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From preparation to online control: Reappraisal of neural circuitry mediating internally generated and externally guided actions

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Action plans internally generated (IG) from memory are thought to be regulated by the supplementary motor area (SMA), whereas plans externally guided (EG) online using sensory cues are believed to be controlled by the premotor cortex. This theory was investigated in an event-related fMRI study that separated the time course of activation before and during movement to distinguish advance planning from online control. In contrast to prevailing theory, the SMA was not more important for online control of IG actions. EG movement was distinguished from IG movement by greater activation in a more distributed right hemisphere parietal–frontal network than previously reported. Comparisons between premovement and movement periods showed that frontostriatal networks are central for preparing actions before movement onset. However, unlike cortical and cerebellar regions, the basal ganglia exhibited planning-related activity before, but not during, movement. These findings indicate that the basal ganglia mediate planning and online control processes in different ways and suggest a specific role for the striatum in internally planning sequences of actions before they are implemented.

Keywords: Basal ganglia; Cerebellum; Functional magnetic resonance imaging; Motor cortex; Motor sequencing; Parietal cortex; Premotor cortex; Supplementary motor area; Thalamus

Introduction

Humans are remarkably proficient at learning large repertoires of skills, nearly all aspects of which require sequencing actions. Central to controlling action sequences are planning operations, which encompass a broad range of cognitive processes that allow us to anticipate events, select movements, specify their ordering, and control actions online. Plans for some sequential behaviors, like performing the tango, are internally generated (IG) since dance steps are implemented by retrieving a memory representation of an action sequence that fits the music. Plans for other sequential behaviors, like stepping on the brakes and steering to avoid an oncoming car, are externally guided (EG) because the actions are strongly associated with visual or other sensory cues that dictate when and how to act. It remains a matter of considerable debate, however, as to whether IG and EG actions involve fundamentally different planning processes that are mediated by distinct brain systems. The prospect that IG and EG movements come under different neural control is suggested by the observation that people with Parkinson's disease have problems performing movements generated from memory but often overcome this difficulty when provided with an external sensory cue (Glickstein and Stein, 1991).

To explore this issue, previous studies have used "free-movement", "free-selection", or "spontaneous willed-action" tasks wherein different movements or sequences of movements are self-generated on each trial (Hunter et al., 2003). Functional activity during these tasks is contrasted with tasks in which the same movements are guided by auditory or visual cues. An assumption is that plans for IG actions are intention-based because they are driven by an internal "urge" or desire whereas plans for EG actions are stimulus-based because they are guided online by external cues. The common finding is that supplementary motor area (SMA) activation is greater during IG movement and lateral premotor activation is greater during EG movement (Jenkins et al., 2000; Tanji, 1996). This suggests that the SMA is crucial for planning and executing actions generated from memory whereas the lateral premotor cortex mediates planning movements that are guided by visual or other sensory cues (Goldberg, 1985).

Still, evidence supporting neuroanatomically distinct mechanisms for these two routes to action is limited in part because the tasks used to study IG behaviors place greater demands on processes that are only peripherally related to planning movements from memory. This is because in IG tasks the subject

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selects an action from a repertoire of behaviors, with the constraint that the same action cannot be repeated on successive trials. For this reason, differences in activation patterns between IG and EG actions may be more related to the greater demands of IG actions on maintaining and updating working memory, attending to multiple actions, and/or response conflict monitoring (Lau et al., 2004). It has also been difficult to elucidate distinct neural mechanisms for intention- and stimulus-based planning because in the laboratory IG and EG actions are highly predictable since the repertoire of potential movements is typically quite small (e.g., one or two movements) to ensure that both types of actions are equivalent. As a consequence, IG actions are partly stimulus-guided in that they are well specified by external task instructions rather than "spontaneously" generated as sometimes implied. In fact, the distinction between these two routes of action may be overdrawn in the laboratory and real world (Waszak et al., 2005) since IG behaviors require some level of stimulus guidance from the environment to specify actions for a behavioral context. Similarly, though EG actions are guided online by stimulus information, they require some internal planning. Thus, a more pivotal distinction may be that IG-generated behaviors are planned and implemented from memory whereas EG behaviors are planned online with the aid of sensory information.

In the present study, subjects underwent event-related fMRI while performing IG and EG motor sequences. We asked whether IG and EG actions are modulated by neuroanatomically distinct mechanisms when executive processing demands of IG movements are minimized. To investigate this question, we focused on a central difference between the two routes to action, namely that IG action plans are prepared, retrieved, and implemented from memory whereas EG action plans are formulated online using sensory cues to guide performance. To increase planning and online control demands, a large repertoire of actions (i.e., 9 different sequences) was used so that movements were not highly predictable from trial to trial. We also separated the time course of activation associated with planning and executing movements, which enabled us to (1) identify the neural systems that were associated with planning IG movements and holding them in memory (IG premovement) from those involved in motor readiness/anticipation (EG premovement) and (2) determine whether the neural control of IG and EG actions differed during movement (IG versus EG movement). This design also allowed us to distinguish neural systems principally associated with generating action plans (IG premovement) from those involved in retrieving and implementing plans from memory (IG movement). Despite its theoretical importance, this issue has received little consideration in neuroimaging studies of motor control. Unlike previous studies, two levels of sequence complexity were also used to identify differences in neural activation patterns associated with increased difficulty in advanced planning and online control (Harrington et al., 2000). We reasoned that sequence complexity should exert a differential effect on brain activation for IG and EG sequences during movement if they differ in the difficulty of online control processes. Similarly, regions principally associated with formulating plans in memory should show a greater effect of sequence complexity before movement (IG premovement), whereas those more involved in retrieving and implementing plans from memory should show a greater effect of sequence complexity during movement (IG movement).

Methods

Participants

Twenty-six healthy volunteers participated in this study (14 females; mean age = 29.3 years, range = 19 and 50; mean education = 16.2 years, range = 12 to 22). All subjects were strongly right-handed according to the Edinburgh Handedness Inventory (Oldfield, 1971) (mean laterality quotient = 89.0, range = 65 to 100). Subjects were excluded if they had significant neurological, psychiatric, or other medical history, were taking psychoactive medications, or if their response accuracy fell below 70% correct on one or more of the experimental conditions. Additional exclusion criteria were specific to MR scanning: pregnancy, weight inappropriate for height, ferrous objects within the body, low visual acuity, and a history of claustrophobia. Written informed consent was obtained from each subject in accordance with institutional guidelines approved by the Medical College of Wisconsin.

Motor sequencing task

The sequencing task in the current experiment replicated two of the eight conditions reported in our previous study (Harrington et al., 2000). Subjects performed finger key presses in response to numeric sequences presented on a computer-generated display rear-projected onto an opaque screen located at the subject's feet. Subjects viewed the screen through prism glasses and corrective lenses, if necessary; viewing distance was 230 cm. The index (1), middle (2), and ring (3) fingers of the right hand were placed on piano-like response keys that were arranged horizontally on a box taped to the subject's right thigh and occluded from sight. Digits 1, 2, and 3 corresponded to the left, middle, and right keys. Two sequence conditions were employed: the *simple* (S) condition required five consecutive key presses using the same finger and cued with a numerical sequence consisting of "11111", "22222", or "33333", whereas the *complex* (C) condition consisted of heterogeneous sequences involving all 3 fingers and cued with the following sequences: "12131", "23231", "32321", "13121", "21313", or "31212". Subjects were instructed not to move the left hand. A typical trial (Fig. 1) consisted of a "READY" signal (500 ms) followed by a *premovement* cue (1500 ms), a delay (4000 or 6000 ms), a *movement* cue (3500 ms), and visual feedback ("correct" or "wrong"; 500 ms). During the inter-trial interval (ITI; 2000 or 4000 ms), subjects fixated a central fixation cross.

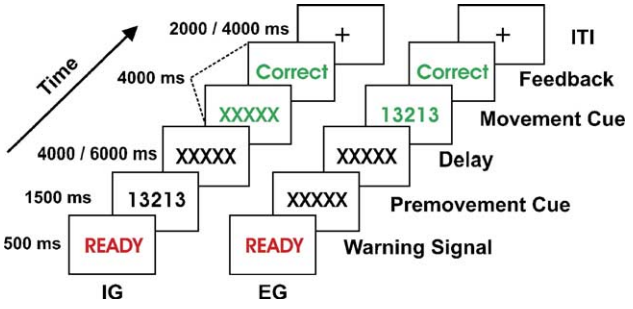

Fig. 1. Temporal relationship between trial events for the internally generated (IG) and externally generated (EG) conditions. An example complex sequence is shown.

Two cuing conditions (Fig. 1) were employed: for the *externally guided* (EG) condition, subjects were presented a non-informative premovement cue ("XXXXX") followed by an informative movement cue (e.g., 12131), whereas for *internally guided* (IG) condition, subjects were presented an informative premovement cue (e.g., "12131") followed by a non-informative movement cue ("XXXXX"). For both the IG and EG conditions, subjects were instructed to perform the sequences as quickly and accurately as possible following the presentation of the green-colored movement cue. Thus, for the EG condition, subjects performed the sequences based on a visual cue; for the IG condition, subjects performed the motor sequence based on information held in working memory. During the IG trials, subjects were instructed to think about the sequence, but to refrain from moving their fingers and lips during the delay period. All four trial combinations (EG-S, EG-C, IG-S, IG-C) were randomly presented within each experimental block.

The study design consisted of two sequence types (S and C), two cue types (EG and IG), and two delay periods, yielding eight conditions. Each condition was randomly presented six times within one block, for a total of 48 trials per block. Subjects performed 4 blocks (i.e., 4 imaging runs) during the scanning session. Subjects briefly practiced the sequencing conditions prior to scanning (25 trials).

The behavioral-dependent measures were accuracy (percent correct), reaction time (RT), and movement time (MT). All five key presses are needed to be executed in the specified order for the trial to be classified as correct. Incorrect trials were excluded from the RT and MT analyses. RT was defined as the time between the presentation of the movement cue and the first key press; MT was the time between the first and last (fifth) key press. RT generally reflects time to plan the movement sequence, although motor implementation time for the first key press is also included. MT reflects online planning, motor implementation processes, and the influence of biomechanical factors associated with different effectors. Separate repeated measures analyses of variance were used to determine whether accuracy, RT, and MT were affected by sequence complexity, cuing type, or their interaction.

Functional imaging acquisition

Functional MRI was conducted on a 1.5 T General Electric Signa scanner equipped with a prototype 30.5 cm i.d. three-axis local gradient head coil and an elliptical endcapped quadrature radiofrequency coil allowing whole-brain functional imaging. Echo-planar (EP) images were collected using a single-shot, blipped, gradient-echo echo-planar pulse sequence: echo time (TE) = 40 ms, repetition time (TR) = 2 s, 90° flip angle, data acquisition time = 40 ms, field of view (FOV) = 24 cm, resolution = 64 × 64. Nineteen contiguous sagittal 7-mm thick slices provided coverage of the entire brain (voxel size: 3.75 × 3.75 × 7 mm). Scanning was synchronized with the onset of the first trial and each trial thereafter, with a total of 324 images per run. There were 24 14-s trials, 12 16-s trials, and 12 12-s trials, for a total scanning duration of 696 s. An additional 6 images (12 s) were added to the beginning of the run to allow the MR signal to reach equilibrium and were discarded from further analysis. Six images were also added to the end of the run to accommodate the delayed fall of the hemodynamic response. Prior to functional imaging, high-resolution 3D spoiled gradient-recalled at steady-state (GRASS) anatomic images were collected: TE = 5 ms, repetition time (TR) = 24 ms, 40° flip angle, number of excitations (NEX) = 1, slice thickness = 1.2 mm, FOV = 24 cm, resolution = 256 × 192, for anatomic localization and co-registration.

Functional image analysis

Each image time series was spatially registered in-plane to reduce the effects of head motion using an iterative linear least squares method. A deconvolution analysis was used to generate hemodynamic response functions (HRFs) of the fMRI signal on a voxel-wise basis. Only correct trials were incorporated into the estimate of the HRF, which was modeled for the 2–16 s period post-trial onset. This analysis produced an HRF estimate for each condition (EG-S, EG-C, IG-S, IG-C) relative to a baseline state (rest), without making a priori assumptions regarding the shape, delay, or magnitude of the HRF. Anatomical and functional images were then interpolated to volumes with 1 mm^3 voxels, co-registered, converted to Talairach stereotaxic coordinate space, and blurred using a 4 mm Gaussian full-width half-maximum filter. For the *premovement* period, we calculated the change in the MR signal intensity, defined as the area under the curve (AUC) of the HRF, for the images obtained 4–8 s post-trial onset. The *movement* period was defined as the AUC occurring 4–6 s post-presentation of the movement cue (i.e., 10–12 or 12–14 s post-trial onset depending on the delay length).

The first stage of the group analysis consisted of defining functional regions of interest (ROI). This was accomplished by identifying voxels that exhibited a difference in HRF across any of the four conditions (EG-S, EG-C, IG-S, or IG-C). Voxel-wise one-way ANOVAs were conducted separately on the AUC estimates derived from the movement and premovement periods. Significant ROIs were defined by both a statistical threshold (Omnibus $F(1,25) = 22.72$, $P < 1 \times 10^{-10}$) and a minimum cluster size (200 μl). This threshold was chosen to maximize differentiation of regions, without sacrificing functional regions that might otherwise be included at a more liberal threshold. Twelve functional ROIs were defined by conjoining the premovement and movement maps (that is, any voxel found to be significant by either of the two ANOVAs was included in the final map). Averaged HRFs were then calculated for each of the 12 functional ROIs for each subject as a function of cue type and sequence complexity.

For each functional ROI, we performed three comparisons using 2 × 2 repeated-measures ANOVAs (see Introduction and Results for rationale). The first comparison focused on the effect of cue type (IG, EG) and sequence complexity (S, C) during the premovement period. The second examined the effect of cue type and sequence complexity during the movement period. The third focused only on the IG condition, comparing period (premovement, movement) and sequence complexity. To adjust for multiple comparisons, a Bonferroni correction was applied (significance threshold set at $P < 0.004$).

Results

Behavioral findings

All participants performed the sequences at a minimum accuracy level of 90% correct per sequence condition (Fig. 2, top panel). Simple sequences were performed more accurately than complex sequences [$F(1,25) = 22.5$, $P < 0.0001$], but neither

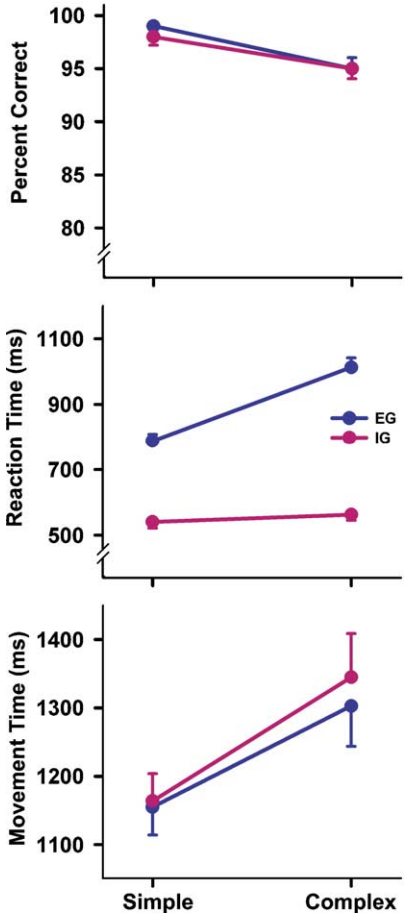

Fig. 2. Percent correct (top panel), reaction time (middle panel), and movement time (bottom panel) for the simple and complex motor sequences as a function of cue type (IG, internally guided; EG, externally guided). Error bars = SEM.

the main effect of cue type (IG vs. EG) nor the interaction of cue type with complexity was significant. For reaction time (RT; Fig. 2, middle panel), significant effects were observed for cue type [$F(1,25) = 470.0$, $P < 0.0001$], complexity [$F(1,25) = 86.5$, $P < 0.0001$], and their interaction [$F(1,25) = 123.8$, $P < 0.0001$]. The interaction demonstrated that, while RTs were faster for IG than EG sequences, the effect of complexity on RT was attenuated when participants were provided information about the to-be-performed sequence (IG) well before movement initiation. These results show that some aspects of preparing IG sequences facilitated RTs. The fact that complexity still affected RTs for IG sequences is likely due to the longer time needed to retrieve and reactivate more complex programs for IG sequences (Sternberg et al., 1978). For movement time (MT; Fig. 2, bottom panel), significant effects were observed for cue type [$F(1,25) = 7.8$, $P < 0.01$], complexity [$F(1,25) = 24.2$, $P < 0.0001$], and their interaction [$F(1,25) = 4.4$, $P < 0.05$]. The interaction effect indicated that MT was longer for IG than EG complex sequences [$F(1,25) = 8.01$, $P < 0.01$)], but not for simple sequences. Though EG sequences also involve preplanning (i.e., complexity effects on RT), these findings demonstrate that visual information aided in planning more complex movements as they were executed, perhaps because less demand is placed on internal control processes.

Functional imaging findings

Table 1 and Fig. 3 display 12 functional ROIs demonstrating differential brain activation patterns across the four sequence conditions (IG-S, IG-C, EG-S, EG-C) and two trial periods (premovement, movement) (see Methods for details). Fig. 4 displays the HRFs for each of the 12 ROIs as a function of cue type (IG, EG) and complexity (S, C). For each subject, MR signal intensity values were averaged within each functional ROI for each condition (IG-S, IG-C, EG-S, EG-C) and trial period (Premovement, Movement) and subjected to three 2-way analyses of variance (ANOVA) analyses. The three ANOVAs, summarized in Table 1, consisted of the following comparisons: (1) IG premovement vs. EG premovement, (2) IG movement vs. EG movement, and (3) IG premovement vs. IG movement.

IG premovement vs. EG premovement

First, we compared functional activation between the IG and EG premovement periods to determine if activation in the ROIs differed when action plans are generated and held in memory (IG premovement) than when an action is anticipated, but the specific movements are unknown (EG premovement). This analysis identified regions that were involved in (1) response selection (main effect of cue) and (2) perception, planning, and representation of actions (main effect of complexity and interaction), irrespective of the "readiness" to perform an action (EG premovement). We did not expect complexity effects in the EG premovement condition because the cue was uninformative regarding sequence structure.

Table 1 (IG-PRE vs. EG-PRE column) summarizes the results from the Cue × Complexity repeated-measures ANOVA. There were three main findings. First, as expected, all 12 regions demonstrated greater activation during IG premovement than EG premovement (cue main effect). Second, all 12 regions demonstrated greater activation during complex than simple movement sequences (complexity main effect). Third, complexity and cue type interacted in all regions with the exception of the left sensorimotor cortex (SMC). Follow-up tests of this interaction showed a complexity effect for the IG premovement, but not for the EG premovement period. These results are illustrated in Fig. 5 for selected regions, including the SMC.

IG movement vs. EG movement

Next, we compared functional activation between IG and EG movements to determine if movements under visual control differed from movements performed from memory. Results of the Cue (IG vs. EG) × Complexity (Simple vs. Complex) ANOVA are presented in Table 1 (IG-MOV vs. EG-MOV column). Right hemisphere parietal (superior and inferior), premotor (dorsal and ventral), and frontal eye fields (FEF) regions were activated more during the EG than the IG condition (cue main effect; Table 1 and Fig. 6) independent of sequence complexity. Similar regions in the left hemisphere did not demonstrate this relationship. In addition, complex movements produced greater MR signal change than simple movements (main effect of complexity) in virtually all regions, irrespective of whether the sequences were IG or EG (Table 1).

IG premovement vs. IG movement

This analysis asks whether neural networks that support generation of action plans (IG premovement) are distinct from those

Table 1
Coordinates, volume and two-way ANOVA results for functional regions of interest (ROI)

	Coordinates			VOL	IG-PRE vs. EG-PRE			IG-MOV vs. EG-MOV			IG-PRE vs. IG-MOV		
Functional ROI (BA)	*x*	*y*	*z*	ml	Cue	Com	Int	Cue	Com	Int	Per	Com	Int
Frontal													
[1] B SMA, CMA (6, 24, 32)	−3	0	50	4.4	*	*	*[a]	–	*	–	–	*	*[b]
[2] L SMC	−36	−21	51	1.5	*	*	–	–	*	–	*	*	–
[3] L premotor (6)	−47	−4	30	3.5	*	*	*[a]	–	*	–	–	*	–
[4] R premotor (6)	44	1	24	0.3	*	*	*[a]	*	*	–	–	*	*[b]
[5] L frontal eye field (6)	−27	−8	51	2.3	*	*	*[a]	–	*	–	–	*	–
[6] R frontal eye field (6)	26	−9	51	0.9	*	*	*[a]	*	*	–	–	*	–
Parietal													
[7] L parietal, precuneus (40,7)	−33	−50	43	13.3	*	*	*[a]		*	–	–	*	*[c]
[8] R parietal, precuneus (40, 7)	29	−56	43	5.6	*	*	*[a]	*	*	–	–	*	–
Subcortical													
[9] L basal ganglia (P, GP, LN)	−16	−1	9	1.5	*	*	*[a]	–	–	–	–	*	*[b]
[10] R basal ganglia (P, GP, LN)	14	1	8	0.4	*	*	*[a]	–	–	–	–	*	–
[11] L thalamus	−13	−17	9	1.8	*	*	*[a]	–	*	–	–	*	–
[12] R cerebellum (IV, V, VI)	27	−51	−23	0.8	*	*	*[a]	–	*	–	–	*	–

Numbers in brackets refer to ROIs defined by voxel-wise analysis (see Methods) and shown in Fig. 3. Coordinates (center of mass) represent distance in millimeters from anterior commissure: *x*, right (+)/left (−); *y*, anterior (+)/posterior (−); *z*, superior (+)/inferior (−). Abbreviations: BA, Brodmann area; VOL, volume; IG, internally generated; EG, externally generated; PRE, premovement; MOV, movement; Cue, externally generated > internally generated; Com, complexity (complex > simple); Per, period (movement > premovement); Int, interaction effect; L, left; R, right; B, bilateral; SMA, supplementary motor area; CMA, cingulate motor area; P, putamen, GP, globus pallidus; LN, lentiform nucleus; SMC, sensorimotor cortex. *$P < 0.004$; –= nonsignificant.
Simple effects analysis of interaction effects: [a]IC > IS > EC = ES; [b]complexity effect larger during IG-PRE than IG-MOV; [c]complexity effect larger during IG-MOV than IG-PRE.
[d]Schmahmann et al. (1999) atlas.

involved in retrieving and implementing them from memory (IG movement). Table 1 (IG-PRE vs. IG-MOV column) displays results from the Period (IG-PRE, IG-MOV) × Complexity ANOVA. There were three main findings. First, as demonstrated in previous analyses, activation in all regions was greater for complex than simple sequences and the left SMC exhibited greater activation during the movement than premovement period. Second, an interaction of Period × Complexity was observed in the left basal ganglia, SMA/CMA, and right premotor cortex (Fig. 7), indicating that sequence complexity had a greater effect on activation before than during movement. Again, this pattern of activation was especially prominent in the left basal ganglia, which showed no effect of sequence complexity on activation during movement. Third, the left parietal cortex exhibited a significant interaction, but, in this instance, sequence complexity played a greater role during the movement than premovement period (Fig. 7).

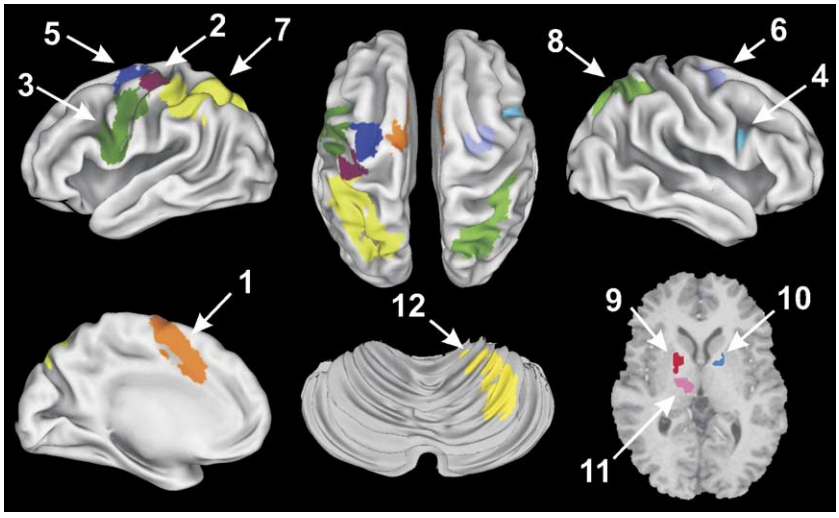

Fig. 3. Twelve functional regions of interest (ROIs) corresponding to Table 1 (numbers in brain images correspond to bracketed numbers in table). See Methods for details regarding generation of functional ROIs. Region 3 includes dorsal and ventral premotor areas; region 11 includes medial and lateral dorsal thalamic nuclei; region 7 includes supramarginal gyrus.

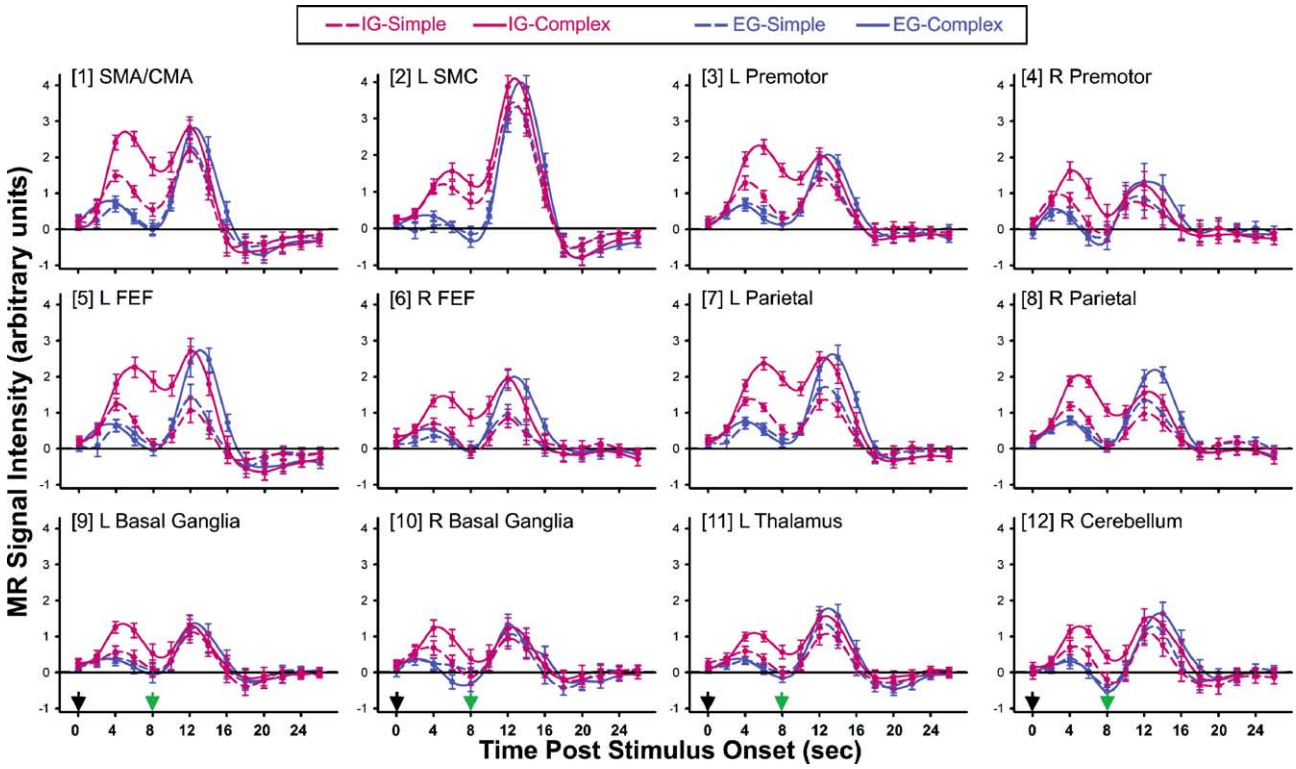

Fig. 4. Hemodynamic response functions (HRFs) representing the 26 s period post-trial onset (Fig. 1) for the 12 functional ROIs (Table 1, Fig. 2). Four HRFs are presented as a function of cue type (IG, internally generated; EG, externally generated) and sequence complexity (Simple, Complex). Premovement period began at 0 s (black arrow) and movement period at 6 or 8 s (green arrow) depending on length of delay interval (HRFs displayed for trials with 6-s delay only). SMA/CMA = supplementary motor area/cingulate motor area; SMC = sensorimotor cortex; FEF = frontal eye fields; L = left; R = right. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

SMA proper versus pre-SMA activation

The SMA proper and pre-SMA are hypothesized to be functionally distinct with regard to IG and EG movements (Deiber et al., 1999; Hoshi and Tanji, 2004). To address this issue, we subdivided the SMA/CMA ROI (4.4 ml) into two regions (pre-SMA and SMA/CMA) based on anatomical landmarks. The pre-SMA ROI was defined as any voxel located anterior to the vertical anterior commissure (VAC) line and rostral and superior to the

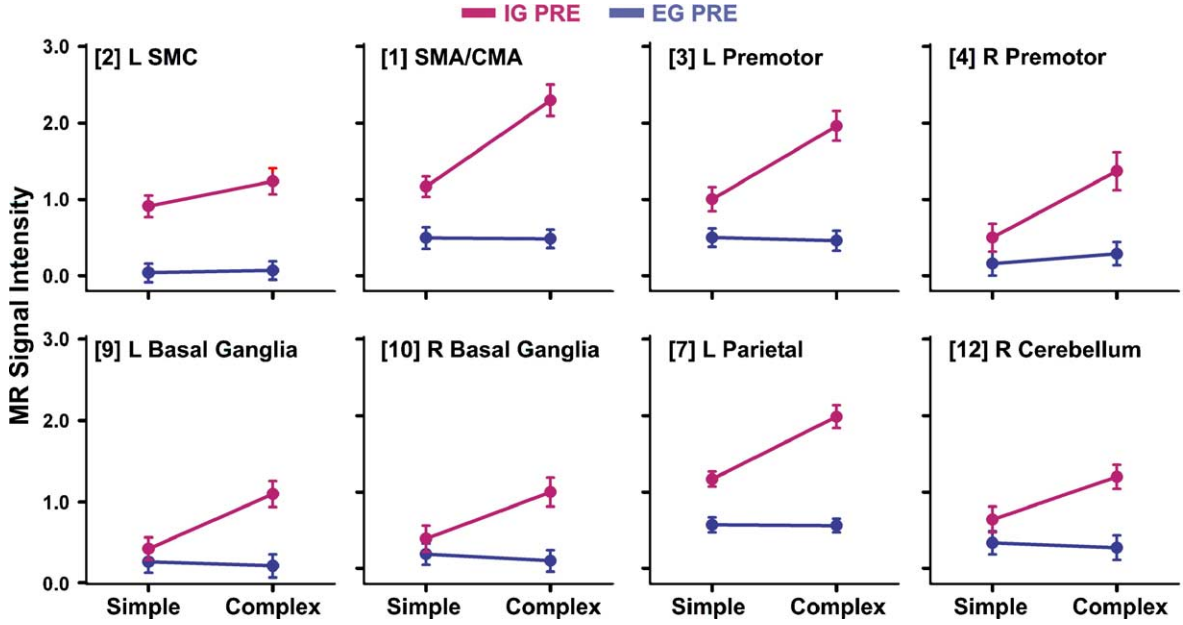

Fig. 5. MR signal intensity for the cue (IG-PRE, EG-PRE) and complexity (Simple, Complex) conditions for eight ROIs: left sensorimotor cortex (SMC), midline supplementary motor/cingulate motor areas (SMA/CMA), left parietal cortex, bilateral premotor cortex, bilateral basal ganglia, and right cerebellum. All interactions were significant except the left SMC, indicating an absence of a complexity effect during the IG-PRE condition. Error bars = SEM.

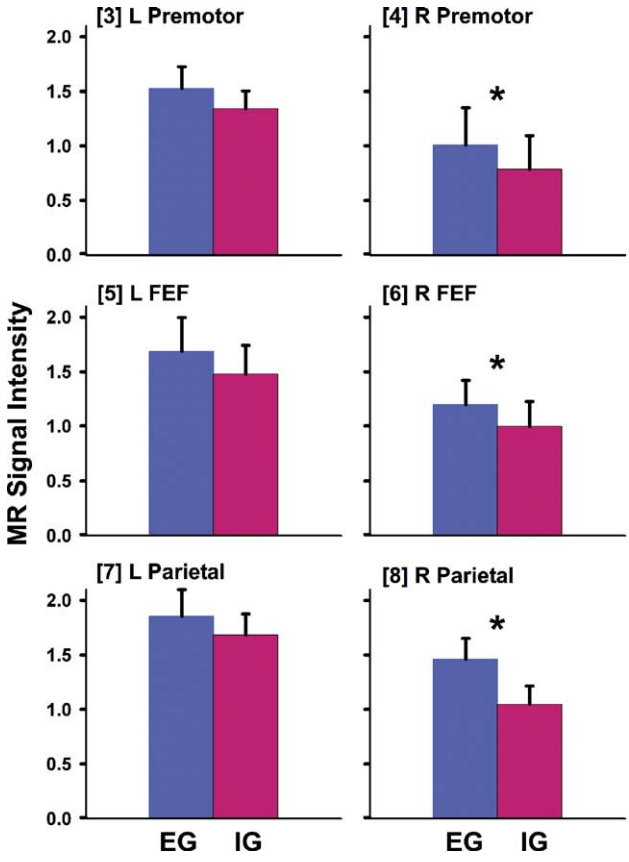

Fig. 6. MR signal intensity for the IG-MOV and EG-MOV conditions collapsed over sequence complexity for six ROIs: left and right lateral premotor cortex, left and right parietal cortex, and left and right frontal eye fields. Note that only right hemisphere regions demonstrate significantly greater activity during EG than IG movements. L = left; R = right. Error bars = SEM.

cingulate sulcus (Picard and Strick, 1996). The resulting pre-SMA volume was 0.4 ml, approximately 9% of the original SMA/CMA ROI. Thus, most of the original SMA/CMA ROI was comprised of the caudal portion of the SMA (SMA proper). We then compared the effects of complexity and ROI (pre-SMA versus SMA/CMA) in all three comparisons (IG versus EG premovement, IG versus EG movement, and IG premovement versus IG premovement). No significant ROI main effects or interactions were observed.

Discussion

The present results provide new insight into the neural basis and functional significance of purported differences between IG and EG actions and, more generally, planning and online control processes. By separating the time course of brain activity during the premovement and movement periods and comparing the effects of sequence complexity, we showed that IG and EG actions could be distinguished by activation related to controlling movements online. While we did not find that medial premotor areas (SMA/CMA, pre-SMA) were more important for implementing IG than EG sequences, lateral premotor cortex activation was greater for EG than IG sequences, consistent with previous findings. Interestingly, the neural control of online planning processes was similar for IG and EG actions as the effects of sequence complexity on brain activation were the same, irrespective of the route to action. More generally, sequence complexity exerted a larger effect on activation in the basal ganglia, SMA/CMA, and lateral premotor cortex during IG premovement than IG movement, which demonstrates that frontal–basal ganglia circuits play a greater role than other regions in advance planning.

Motor circuit

Activity within the frontal–basal ganglia circuits was further distinguished by the effect of sequence complexity during the IG and EG movement periods on activation in the SMA/CMA and premotor cortex, but not the basal ganglia. This contrasted with the robust effect of sequence complexity on basal ganglia activation during the IG premovement period. Although we could not directly compare the IG premovement period with an analogous EG premovement period, this pattern of findings suggests that one key distinction between the two routes to action may relate to the role of the basal ganglia in internally planning movements before they are executed. This is the first study in humans to dissociate the time course of activation in these regions and report that the basal ganglia specifically modulate planning processes that are engaged when formulating a plan of action before movement. Though many studies have shown that sequence complexity affects SMA and premotor cortex activity, this typically is not found in the basal ganglia (Catalan et al., 1998; Dassonville et al., 1998; Harrington et al., 2000; Rao et al., 1993), possibly due to the use of externally guided sequences or over-learned, predictable sequences, which minimize planning requirements. Exceptions are two studies reporting an association between basal ganglia activation and sequence complexity (Boecker et al., 1998; Lehericy et al., 2006). The functional significance of these findings is unclear, however,

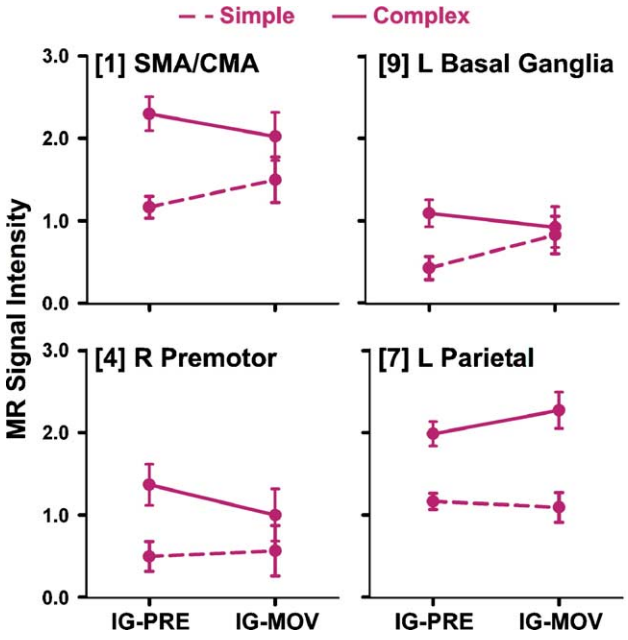

Fig. 7. MR signal intensity for period (IG-PRE, IG-MOV) and complexity (Simple, Complex) for four regions. SMA/CMA, left basal ganglia, and right premotor regions demonstrate a greater complexity effect during IG-PRE than IG-MOV. In contrast, left parietal region demonstrates greater complexity effect during IG-MOV than IG-PRE (Table 1). Error bars = SEM.

because of their reliance on blocked-trial designs, which cannot distinguish planning from movement-related processes. This is a limiting factor when studying traditional "motor" structures because variables that influence activity in primary sensorimotor systems, such as the frequency and quantity of movement, also correlate with basal ganglia, premotor, and SMA activity (Kim et al., 2005; Lehericy et al., 2006; Taniwaki et al., 2003). In contrast, our results clearly show that changes in basal ganglia activity in association with sequence complexity cannot be attributed to motor factors.

The proposal that the basal ganglia play a central role in advance planning is consistent with its role in timing, which is an aspect of predicting "when" a behavior should take place. We have proposed that the basal ganglia structure movement and cognition by controlling temporal aspects of planning, such as sequencing and timing (Harrington and Haaland, 1991; Harrington et al., 1998; Rao et al., 2001), which guide behavior and learning by determining "when" and "how much" motor or cognitive activity, are needed. One physiological model suggests that this is due to striatal neurons' ability to detect synchronized patterns of cortical oscillations that are related to temporally significant events (Matell et al., 2003). The synaptic strength of cortical inputs to the striatum is thought to be modulated by a dopamine reward signal, which trains striatal neurons to respond to patterns of cortical activity that are relevant. This model is compatible with the proposal that the basal ganglia modulate cognition and movement in different ways depending on contextual goals. Before movement, entire sequences are planned, whereas during movement, subroutines for individual movements are implemented. The present results further suggest that, before movement, complex actions engage the striatum more than simple ones, perhaps because cortical input into the striatum is increased. This input may come from interconnected regions that also show stronger effects of planning before than during movement (i.e., SMA, premotor cortex). While sequence complexity did not affect basal ganglia activation during the movement period of IG or EG sequences, this does not mean that the striatum only regulates advance planning. Clearly, this is not the case since during IG and EG movement the level of basal ganglia activation for both simple and complex sequences was similar to that of complex sequences during the IG premovement period. Rather, our results suggest that the differential effect of complexity on basal ganglia activation during premovement and movement periods may relate to differences in the strength and/or type of cortico-striatal interactions associated with internal planning and online control processes. This speculation is consistent with Taniwaki et al. (2003), who reported that corticostriatal interactions were stronger for self-generated than sensory-guided movements. In their study, rate-dependent increases in motor circuit activity were found when performing a sequence that was timed from memory, but not externally paced by a metronome. A connectivity analysis showed strong interactions between the SMA and putamen only for internally timed movements. This result suggests that cortico-striatal interactions may be strengthened when the behavioral context places more demand on planning processes. In our study, the greater complexity effects on basal ganglia, SMA, and premotor cortex activity before than during IG movement might suggest that, once movements are planned, striatal interactions are stronger with sensorimotor centers involved in online control and monitoring of individual movements.

What then is the functional significance of cortical regions of the motor circuit such as the SMA? The role of the SMA in behavior remains elusive as many functions have been ascribed to this region including internal planning (Tanji and Shima, 1994), timing (Macar et al., 2004), sequencing (Shima and Tanji, 1998), and action retrieval (Chen et al., 1995). Our findings provide additional insight into this issue by showing that the magnitude of the BOLD response in SMA/CMA did not differ between IG and EG sequences during movement, or between IG premovement and movement, consistent with another study (Richter et al., 1997). During movement, sequence complexity also had a similar effect on SMA/CMA activation for both IG and EG sequences, suggesting that it is engaged to the same extent for online control. These results indicate that the SMA does not play a unique role in implementing IG actions, which contrasts with most (Tanji et al., 1996), but not all, studies (Cunnington et al., 2002). However, sequence complexity had a more striking effect on SMA activation before than during movement, suggesting that it is more involved in preparatory processes. These patterns of findings were the same for the pre-SMA and SMA proper, which is at odds with studies suggesting that the pre-SMA modulates internally initiated actions or more "cognitive" processes whereas the SMA mediates motor control processes such as selecting the type of movement (Deiber et al., 1999; Lau et al., 2004; Picard and Strick, 1996). Our results indicate that both regions play a similar role in internal planning and online control, irrespective of the route to action. At the same time, it is likely that our study design was not sensitive to other key underlying functional differences between these regions.

Planning-related activity in the SMA has been widely reported in self-paced movement tasks using imaging techniques that have excellent temporal resolution. Current source density studies of the Bereitschaft potential (Cui et al., 1999) and magnetoencephalography with MRI co-registration (Huang et al., 2004) show that the SMA and CMA are active earlier than primary motor areas. However, single cell recordings in monkeys (Hoshi and Tanji, 2004) suggest that SMA activity both before and during movement relates to using different effectors rather than the location of targets. This is consistent with the direct connections of the SMA to the primary motor cortex and descending output to the spinal cord (Dum and Strick, 1991). Still, SMA lesions do not disrupt execution of a simple movement (Chen et al., 1995; Shima and Tanji, 1998). Rather, they impair the ability to select movements from a repertoire of actions when there is no cue to remind what movement to make. This may explain why SMA activity correlated with the complexity of sequences since complex sequences involved a larger repertoire of finger movements. Collectively, this work seems to implicate the SMA in retrieving effector-dependent representations (Chen et al., 1995), likely from interconnecting cortical systems that represent actions. When the repertoire of movements is larger, retrieval is more difficult and, hence, has greater SMA activation. Retrieval demands are reduced during movement as an action unfolds and the "motor buffer" is emptied. The CMA, which is interconnected to SMA, may assist by monitoring retrieval and assessing conflict with representations of intended movements (Jueptner et al., 1997).

Parietal–lateral prefrontal networks and cerebellum

Sequence complexity also had a larger effect on premotor cortex activation before than during movement, consistent with greater activation in this area when movements are less predictable and more complex (Dassonville et al., 1998; Harrington et al., 2000). Unlike the SMA, however, the premotor cortex responds to

information about which effector to use *and* the goal of the movement, indicating that both types of information converge in this region (Hoshi and Tanji, 2000). This property may situate the premotor cortex for selecting action plans that are represented in the parietal cortex. This proposal would predict that premotor cortex activation should increase with the complexity of an action, even during the premovement period, consistent with our findings. It is also consistent with greater premotor cortex activation during EG than IG movement. Response selection processes should be more demanding during EG movements because, unlike IG movements, no advance information is provided about the sequence. Indeed, premotor, but not primary motor, activation is greater when prior knowledge about which of two fingers to move is not known than when it is given in advance (Schluter et al., 2001).

Although the premotor cortex has been singled out as preeminent for controlling externally triggered actions (Goldberg, 1985), greater activation for EG than IG movement was seen only in the right premotor cortex. In addition, EG movement was distinguished from IG movement by greater activation in a more distributed right hemisphere parietal–premotor–FEF network (Chafee and Goldman-Rakic, 1998; Schluter et al., 2001) than previously reported. The FEF is involved in preparatory processes related to saccadic eye movements (Connolly et al., 2002), whereas the parietal cortex is a multimodal region involved in interpreting sensory information and formulating higher-level representations that support cognition and movement. A right hemisphere parietal–FEF network has not been previously associated with EG movements but can be understood by considering the spatial demands of our sequencing task. Spatial information contained in the digit sequence must be analyzed and then translated into a plan of action involving specific fingers. In humans, hemispheric biases for attending to and processing information in spatial and body-centered frames of reference are commonly found in the right and left parietal cortex, respectively (Goldenberg, 1999). Our finding that sequence complexity exerts a similar effect on right parietal–FEF activation during the premovement and movement periods may suggest that attention to spatial aspects of sequences (e.g., position among fingers) is equally important before and during movement. Altogether, these results show that externally triggered actions place a greater emphasis on online processing in a right hemisphere parietal–prefrontal network that participates in attending to and transforming spatial information into a plan of action.

These results contrast with activation in the left parietal–prefrontal network, which did not differ between IG and EG sequences. Moreover, when IG premovement and movement periods were compared, sequence complexity exerted a greater effect on left parietal cortex activation during movement. This may reflect the greater importance of body-centered representations for executing action sequences (Haaland et al., 2000), perhaps because complex action plans are more difficult to translate into movement. Motor control in this network may be enhanced by the cerebellum, which monitors sensory and cognitive input. Like the left parietal cortex, ipsilateral cerebellar activation did not differ between IG and EG sequences during movement. These results demonstrate that the cerebellum is involved in the online control of movements, irrespective of whether they are self-generated or guided by visual cues (Jueptner et al., 1996). One speculation is that contralateral projections to the left parietal–prefrontal cortex (Dum and Strick, 2003) enable the cerebellum to play a subsidiary role in planning related to detection and adjustment of visuomotor errors (Ellerman et al., 1994). Notably, sequence complexity exerted a similar effect on cerebellar activation during the IG premovement and movement periods. Altogether, this pattern of results is consistent with the role of the cerebellum in monitoring both memory (Desmond et al., 1997) and sensory processes before and during movement.

Clinical implications

The above findings have implications for studying neurological disorders that disrupt cognitive aspects of movement. For example, individuals with Parkinson's disease exhibit striking impairments in using prior knowledge about entire sequences of movements to plan behavior (Harrington and Haaland, 1991). Our results suggest that impaired advance planning in these patients may be due to reduced output from the basal ganglia, which, unlike the cerebral cortex and cerebellum, showed planning-related activity only prior to movement. At the same time, impaired advance planning does not prevent individuals with Parkinson's disease from executing movements, although they move more slowly especially when transitioning between different movements (Benecke et al., 1987). This deficit may be related to akinesia (Laplane et al., 1977) or difficulty initiating voluntary movements, which is also seen after SMA lesions (Halsband et al., 1993). Diminished SMA activity in Parkinson's disease (Elsinger et al., 2003) may cause motor slowing due to problems in retrieving effector-dependent representations (Chen et al., 1995). While self-generated actions might be more vulnerable to diminished SMA functioning, externally triggered movements could also suffer if sensory guidance does not effectively activate effector-specific information. This prospect is consistent with sequencing deficits in Parkinson's disease even when visual cues remain available throughout performance (Georgiou et al., 1993; Harrington and Haaland, 1991). These examples illustrate how cognitive–motor dysfunction in neurological disorders might be better understood by distinguishing the neural mechanisms of planning and online control.

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