymmetric patterns occurring when both hands circled clockwise (CW)/counterclockwise (CCW) and symmetric patterns occurring when both hands circled inward/outward relative to the body midline. To avoid spontaneous transitions, which are easier to induce in an elderly population (Wishart et al. 2000; Heuninckx et al. 2004), participants were paced at a comfortable rate (i.e., at around 1 Hz) well below their spontaneous transition frequency, where stability is equivalent between symmetric and asymmetric patterns (Serrien et al. 2000). Upon presentation of a cue, the participant was required to change direction with only the right hand to switch between coordination patterns. Behavioral studies in which young adults perform this task show that intentional switching from the easier symmetric to the more difficult asymmetric movement pattern takes longer than vice versa, and switching via the dominant right hand frequently disrupts nondominant hand movement (Byblow et al. 1999, 2000; Wenderoth et al. 2009). This selective control of one effector while the other has to maintain ongoing movement is likely to rely on SMA-BG function.

Prominent theories of BG function implicate reciprocal loops with cortex in the selection and inhibition of competing motor programs (Mink 1996; Nambu et al. 2002). Similarly, the supplementary motor areas (pre-SMA and SMA-proper) have been ascribed the function of linking situations (be they environmental triggers or internal states) with appropriate actions (Nachev et al. 2008). In support of these views, selectively inhibiting part of an action is associated with pre-SMA activity (Coxon et al. 2009) and primate research indicates pre-SMA and subthalamic nucleus (STN) are both important for suppressing and replacing a prevailing action plan (Isoda and Hikosaka 2007, 2008). Furthermore, during STN stimulation, Parkinson's disease (PD) patients fail to slow responses in situations of high conflict (Frank et al. 2007). At the nexus between cognitive and motor brain regions, the highly interconnected SMA and BG are likely to effect intentional switching between actions. In particular, the STN is considered a key node in the network for the inhibitory control of action (Aron and Poldrack 2006; Aron, Behrens, et al. 2007; Li et al. 2008) that may be important for suppressing undesired action when switching.

Although previous functional magnetic resonance imaging (FMRI) experiments of complex movement coordination have consistently revealed overactivation in cortical regions of healthy older adults (Heuninckx et al. 2005; Wu and Hallett 2005; Ward 2006; Heuninckx et al. 2008), changes in midbrain structures are inconsistent. Increased age-related activation of the BG has been reported in 2 studies involving relatively simple motor tasks, that is, unimanual button press (Mattay et al. 2002) and hand grip (Ward et al. 2008). In contrast, an age-related decrease within the BG has been reported for a complex motor task requiring interlimb coordination (Van Impe et al. 2009). It is possible that the consistently observed overactivation of cortical regions in the elderly represents an attempt to counteract inefficient subcortical processing.

Even though intentional switching between coordination modes has been studied intensively at the behavioral level, age-related differences have not yet been examined, nor has their neural basis. Here we combined event-related FMRI and a motor switching task targeting the SMA-BG circuit to investigate whether age-related task switching deficits are associated with reduced BG function in older adults. Based on previous studies of reaction time (Salthouse 1996) and cognitive task switching (Kramer et al. 1999; DiGirolamo et al. 2001), we predicted that old participants would take longer to implement pattern change than young participants. We hypothesized that switching to asymmetric coordination would be more difficult than vice versa, with more contralateral disruptions in the old participants, and that this would be associated with reduced function within the SMA-BG circuit. More specifically, we predicted that compared with young adults, the elderly would show less engagement of an inhibitory BG circuit involving the STN when switching coordination patterns. To test this hypothesis, we performed an anatomical region of interest (ROI) analysis and investigated the relationship between activation and behavioral performance. Further, we investigated whether the elderly relied more on cortical regions to perform the task.

Materials and Methods

Participants

Sixteen old adults were screened for inclusion using the Mini-Mental State Examination (MMSE), an assessment of general cognitive function (Folstein et al. 1975). All except one (MMSE 24) scored within normal limits (MMSE ⩾27 of 30). Therefore, 15 older adults (mean age 67.9 years, range 60–74, 6 male) and 15 young adults (mean age 25.2 years, range 21–30, 5 male) participated in this FMRI experiment. The older participants were independent and community dwelling. Participants were right handed (laterality quotient: Old; mean 96.8, range 85.7–100, Young; mean 95.1, range 62.5–100) as verified by the Edinburgh Handedness Inventory (Oldfield 1971). The older participants had fewer years of formal education (Old; mean 15.2 years, range 12–24, Young; mean 17.4 years, range 15–21, $P < 0.05$). The local ethics committee approved the procedure, and all participants gave written, informed consent.

Experiment Setup and Task

Prior to scanning, participants attended a training session consisting of paperwork, a description of the task, determination of maximum stable movement frequency, and practice within a dummy scanner (up to 20 min). During both practice and scanning, subjects lay supine with their upper arms next to their torso and forearms supported at approximately 45° from the horizontal. Left and right index fingers controlled 2 custom joysticks, and circular motions were generated by movements about the wrist and metacarpophalangeal joints (Fig. 1). Joystick movements were registered by 2 FMRI compatible optical

encoders (Hewlett-Packard, Malaysia; spatial resolution 0.18°) mounted along orthogonal axes. Custom LabVIEW software recorded the 2D kinematics of each joystick (sample rate 100 Hz) and generated the visual display. Cues were projected onto a screen and viewed via a 45° mirror, attached to the head coil. Participants could see the visual display, but the joysticks were obscured.

Training Session

Participants were required to make spatially and temporally coupled circular motions of the joysticks. For each hand, the direction of circling could be either CW or CCW. An auditory metronome was used for pacing such that participants completed one circle per tone. Four possible bimanual movement patterns were introduced: Inward circles (left-hand CW and right-hand CCW), outward circles (left-hand CCW and right-hand CW), CW circles (both hands CW), and CCW circles (both hands CCW). Prior to training, a maximum stable movement frequency was determined by online inspection of relative tangential
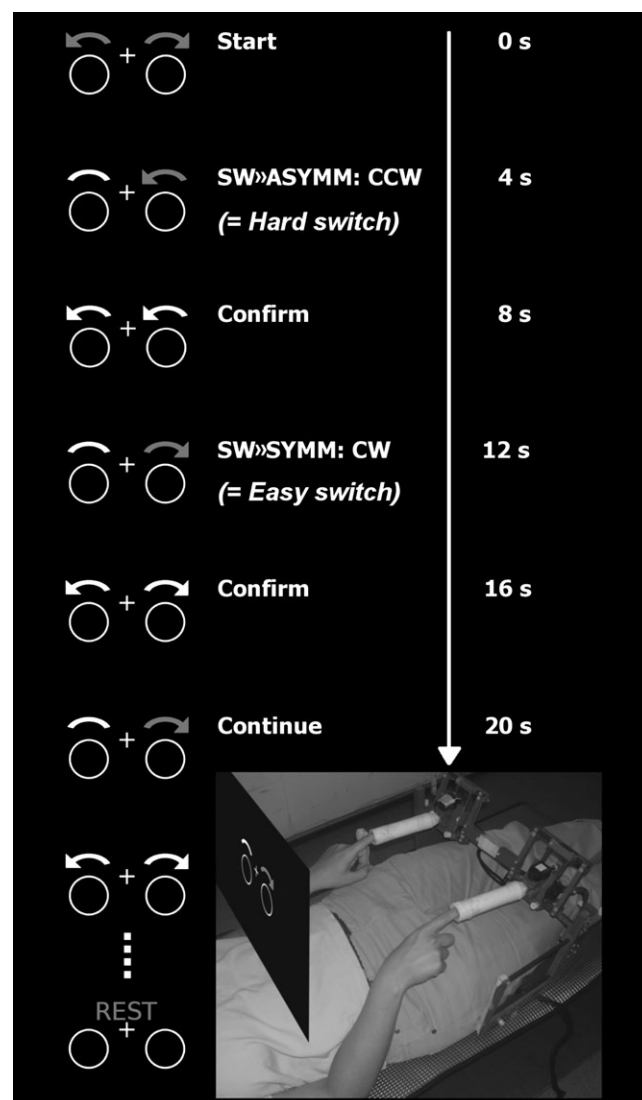

Figure 1. Task performed in the MRI scanner. Subject position and custom MRI compatible joysticks are shown. Visual stimuli were projected onto a screen that occluded vision below the shoulders and were viewed via a 45° mirror. Two circles and a central fixation cross were always visible. Imperative (gray arrows) and confirmation cues (white arrows) were presented for 800 ms, separated by 4 s. Switching from symmetric to asymmetric (SW»ASYMM) or from asymmetric to symmetric (SW»SYMM) movement patterns required the right hand to change circling direction: Clockwise (CW) and counterclockwise (CCW).

angle (Carson et al. 1997). Participants were cued to move in an asymmetric pattern (both hands CW, CCW), and metronome frequency was increased every 8 s from 1 to 3 Hz in 0.25-Hz increments. The participant's maximum stable movement frequency was determined when either a spontaneous transition occurred or the temporal relationship to the metronome could no longer be maintained. During both training and scanning sessions, participants were paced at 50% of their maximum. This procedure served to establish common relative speeds, equating the difficulty of bimanual circling between age groups.

Next, it was explained that visual cues would instruct the movement pattern to be performed. A constant visual display was shown comprising 2 white circles, each with a curved white bar immediately above, and a central fixation cross on a black background. Instruction cues were conveyed by arrows, visible for 800 ms (Fig. 1). Green arrows were used as imperative cues (shown as gray in Fig. 1). Two green arrows indicated the initial pattern to adopt. A single green arrow pointing opposite to the actual movement direction indicated that the right hand must change direction (Switch). A single green arrow pointing in the same direction as actual movement indicated that no change was necessary for the right hand (Continue). In both cases, the left hand was to maintain moving in the already established direction. White arrows indicated the correct movement pattern 4 s after the imperative. For the participant, this served as confirmation that they were performing the correct pattern (90 ± 3% of the time for the old participants) or provided an opportunity to correct their fault.

Scanning Procedure

The experiment consisted of 5 scanning runs, each 351 s in duration. A run comprised alternating movement (68 s) and rest (20 s) epochs to avoid fatigue. There were 14 Switch trials, 14 Continue trials, 4 Reverse trials, and 32 Confirmation trials per run. Reverse trials were signaled by 2 green arrows, cueing a switch of both hands. They were included to change left-hand direction within a movement epoch but were of no interest for the analysis.

An initial cue prompted 1 of 4 possible patterns (both hands circle inward, outward, CW, or CCW circles). A different pattern was used for each movement epoch, and the order was counterbalanced across runs. Switch trials required a change of movement pattern from asymmetric to symmetric circling (SW»SYMM, easy switch) or from symmetric to asymmetric circling (SW»ASYMM, hard switch). In total, there were 70 Switch trials of the right hand (35 SW»SYMM, 35 SW»ASYMM) and 70 Continue trials. An algorithm was used to create pseudorandomized event sequences (Wager and Nichols 2003), optimizing design efficiency for the contrast Switch > Continue while maintaining the unpredictability of the task. The hemodynamic response was effectively sampled every second, as event occurrence (multiples of 4 s) varied with respect to echo planar image (EPI) acquisitions (every 3 s).

Kinematic Analysis and Statistics

MATLAB 7.4 (Mathworks, Sherborn, MA) was used to analyze kinematic data. For each hand, a continuous estimate of angular velocity was determined by $\omega = d\theta/dt$ with $\theta = \arctan(x/y)$, where x and y describe the mean corrected values for vertical and horizontal joystick displacements, respectively. A second-order Butterworth lowpass filter (cutoff 5 Hz) was applied to ω. For trials where the right hand changed direction, switch response time (SwRT) was determined as the interval between stimulus onset and the first zero crossing of ω, indicating that cycling direction had reversed. The right-hand SwRT difference was also calculated for each individual by subtracting SwRT for SW»ASYMM from SW»SYMM (differential switch cost). Additionally, contralateral disruptions were recorded when left-hand direction was involuntarily reversed during the right-hand switch. Contralateral disruptions were divided into 2 types: 1) A partial contralateral disruption was classified when left-hand circling velocity ceased ($\omega = 0$ for at least 200 ms) or transiently reversed (e.g., $+\omega$ to $-\omega$ for at least 100 ms), followed by the resumption of correct left hand circling. 2) When left-hand direction reversed until the correct pattern was displayed, the trial was labeled a complete contralateral disruption. A trial was classified as an error when 1) no right-hand switch occurred or 2) the right-hand SwRT was smaller than 200 ms or longer than 2000 ms (less than 2% of all trials for the old group).

For statistical analysis, SwRT and the variability (standard deviation) of SwRT were normalized to individual pacing rate (i.e., the time between 2 metronome tones) to avoid differences in movement rate between groups confounding the results. These data, along with the percentage of partial and complete contralateral disruptions, and the duration of partial disruptions, were subjected to analysis of variance (ANOVA), with factors Group (Old, Young) and within-subject factors Resultant Pattern (SW»SYMM and SW»ASYMM) and Switch Direction of the right hand (CW, CCW). All statistical analyses were calculated with Statistica 8 (StatSoft, Inc. Tulsa, OK) using an α-level of 0.05. Reported post hoc comparisons survived Bonferroni correction. Results are reported as mean ± standard error.

Image Acquisition

A Siemens 3-T Magnetom Trio MRI scanner (Siemens, Erlangen, Germany) with a standard head coil was used for image acquisition. For all subjects, a high-resolution T1-weighted structural image was acquired using magnetization prepared rapid gradient echo (repetition time [TR] = 2300 ms, echo time [TE] = 2.98 ms, 1 × 1 × 1.1-mm voxels, field of view: 240 × 256, 160 sagittal slices). Functional data (FMRI) were acquired with a descending gradient EPI pulse sequence for T2*-weighted images (TR = 3000 ms, TE = 30 ms, flip angle = 90°, 50 oblique axial slices each 2.8 mm thick, interslice gap 0.028 mm, in-plane resolution 2.5 × 2.5 mm, and 80 × 80 matrix). Three "dummy" scans at the beginning of each run were discarded from the FMRI analysis.

Image Preprocessing

Image preprocessing was conducted using MRIcron (Chris Rorden, University of South Carolina) and SPM5 (Wellcome Department of Imaging Neuroscience, University College, London) within MATLAB 7.4 (Mathworks, Sherborn, MA). EPI image volumes were spatially realigned to the first volume in the time series, then corrected for differences in slice acquisition time by temporal interpolation to the middle slice (reference slice = 25). Head movement across all scanning runs was <2 mm. The mean EPI image was normalized to the Montreal Neurological Institute (MNI) functional template (EPI.nii) and the same transformation was applied to all EPI images. These warped images (2.5 × 2.5 × 2.5-mm voxels) were spatially smoothed with an isotropic Gaussian kernel of 10-mm full width at half maximum.

Event-Related Hemodynamic Response Analysis

Events were specified at the time of cue onset and modeled as delta functions convolved with the canonical hemodynamic response function (HRF) and its temporal derivative within a general linear model. Five conditions were specified: correct SW»ASYMM trials, correct SW»SYMM trials, correct Continue trials, Confirmation, and Rest. Switch conditions were parametrically modulated by response time. An additional regressor modeled events of no interest such as initiation trials, reversals, Switch trials with complete contralateral disruptions, and their subsequent correction on Confirmation trials. In addition, realignment parameters were included as covariates of no interest to correct for confounding effects of head movement. Data were filtered in the temporal domain using a high-pass cutoff of 1/128 Hz, and global differences in blood oxygen level–dependent signal were removed by scaling to the grand mean. For each subject, the contrast of Switch > Continue was created (by applying weights to the canonical HRF for each condition). Both Switch and Continue conditions consisted of identical visual cues, but only the Switch trials required a change of movement plan. The more difficult SW»ASYMM > Continue contrast was also specified, as this condition differentiated the age groups behaviorally. Further, we created a contrast for Continue trials only, to check that the age groups did not differ for this baseline condition. These contrast images were used as input for random effects (RFX) analysis of the 2 groups.

ROI Analysis

A priori ROIs were informed by previous studies of motor task switching and neurodegenerative changes in the elderly (see Introduction). The AAL template (Tzourio-Mazoyer et al. 2002) was used

to construct anatomical ROIs for the BG (caudate nucleus, putamen, and globus pallidus of each hemisphere) and the medial frontal cortex (SMA: pre-SMA and SMA-proper). As the STN region is not included in the AAL template, it was defined as a $10 \times 10 \times 10$-mm cube centered at coordinate $x, y, z = \pm 10, -15, -5$ (Aron and Poldrack 2006; Li et al. 2008). Note that STN is a small structure and the resolution of whole-brain FMRI is limited. We use the term to refer to STN and surrounding structures that may also fall within the boundary of the ROI. The SMA was divided into pre-SMA and SMA-proper by a vertical line from the anterior commissure ($y = 0$) (Picard and Strick 1996; Johansen-Berg et al. 2004). The volume of the caudate nucleus ROI was reduced by segmenting the average normalized anatomical image of the old group and removing voxels classified as cerebrospinal fluid from the ROI. We adopted this conservative approach to compensate for slight ventricular enlargement in the elderly that remained after normalization. For each ROI, the marsbar toolbox (Brett et al. 2002) was used to extract the mean time course of all voxels. Unsmoothed images were used to avoid including signal from neighboring regions. The hemodynamic model used for whole-brain event-related analysis was applied to each ROI time course and percent signal change (PSC) for SW»ASYMM > Continue and SW»SYMM > Continue was determined from the parameter estimates.

A 2 Group (Old, Young) × 2 Switch trial type (SW»SYMM, SW»ASYMM) × 10 Brain Region (pre-SMA, SMA-proper, along with left and right caudate nucleus, putamen, globus pallidus, and STN) ANOVA was performed. Post hoc comparisons (Tukey HSD) explored between-group differences for each type of switch trial, and within each group, switch trial type differences for each region. Moreover, a planned contrast was conducted to test whether the more difficult switch condition would require higher BG activation and whether this effect differed between the age groups. As a control analysis, a 2 Group × 10 Region ANOVA investigated the suitability of Continue trials as the baseline for PSC calculations. Statistical analyses were implemented using Statistica 8 (StatSoft, Inc.), and an α-level of 0.05 was adopted.

Results

Behavior during Motor Switching
Here, we report analysis of movement kinematics obtained online during scanning. A continuous measure of signed radial velocity was determined offline for each hand (see Materials and Methods, and Fig. 2A). We then extracted the dependent variables SwRT, which reflects the time taken to initiate the switch by the right hand, and contralateral disruptions, which reflect the involuntary consequence of the switch for the left hand. These analyses investigate manipulation of switch trial difficulty and the conditions that are most influenced by aging.

Baseline Motor Behavior
Movements were paced at 50% of maximum movement frequency obtained during asymmetric circling. The size of the circles made with each hand was equivalent for the old and young groups (diameter of circle at left fingertip: Old 54 ± 4.8 mm, Young 52 ± 3.5 mm, $P = 0.69$; Right fingertip: Old 49 ± 5.5 mm, Young 46 ± 3.4 mm, $P = 0.65$). On average, the 2 groups had different maximal stable frequencies for asymmetric coordination and thus moved at slightly different rates (Young 1.13 ± 0.02 Hz, Old 1.03 ± 0.02 Hz, 2-sample t-test, $P < 0.01$). Importantly, this procedure ensured relatively equivalent difficulty of continuous circle drawing for old and young participants.

Right Hand: Switch Response Time
Task performance by each group is summarized in Figure 2. For right-hand SwRT, there were main effects of Resultant Pattern, with SW»ASYMM trials requiring more time than SW»SYMM trials (SW»ASYMM 723 ± 35 ms, SW»SYMM 653 ± 33 ms; $F_{1,28} =$

68.9, $P < 0.001$), and Group, with old participants responding slower compared with young (Old 745 ± 37 ms, Young 630 ± 34 ms; $F_{1,28} = 7.0$, $P < 0.05$). No other effects reached significance (notably, there was no Group × Resultant Pattern interaction, $F_{1,28} = 0.02$, $P = 0.9$). For variability of right-hand SwRT, there were main effects of Group (Old 196 ± 24 ms, Young 142 ± 13 ms; $F_{1,28} = 7.2$, $P < 0.05$), Resultant Pattern (SW»ASYMM 191 ± 15 ms, SW»SYMM 146 ± 16 ms; $F_{1,28} = 29.8$, $P < 0.001$) and Direction (CW 180 ± 19 ms, CCW 158 ± 19 ms; $F_{1,28} = 4.9$, $P < 0.05$). The Group × Resultant Pattern interaction was significant ($F_{1,28} = 4.7$, $P < 0.05$) with post hoc comparisons indicating that variability between groups did not differ significantly for SW»SYMM (Old 165 ± 21 ms, Young 129 ± 10 ms; $P = 0.2$) but was significantly greater for SW»ASYMM in the old participants (Old 228 ± 21 ms, Young 155 ± 9 ms; $P = 0.004$). These results confirm 1) that SW»ASYMM is "hard," whereas SW»SYMM is "easy," 2) that the elderly exhibit a general slowing of cognitive–motor performance, and that performance variability increases with task difficulty to a greater extent than in younger adults.

Left Hand: Contralateral Disruptions during Right-Hand Switch
Partial contralateral disruptions in the left hand were more prevalent for SW»ASYMM (SW»ASYMM 36 ± 4%, SW»SYMM 28 ± 3%; $F_{1,28} = 11.2$, $P < 0.01$), but no other effects were significant. For the duration of partial disruptions, there was a main effect of Resultant Pattern with longer disruptions for SW»ASYMM than SW»SYMM ($F_{1,27} = 35.1$, $P < 0.001$) and a Group × Resultant Pattern interaction ($F_{1,27} = 5.0$, $P < 0.05$). Complete contralateral disruptions were more prevalent in the old group (Group main effect $F_{1,28} = 9.7$, $P < 0.01$) and for SW»ASYMM trials (Resultant Pattern main effect $F_{1,28} = 10.0$, $P < 0.01$). Both the Group × Resultant Pattern ($F_{1,28} = 7.1$, $P = 0.01$) and Direction × Resultant Pattern ($F_{1,28} = 6.4$, $P = 0.01$) interactions were significant. Specifically, the old participants exhibited more complete disruptions on SW»ASYMM trials, when the right-hand switched direction CCW (Old 20 ± 6%, Young 3 ± 1%; $P = 0.02$). This was also the condition in which partial disruptions were longest for the old group. In this instance, an outward circling pattern (left-hand CCW and right-hand CW) should become a CCW circling pattern (both hands CCW). However, the nondominant hand of the old participants was involuntarily drawn to the production of symmetrical inward movement (CW circles) with respect to the body midline. Interestingly, spontaneous phase transitions favor simultaneous inward movements (Byblow et al. 1994). It appears that older individuals find it particularly difficult to suppress this innate preference.

Neural Basis of Motor Switching
Below we report the results of our event-related FMRI analysis of motor task switching. We first outline the common network for motor task switching by the conjunction of each groups Switch > Continue activation. We then report the results of our hypothesis driven ROI analysis of the SMA's and BG nuclei. Next, we outline the regions where activation is greater in the old group. Based on our results indicating reduced BG function and a higher incidence of contralateral disruption in the elderly for SW»ASYMM, we examine whether any of the overactive cortical areas scale with the differential difficulty of this condition. Finally, we report an exploratory analysis highlighting the potential neural correlates of contralateral disruptions.
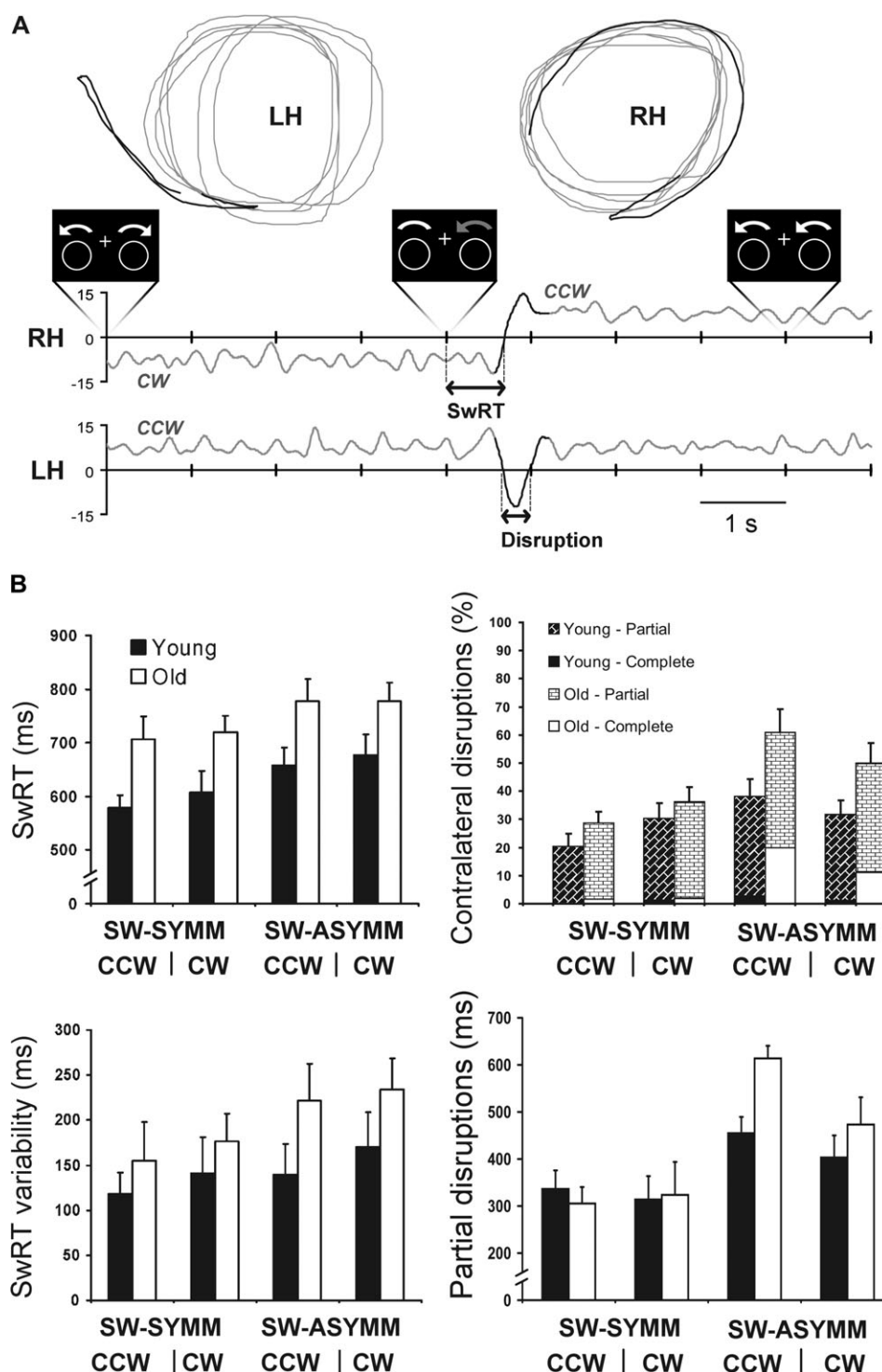
Figure 2. Behavioral task performance. (*A*) Representative trace from 1 participant performing symmetric circles followed by a switch to asymmetric circles (LH: left hand and RH: right hand). Top—Left- and right-hand joystick displacement, bottom—Radial velocity plotted against time. Positive radial velocity, CW circles. Negative radial velocity, CCW circles. The trace segments in dark gray highlight the right-hand Switch and Contralateral Disruption of the left hand. (*B*) Young and Old participant's behavior. Top left—SwRTs of the right hand. Bottom right—SwRT variability. Top right—Disruptions of the contralateral (left hand) during a right-hand Switch. Bottom right—Duration of partial contralateral disruptions. Within-subject factors Resultant Pattern (SW»SYMM; SW»ASYMM) and Switch Direction of right hand (CW; CCW). The combination of these factors indicate the specific movement pattern following a switch, for example, SW»SYMM resulting from right hand CCW = Inward bimanual circles, SW»ASYMM resulting from right-hand CW = Clockwise bimanual circles.

The General Network for Motor Task Switching: Common Activation in the Young and Elderly

We investigated brain regions that were similarly activated during motor task switching by first determining Switch > Continue statistical parametric maps (SPMs) for each age group (RFX analysis, 1-sample *t*-tests). Then, the conjunction Old ∩ Young was calculated using the method suggested by Nichols et al. (2005). To correct for multiple comparisons, a common false discovery rate (FDR *P* < 0.01 overall) was used. Using this approach, common activation reflects that SPMs of both groups

survive the FDR correction, that is, each group map is individually significant, whereas distinct activation indicates only one SPM survived correction. The results of this analysis are shown in Figure 3 (for coordinates and *t* values, see supplementary online material, Table 1). Activation common to both groups included bilateral insular cortex, inferior frontal gyrus (IFG), dorsolateral prefrontal cortex (DLPFC), dorsal and ventral premotor cortex, the BG (putamen, pallidum, STN region), superior and inferior parietal lobes, and cerebellum (lobules VI and crus 1). Within the medial wall there was activation of anterior cingulate cortex (both anterior and posterior rostral cingulate zones; RCZa, RCZp), pre-SMA, SMA-proper, and precuneus.

Between-Group Analysis of A Priori ROIs

The behavioral results confirmed that motor switching required more time for the elderly and was most difficult for SW»ASYMM trials. To test our hypothesis that behavioral decline is associated with reduced function within the SMA-BG circuit, we conducted an ROI analysis (2 Group × 2 Switch trial type × 10 Brain Region ANOVA). The PSC for each group and switch trial type is shown in Figure 4. There was a main effect of Region ($F_{9,252} = 10.2$, $P < 0.001$), a Region × Group interaction ($F_{9,252} = 2.2$, $P < 0.05$), and a Region × Switch trial type interaction ($F_{9,252} = 7.7$, $P < 0.001$). The Group × Region × Switch trial type interaction was also significant ($F_{9,252} = 2.7$, $P < 0.05$).

A planned contrast revealed that old and young participants differed with respect to BG activation for the 2 types of Switch trial. Compared with the young group, the old group showed slightly stronger activation in many BG nuclei for SW»SYMM. In contrast, the old group showed relatively weaker BG activation for the difficult SW»ASYMM condition (SW»SYMM: Old 0.16 ± 0.04%, Young 0.11 ± 0.05%; SW»ASYMM: Old 0.06 ± 0.05%, Young 0.16 ± 0.04%; $F_{1,28} = 5.1$, $P = 0.03$). Post hoc comparisons revealed that when old participants switched to the
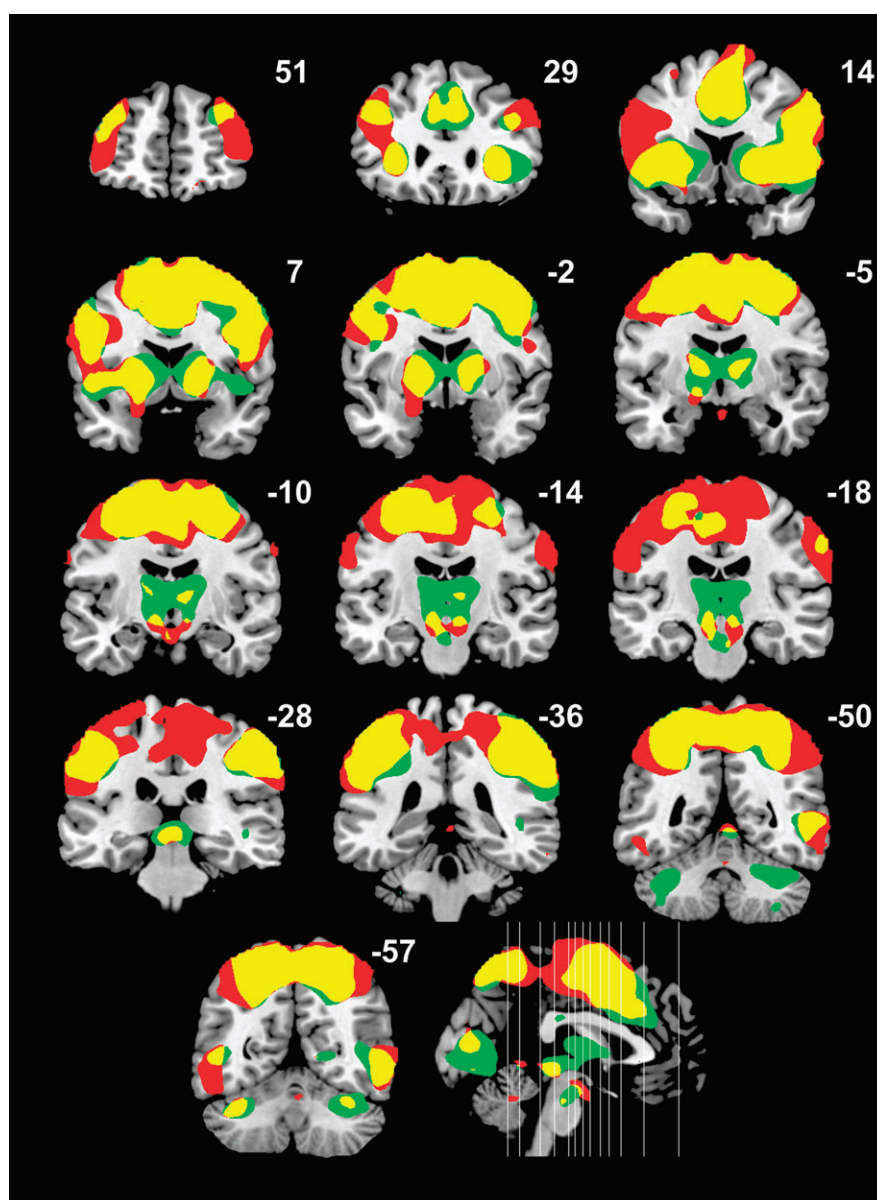
Figure 3. Event-related analysis of Switch > Continue. Coronal sections. Yellow—Conjunction Old ∩ Young. Red—distinct activation in the Old. Green—distinct activation in the Young. Activations survived correction for multiple comparisons (RFX analysis, FDR < 0.01).
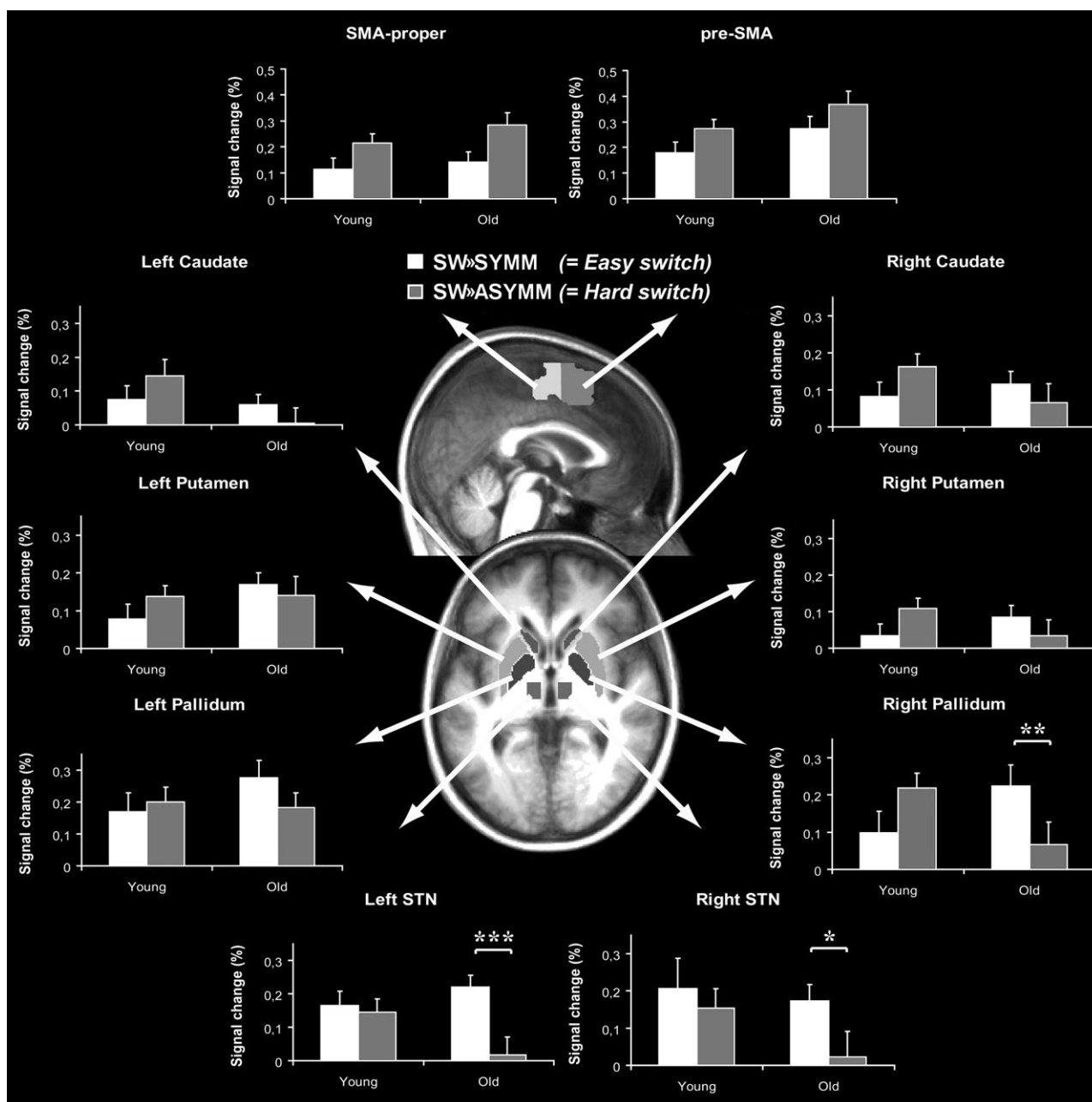
Figure 4. ROIs are overlaid on the average anatomical image of the Old group (MNI space). PSC is shown for each region, group, and switch trial type. White bars—Switches to symmetric movement patterns (SW»SYMM). Gray bars—Switches to asymmetric movement patterns (SW»ASYMM). Significant post hoc comparisons *$P < 0.05$, **$P < 0.01$, and ***$P < 0.001$.

asymmetric pattern (i.e., a hard switch), activation in bilateral STN and right globus pallidus was significantly reduced (Fig. 4).

An additional analysis confirmed that group differences did not result from differential responses to the baseline condition, that is, Continue trials. For this ANOVA, both the main effect of Group and the Group × Region interaction did not reach significance ($F_{1,9} \leqslant 0.92$, $P \geqslant 0.51$).

To further explore the relationship between BG activation and behavior, we correlated PSC on SW»ASYMM trials with the right-hand differential switch cost (i.e., the SwRT difference: SW»ASYMM − SW»SYMM), for each region and group. Consistent with the finding of reduced BG activation, there were no regions in the old group showing correlations that were significantly different from zero. In contrast, the young group showed significant positive correlations with differential switch cost in SMA-proper, left putamen, right STN, and the right globus pallidus, that is, subjects with greater differential switch costs had larger activation on SW»ASYMM trials (SMA-proper: Young $r_{15} = 0.66$, Old $r_{15} = -0.00$; Left putamen: Young $r_{15} = 0.52$, Old $r_{15} = -0.16$; Right STN: Young $r_{15} = 0.53$, Old $r_{15} = -0.07$; Right globus pallidus: Young $r_{15} = 0.53$, Old $r_{15} = -0.12$, all Young $P < 0.05$).

Between-Group Analysis Revealing Overactivation in the Old Group for Switch > Continue

The location of distinct activation for each group in Figure 3 suggests the old participants relied more on cortical regions

(DLPFC, IFG, and sensory and parietal cortex bilaterally) to perform motor task switching, whereas the young group showed more prominent subcortical activation (distinct activations in BG and cerebellum). To determine whether activation was significantly greater in the old group, an independent samples t-test was performed for the event-related analysis of Switch > Continue. Directly comparing the old and young group revealed several cortical regions where activation was greater in the old group including left angular gyrus and IFG, and right inferior parietal cortex, SMA, and DLPFC (Fig. 5A, for coordinates and $t$values, see supplementary online material, Table 2). There were no areas with significantly greater activation in the young group. Further, there were no differences between the age groups when only looking at Continue trials.

Overactivation Correlates Positively with Differential Switch Cost in the Old Group

Positive correlations with differential switch cost were found in the BG for the young but not the old group (as mentioned earlier). To investigate whether any cortical regions correlated with this measure in the old group, we conducted a multiple linear regression analysis for SW»ASYMM > Continue, with differential switch cost as the covariate. A mask was used to constrain the search to those regions that were more active for the old group (Old$_{Switch>Continue}$ > Young$_{Switch>Continue}$ at a height threshold of $P < 0.01$). A significant positive relationship was observed in right DLPFC, only for the old group (RFX analysis, family wise error correction (FWE) $P < 0.05$ at the cluster level, Fig. 5B). That is, old participants with greater differential switch costs had larger DLPFC activation on SW»ASYMM trials. Furthermore, the slope of the relationship was significantly greater in the old group than the young group (using the same statistical criteria).

Neural Signatures of Contralateral Disruptions of the Left Hand Accompanying the Right-Hand Switch

The total percent contralateral disruptions (partial + complete) of the left hand (due to the right hand switch) for each individual was entered as a covariate into a multiple linear regression model. This analysis tests whether activity in any brain regions predicted the likelihood of left hand disruption. This whole-brain analysis of SW»ASYMM > Continue revealed 2 clusters exhibiting a significant negative main effect (RFX analysis, FWE $P < 0.05$ at the cluster level). The right anterior precuneus and left caudal putamen were more active in those subjects with fewer disruptions (Fig. 5C). This was a general effect that did not significantly differ between groups.

Discussion

This study examined, for the first time, age-related changes in behavior and neural activity when intentionally switching between coordinated movement patterns of differential difficulty. Such flexible adjustments of behavior are an expression of executive function, reflecting one's ability to adapt to sudden environmental contingencies (Gilbert and Burgess 2008). Here, we show that older individuals have decreased agility, that is, difficulty suppressing and flexibly adapting their motor behavior. Further, the elderly exhibited insufficient activation of key BG nuclei in the most difficult conditions, that is, where SwRT was longest and the right-hand switch frequently interfered with left-hand movement (contralateral disruptions were most prevalent

for SW»ASYMM). Activation in several of the SMA-BG ROIs correlated positively with differential switch cost in the young but not in the old group. Engaging these regions may be necessary on SW»ASYMM trials to break the spatiotemporal coupling of homologous muscles, inherent to mirror-symmetric coordination patterns. In contrast, overactivation in a cortical area, right DLPFC, correlated positively with differential switch cost in the old group, suggesting the use of an alternate strategy with increased demands on cortical executive areas to counteract reduced BG function.

Behavioral Observations and the General Network Supporting Motor Task Switching

The behavioral results showed that switching to an asymmetric movement pattern (hard switch) required more time, was more variable, and resulted in more contralateral disruptions than when the switch resulted in symmetric movements (easy switch). These findings corroborate previous behavioral experiments in young individuals (Byblow et al. 1999, 2000; Wenderoth et al. 2009). Here, we extend these observations by showing that they are more pronounced in the elderly, despite movements being paced at a slower rate. Although older individuals had longer SwRT's than young adults, indicative of a general age-related slowing, they were easily able to switch right hand direction according to the visual cue. However, they experienced greater contralateral disruption, that is, involuntary left-hand direction change, when switching to asymmetric patterns, compared to their younger counterparts.

Both groups showed common activation of many regions when performing the right-hand switch, including bilateral insular, dorsolateral prefrontal and premotor cortex, and right IFG along with mesial frontal cortex; RCZa, RCZp, pre-SMA, and SMA-proper. The majority of these regions have been identified as reflecting a "core" network for the implementation of task sets (Dosenbach et al. 2006), in particular, pre-SMA is essential for initiating a switch of task set (Rushworth et al. 2002).

We observed strong activation of the SMA's in both groups during motor task switching. Further, activation of both pre-SMA and SMA-proper increased with increasing task demands (i.e., was higher for SW»ASYMM than SW»SYMM). Recordings from neurons in primate cortex while switching between movements indicate that pre-SMA contributes to both suppressing an automatic action and resolving preresponse conflict so that the desired action can be selected (Isoda and Hikosaka 2007). In contrast, the STN, which receives direct projections from the SMA's, appears selective for suppressing the automatic action (Isoda and Hikosaka 2008). In the next section, we focus on results associating reduced BG function (STN in particular) with task switching deficits of the elderly.

Age-Related Differences in Basal Ganglia Activation When Switching between Coordination Modes of Differential Difficulty

Our study revealed reduced BG activation in the old group for the more difficult SW»ASYMM condition. Structural equation modeling, a measure of functional connectivity, provides evidence of an age-related decline in cortico-subcortial (BG) connectivity during movement initiation (Taniwaki et al. 2007). Reduced BG activation in the present study could be the result of altered cortico-subcortical functional connectivity that occurs with advancing age.
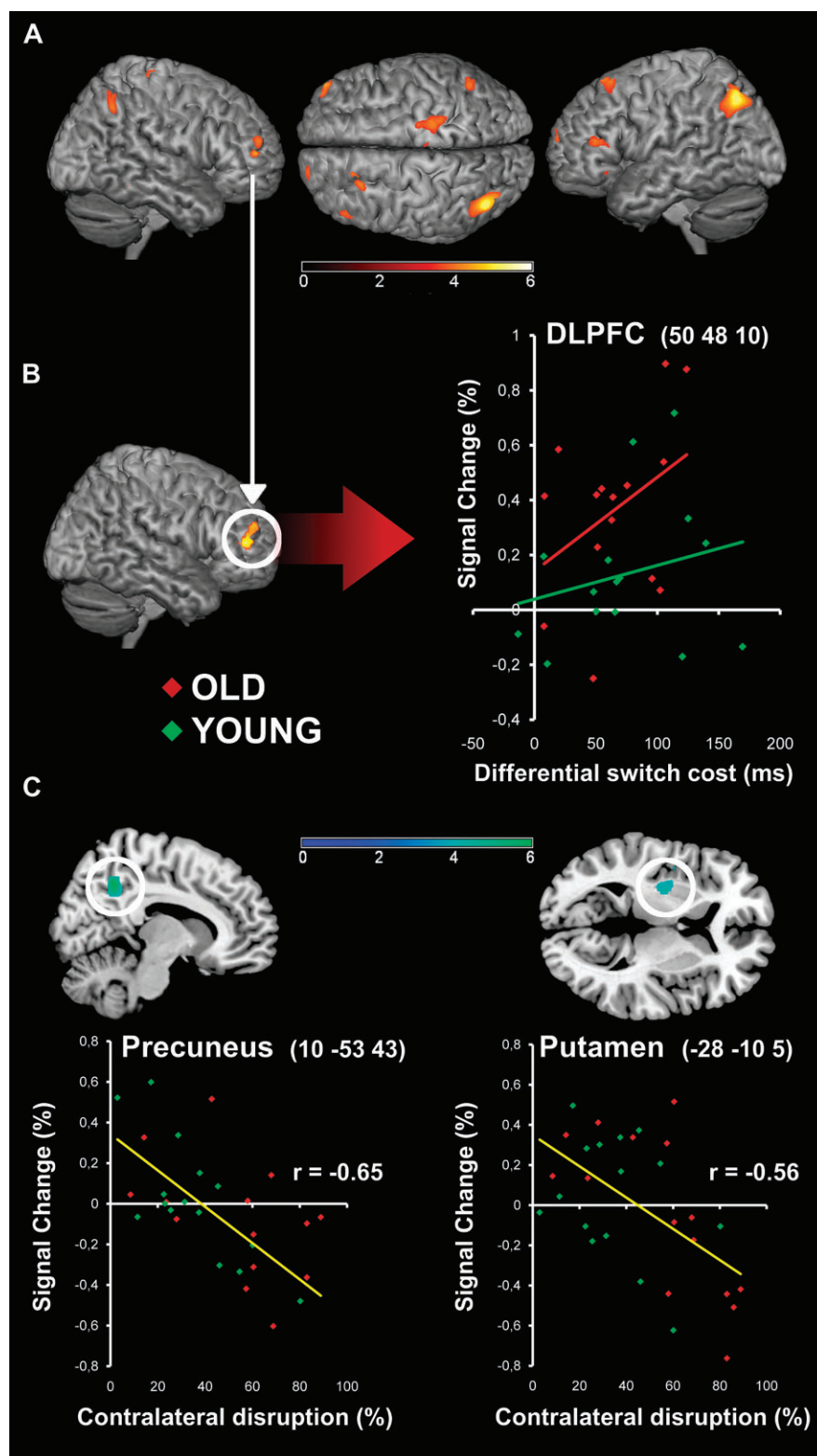
Figure 5. (A) Regions that were more active for Old than Young for the event-related analysis of Switch > Continue (RFX analysis, height threshold $P < 0.001$). (B) Multiple linear regression of SW»ASYMM > Continue with cost of switching to an asymmetric movement pattern via the right hand as the covariate. Within the regions that were more active in the old (i.e., masked using contrast depicted in A, at a reduced height threshold $P < 0.01$), a significant positive relationship was observed in rDLPFC, only for the old group (RFX analysis, height threshold $P < 0.001$, FWE $P < 0.05$ cluster corrected). Color bar is the same as for A. (C) Multiple linear regression of SW»ASYMM > Continue with contralateral disruption prevalence in the left hand as the covariate. A significant negative main effect was found in right precuneus and left caudal putamen (RFX analysis, height threshold $P < 0.001$, FWE $P < 0.05$ cluster corrected). Both of these regions were also shown for the conjunction of Old ∩ Young.

The elderly failed to activate the bilateral STN region and the right globus pallidus to a similar extent as young subjects. In contrast to the direct BG pathway, the indirect and hyperdirect BG pathways involve the STN and are thought to participate in the suppression of undesired actions (Mink 1996; Nambu et al. 2002). The STN inhibits cortex by reducing thalamocortical drive via its excitatory influence over the globus pallidus, which in turn has an inhibitory influence over thalamus. We interpret the elderly's reduced BG activation by considering this physiologically plausible model of cortico-BG interactions. There are prominent cortico-subthalamic projections from the SMA complex (pre-SMA and SMA-proper) (Nambu et al. 1996, 2002; Inase et al. 1999; Aron, Behrens, et al. 2007), and this projection is thought to play a critical role in the inhibition of motor responses (Aron and Poldrack 2006; Aron, Durston, et al. 2007; Duann et al. 2009). It is tempting to relate the elderly's deficit of motor task switching, as evidenced by their greater incidence of contralateral disruption, to impaired inhibitory control and/or movement initiation difficulties as discussed next.

More specifically, it is possible that STN activation is needed to temporarily decouple the left hand from the right hand when the right hand switches. This would be necessary if the dominant hemisphere plays a superordinate role during bimanual movement, for which there is some evidence (Swinnen et al. 1996; Viviani et al. 1998; Serrien et al. 2006; Coxon et al. 2007). The inability to recruit STN and right globus pallidus to suppress undesired BG output to cortex on SW»ASYMM trials may have exposed the elderly right hemisphere to planning of the right hand switch by the left hemisphere. In contrast, young participants may have been more able to overcome this source of interference due to activation of the SMA-BG circuit. This is supported by the observation of positive correlations between SW»ASYMM > Continue activation in SMA-proper and several BG nuclei with the differential switch cost and a lower incidence of contralateral disruption in this group.

An alternative account for our results is that the changes observed in the elderly BG reflect a decreased ability to initiate the more difficult asymmetric bimanual coordination pattern. In young adults, increased activation of the putamen has been shown during the initiation of asymmetric as compared with symmetric patterns (Kraft et al. 2007). This is perhaps related to direct pathway activation to facilitate desired action. We show changes in a different part of the BG, the STN, which is not part of the direct pathway and therefore consider this alternative account less likely. Nevertheless, the elderly exhibited reduced BG activation for SW»ASYMM overall, and we cannot exclude this interpretation.

Overactivation of Cortical Regions May Counteract Reduced Basal Ganglia Function

The elderly may have adopted a different strategy when switching to the more difficult coordination mode. The right DLPFC showed a significant positive correlation with differential switch cost in the old group, the same measure that revealed correlations in the SMA-BG circuit of young participants. Old participants with greater differential switch costs potentially relied on working memory to a greater extent when selecting the required movement pattern (Curtis and D'Esposito 2003; Passingham and Sakai 2004). The DLPFC (Brodmann area 46) is strongly connected with pre-SMA (Luppino et al. 1993), which in turn has recently been suggested to directly influence primary motor cortex during task switching (Mars et al. 2009). Using paired-pulse transcranial magnetic stimulation, a pre-SMA to primary motor cortex pathway (unlikely to involve the BG), was shown to facilitate the desired movement representation during switching but it did not produce strong inhibition of the undesired movement representation. This cortico-cortical pathway may have been relied upon to mediate switching in a less efficient way by some of the old participants in our study.

Neural Correlates of Contralateral Disruption Prevalence

Although contralateral disruptions were more frequent in the elderly overall, there was high interindividual variability within both groups. Some participants had virtually no disruptions, whereas others had a high incidence of disruption. Two regions correlated negatively with contralateral disruption prevalence. In both anterior precuneus and left caudal putamen, better performance (less disruption) was associated with greater activation on difficult switch trials. This was the case for both the main effect and when each group was looked at separately. The anterior precuneus has been associated with top down attentional control and monitoring of the spatial relationship between limbs (Wenderoth et al. 2005; Cavanna and Trimble 2006). Participants activating this region may have been more effective at directing attention toward both hands during the right-hand switch. The caudal putamen is involved in motor functions, receiving strong efferent input from both primary motor cortex and SMA-proper that overlap substantially (Inase et al. 1996; Lehericy et al. 2004). SMA-proper is frequently coactive with caudal putamen (Postuma and Dagher 2006), and to some extent, connections originate from both hemispheres (Lehericy et al. 2004). Precisely how left caudal putamen mediates a motor phenomenon in the ipsilateral left hand is unclear. We speculate that reciprocal loops with secondary motor areas, for example, SMA-proper, determine whether an individual's nonswitching hand is susceptible to disruption.

Motor Task Switching, Age, and Neurodegenerative Disease Involving the Basal Ganglia

Our result of decreased BG function when healthy elderly switch between motor tasks is interesting in light of findings in PD. We have shown that BG activations are positively correlated with switch costs in young adults. Further, healthy elderly show insufficient activation of key BG nuclei during the most difficult switch conditions and there appears no correlation between BG activation and switch cost in this group. Cognitive task switching deficits in PD patients appear to depend on disease progression and medication state at the time of testing (Cools et al. 2001, 2003; Kehagia et al. 2009). Furthermore, a positive relationship between switch cost and increasing disease severity exists (Helmich et al. 2009; Kehagia et al. 2009), and this is associated with decreasing globus pallidus activation (Helmich et al. 2009). Together these findings suggest that a continuum exists for the relationship between motor task switching and BG function that parallels BG integrity. It is interesting that the switching deficits in old compared to young participants appear more pronounced than those between PD and healthy age-matched controls (Byblow et al. 2002; Kehagia et al. 2009). Stated differently, it appears that the healthy old lie closer to (early stage) PD patients along the BG functional continuum than to young adults.

Summary and Conclusions

Using event-related FMRI, we investigated intentional switching between bimanual coordination tasks in aged adults for the first time. The old group showed less functional engagement of the BG (bilateral STN and right globus pallidus) when switching to the more difficult coordination mode, and left-hand movement was strongly influenced by the right-hand switch. Although young participants activated an SMA-BG circuit to overcome the potent coupling inherent to mirror-symmetric coordination, the elderly relied on cortical areas to a greater extent, with overactivation of right DLPFC presumably counteracting reduced BG function. We propose that the elderly were less successful than young participants in recruiting an inhibitory BG circuit during switching, needed to temporarily decouple the nondominant hand from dominant hand to promote an alternative coordination mode.

Funding

Supplementary Material

Supplementary material can be found at: http://www.cercor.oxfordjournals.org/.

Notes

Conflict of Interest: None declared.

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