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## Human basal ganglia and the dynamic control of force during on-line corrections

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### Abstract

Natural movements are corrected in part by the generation of submovements, occurring early in a movement such that they amend an ongoing action. Submovements are associated with activity of the basal ganglia, implying a role for the structures in error correction. In parallel, the basal ganglia are linked to the generation and control of force amplitude, change and duration. Here we tested if activity in human basal ganglia is associated with submovements generally, or was specific to a condition where the submovements only occurred in the face of unexpected proprioceptive error. Submovements were induced by introducing unexpected and variable viscous loads (augmenting the need for trial specific grip forces) or by reducing target size (augmenting the need for visually guided on-line control) in a 1-D target capture task. In both cases, subjects compensated for the increased task difficulty by generating corrective submovements, which were closely matched in frequency and type. Activity in the internal segment of the globus pallidus and subthalamic nucleus correlated strongly with the number of submovements during the viscous challenge but not with the target challenge. The effects could not be explained by kinematic differences, i.e. movement amplitude or average number of submovements. The results support a specific role for the basal ganglia in error correction under conditions of variable load where there is a need for the dynamic control of force within an ongoing movement.

### Keywords

Motor control; on-line correction; error; adaptation; basal ganglia; human

### Introduction

Even under the best of conditions the control of visually guided behavior requires on-line corrections to reconcile performance errors. On-line corrections can be observed early in a movement, suggesting they rely on an internal model of expected plant dynamics (Kawato, 1999; Desmurget and Grafton, 2000). One approach for detecting early error correction is the identification of submovements in the kinematic trace during 1-D target capture. Submovements are identified as distinct peaks in the velocity trace (Novak et al., 2000, 2002), modeled as small bell shaped velocity profiles either superimposed onto or occurring after the primary movement (Fishbach et al., 2005). Single unit physiological recordings of

monkeys performing 1-D target capture demonstrate a modulation of neuronal activity in the internal segment of the globus pallidus (GPi) in association with submovement generation (Roy et al., 2008). In a 1-D target capture task in the presence of unpredictable viscous loads, human imaging shows a correlation of putamen activity with the number of submovements per trial (Tunik et al., 2009).

In parallel, there is strong functional imaging evidence that the human basal ganglia (BG) play a role in controlling many kinematic properties including movement velocity and amplitude in putamen and GPi (Turner et al., 1998; Turner et al., 2003; Spraker et al., 2007b), force duration in putamen (Vaillancourt et al., 2004; Prodoehl et al., 2008) and force rate of change and amplitude in GPi and subthalamic nucleus (STN) (Spraker et al., 2007b; Prodoehl et al., 2008). Of note, behavioral experiments show that both agonist and antagonist muscles will generate increased grip force in response to mechanical perturbations (Koshland and Hasan, 2000; Spraker et al., 2007b), including those used in 1-D target capture.

Given these two lines of evidence, it is unclear if the correlation of submovements with BG activity observed in humans (Tunik et al., 2009) is a general property of error correction or a specific product of generating forces to overcome viscous perturbations. The goal of the current study was to reconcile these alternative hypotheses. We focused specifically on parametric differences of activity in globus pallidus and putamen. To test the alternatives, half the trials were performed with a “viscous challenge” where a torque motor applied resistive forces that varied unpredictably in severity from trial to trial. The other trials used a “target” challenge, where the motor was off and hence reactive grip forces were relatively constant across trials and submovements. Instead, the task was made difficult, by varying the target width unpredictably across trials (Fitts, 1954). The two tasks were adaptively matched for movement amplitude and the number of submovements across trials. The critical prediction was that the BG would only scale with the number of submovements under the viscous challenge task, demonstrating specificity of the BG for generating force pulses during error correction. As an exploratory analysis the specific and general hypotheses were also tested in the cerebellum and cortex.

## Materials and Methods

### Subjects

Twenty-four right-handed (Oldfield, 1971) healthy young adults (mean age 23, range 18–33), 12 men: 12 women volunteered for the study after informed consent was obtained in accordance with the UCSB Human Subjects Committee.

### MRI

Functional MRI recordings were conducted using a 3T TIM Trio Siemens Magnetom with a 12-channel phased-array head coil. Foam padding was used for head stabilization. Each subject completed 6 functional runs using an echo planar gradient-echo imaging sequence sensitive to BOLD contrast with 33 slices per repetition time (TR) (3 mm thickness, .5mm gap), 236 TRs, and a TR of 2000ms, echo time (TE) of 30ms, flip angle of 90 degrees, field of view (FOV) of 192 mm, 64 × 64 matrix (voxel resolution 3×3×3.5mm). A gradient field map of the same image size was obtained to correct for geometric distortions. A high-resolution T1-weighted sagittal MPRAGE sequence of the whole brain was acquired for anatomic localization.

## Task

Participants performed the target capture task using their right-hand. They held a long PVC rod (with a comfortable wooden dowel handle) attached to a torque motor and position sensing hardware. The torque motor device and RF shielding have been described previously (Tunik et al., 2007b; Tunik et al., 2009). Participants viewed a back-projected flat screen 102 cm from the eyes, subtending 50° horizontal view with five (1° × 6°) rectangular targets aligned horizontally every 10°. Horizontal position of a 1° circular cursor was controlled by 1-D forearm rotation and used to capture targets appearing in random order. The timing of events is shown in figure 1. A trial started with the cursor held stationary in a target. Then a new target boundary was illuminated and subjects had to shift the cursor into this new position. Subjects were told to go as quickly as possible. The cursor became invisible at movement onset. Whenever the cursor was positioned over the target the latter instantly became color filled and would de-color if the cursor overshot the target. The cursor reappeared once it was stationary over a target for 300ms or when a trial timed out (1500ms). The position of the reappearing cursor provided knowledge of results and became the starting position for the subsequent trial. The average intertrial interval was 8.1 sec and varied from 5.2 to 12.8 sec. 50 trials were acquired per scan, with a total of 300 trials. In 3 scans of 50 trials each a torque motor was programmed to provide a positive velocity-dependent (viscous) torque field proportional to the subjects' velocity. Torque strength was randomly varied on a trial by trial basis with a maximum of  $-0.5 \text{oz-in/}^\circ\text{s}^{-1}$  [ $0.004 \text{Nm/}^\circ\text{s}^{-1}$ ] (Tunik et al., 2007b; Tunik et al., 2009). In the 3 other scans of 50 trials each, the torque field was off, but the width of the target was randomly varied between 3° to 9° from trial to trial. In pilot testing an adaptive algorithm was used to define a range of target widths so that the viscous and target challenge tasks were balanced in the distribution and number of submovements. The ordering of viscous and target challenge scans was randomized across subjects.

## Performance Analysis

Cursor position was sampled at 1500 Hz and smoothed offline with a Butterworth lowpass filter at 10 Hz. The position data was differentiated to yield a velocity trace. Movement onset was defined as the time at which the angular velocity exceeded and remained above 5% of the peak angular velocity for >100 ms. Movement offset was defined as the time at which the knob angle did not change by more than 5° for >0.4 sec. Movement time was defined as the interval between movement onset and offset. Movement amplitude was defined as the displacement (in angular terms) between the angle at the start and the maximal angular displacement in the corresponding trial. Each movement was decomposed into a primary movement and any submovements by computing the third derivative of the position (jerk) and identifying all zero crossings occurring between the movement onset and offset. The number of zero-crossings was divided by two to determine the total number of movements (velocity peaks) in a given trajectory. Subtracting the single primary movement from this number determined the number of submovements. The proportion of submovements overlapping with the primary movement was estimated as described previously (Tunik et al., 2009). Peak velocity and peak acceleration of the primary movement and time to first submovement were derived from the velocity and acceleration trace. Statistical tests were determined by paired t-test after averaging all trials within each condition per subject. Significance was adjusted for six multiple pairwise two-way comparisons of the kinematic measures (threshold  $p < 0.008$ ).

## Image Analysis

BOLD fMRI was preprocessed in SPM 5 by correcting functional scans for geometric distortion (Jezzard and Balaban, 1995) using the FieldMap V2.0 toolbox available in SPM 5, registering fMRI data within runs to each other, fitting this realigned fMRI data to each

subjects high resolution scan, spatially normalizing the anatomic and fMRI data to the canonical T1 template in SPM 5 and spatially smoothing the resultant functional data with an 8mm Gaussian filter. The cerebellum and brain stem were spatially normalized separately (Diedrichsen, 2006).

### Event Estimation

All trials were included in the analyses. Condition-specific components of the BOLD signal were identified with a general linear model and event-related fMRI. A design matrix was created for each subject with vectors containing the onset and duration of each movement, coded separately for each viscous or target challenge run. Vectors for the number of submovements per trial and movement amplitude (each adjusted to create a zero mean vector) were included separately for each run. This made it possible to correlate the mean number of submovements with the corresponding magnitude of the BOLD response on a trial by trial basis independent of movement related activity. Temporal derivatives for task, submovement, and amplitude events were included, along with blocking factors of non-interest to denote different scan runs. The design matrix was convolved with a canonical hemodynamic response function defined in SPM 5 and beta weights were estimated with the general linear model using restricted weighted least squares (Diedrichsen and Shadmehr, 2005).

### Contrast Estimation

For each subject, the following contrasts were generated: (1) an all trial (viscous + target) versus baseline contrast was generated to identify all task related areas. This contrast (with a threshold controlling for a false discovery rate FDR of  $p < 0.05$  to account for multiple testing) was used as an inclusive mask for all subsequent analyses of effects in the cortex (Supplemental figure 1). (2) Correlations between the number of submovements and BOLD activity were calculated separately for viscous and target challenge tasks. (3) Task specific differences between the correlation of BOLD activity with submovements were calculated by contrasting the viscous and target task parametric correlations calculated in (2) with each other. (4) Correlations between amplitude and BOLD activity were calculated separately for viscous and target challenge tasks. (5) Task specific differences between the correlations of BOLD activity with amplitude were calculated by contrasting the two task specific correlations in (4).

### Population Estimation

The above contrast images were entered into random effects analyses to characterize population-based effects. Based on the a priori anatomic hypothesis, a BG volume was drawn as a single contiguous anatomically defined large region of interest covering the striatum, insula, internal capsule, pallidum and midbrain. Task differences of submovement and amplitude modulation of BOLD activity in this region was tested at a threshold of  $p < 0.05$ , FDR, corrected for search volume. A second anatomically defined large region of interest covering the upper half of the cerebellum and brainstem was analyzed both with FDR correction and at  $p < 0.01$  uncorrected for exploratory purposes. Task differences in the cortex were tested at a threshold of  $p < 0.05$  FDR corrected within a mask defined by all trials versus rest.

## Results

### Behavior

Differences of movement kinematics were compared for trials performed under a viscous and target challenge. After correcting for multiple comparisons, there were no significant

differences in the movement amplitude (Viscous:  $23.0^{\circ} \pm 0.2^{\circ}$ , Target:  $22.7^{\circ} \pm 0.2^{\circ}$ ), time to peak acceleration (Viscous:  $218.9^{\circ}/s^2 \pm 19.0^{\circ}/s^2$ , Target:  $257.6^{\circ}/s^2 \pm 23.9^{\circ}/s^2$ ) the number of submovements (Viscous:  $2.66 \pm 0.17$ , Target:  $2.45 \pm 0.23$ ), or percentage of overlapping (Viscous: 91.6%, Target: 93.5%), discrete (Viscous: 7.6%, Target: 7.1%) or reversing (Viscous: 1.2%, Target: 1%) submovements. The distributions in the movement amplitude and in the number of submovements were similar for the two types of trials (supplemental figure 2). The time to onset for the first overlapping submovement was significantly faster for viscous ( $149.0 \pm 5.2$  ms) than target ( $175.2 \pm 6.8$  ms) trials ( $t: 6.51$ ,  $p < 0.001$ ,  $df: 23$ ). These compensatory response latencies are consistent with those reported in other online perturbation paradigms (Day and Marsden, 1982; Prablanc and Martin, 1992). Peak velocity (Viscous:  $35.0^{\circ}/s \pm 2.5^{\circ}/s$ , Target:  $45.7^{\circ}/s \pm 3.6^{\circ}/s$ ,  $t: 4.23$ ,  $p < 0.004$ ,  $df: 23$ ), and total time to complete a movement (Viscous:  $1.39s \pm 0.01$ , Target:  $1.47s \pm 0.01$ ,  $t: 11.07$ ,  $p < 0.001$ ,  $df: 23$ ) were significantly less for the viscous than the target task. In summary there was no difference in the frequency of submovements between tasks. There was a small difference in the timing of submovement generation, likely related to the proprioceptive feedback available in the viscous task. There was no evidence for greater velocity or acceleration in generating the primary movement in the viscous condition.

### Basal Ganglia activity during on-line correction

Image analysis was designed to identify where there was a positive correlation between the number of submovements generated per trial and BOLD activity in basal ganglia nuclei for the viscous, but not the target challenge.

At the group level, a random effects analysis corrected for multiple test comparisons demonstrated multiple sites in bilateral GPi, STN and putamen that correlated with the number of submovements in the viscous challenge task, as shown in red in figure 2. Critically, there was no positive correlation between submovements and activity in the same BG regions when subjects performed the target challenge task. These different effects of viscous and target challenge on basal ganglia activity and submovements was confirmed by comparing these parametric correlations directly. As shown in figure 2 in yellow, there was a significantly stronger correlation in the left GPi and STN with submovements formed with a viscous than target challenge. The exact loci and effect sizes for all of these areas are summarized in supplemental table 1. This pattern of activity is shown for activity in the left GPi/STN from a representative subject in figure 3. In addition, note that in the same region there is no correlation with overall movement amplitude for either task. Although movement duration differed between tasks, this was modeled explicitly for each trial in the image analysis and not likely to explain these effects.

The amplitude of a movement correlated significantly with activity in both caudate and putamen, with a left sided predominance, figure 4. This was true for both the target (blue) and viscous (red) challenge tasks. They overlapped in the right putamen/insula (purple). There was a stronger correlation between amplitude and BOLD activity for the target challenge task in a small portion of left dorsal putamen and caudate nucleus (green). Of note, none of the correlations of amplitude and BOLD activity in the basal ganglia overlapped spatially with the BOLD correlates with submovements (figure 2).

### Cerebellar and cortical activity during on-line correction

Within the cerebellum there was no significant correlation between the number of submovements and BOLD activity for either task. Nor was there a significant difference between tasks. Within the cortex, there was a significant correlation between the number of

submovements and BOLD activity in the viscous challenge task located within the bilateral intraparietal sulcus and right inferior parietal lobule as shown in supplemental figure 3.

Within the right anterior cerebellar cortex there was a modest correlation of activity with movement amplitude for both tasks with relatively greater amplitude modulation for the viscous than target challenge tasks. Within the cortex, both tasks showed a correlation between movement amplitude and activity in left premotor, motor and superior parietal cortex, supplementary motor area and cingulate motor area as shown in supplemental figure 4.

## Discussion

The main finding of this study was a selective correlation between the number of submovements generated per trial with activity in bilateral GPi and left STN, but only under conditions of a variable viscous load. This association was not observed when submovements were generated in the face of error due to difficult targeting requirements. This interaction of task and parametric modulation cannot be attributed to the main effect when comparing the two tasks directly, which by definition will differ in at least some measures of kinematics and task requirements. Indeed, while we observed modest kinematic differences in peak velocity and peak amplitude of the primary movement, these were greater for the target challenge task and this is unlikely to explain the critical association of submovement and viscous load. It is also unlikely that the small difference in the time to first submovement (28ms) is sufficiently large to explain these parametric effects, given the insensitivity of fMRI due to the smooth hemodynamic response function for detecting differences at such a fine time resolution. In summary, the parametric correlation approach adopted here allows us to establish the specific role of BG in submovement formation in the face of proprioceptive loads.

The dissociation between the viscous and target challenge tasks on submovement formation suggests that the GP and STN are involved in the on-line control of a movement under conditions where force control is particularly important. Whether this is related to detection/correction processes or force generation cannot be inferred directly as grip force was not measured. However, a number of human studies are consistent with the latter interpretation. Specifically, when challenged with a viscous perturbation there is a well-defined increase of force in agonist and antagonist muscles, irrespective of movement amplitude or duration (Koshland and Hasan, 2000). Thus, in our task, each submovement that was generated in the face of a viscous load led to a transient increase in grip force. The involvement of GP and STN in this process extends recent studies showing that under conditions of dynamic, continuous control the rate of change of grip force, as well as grip force amplitude correlate with activity in the same areas observed in the current experiment (Spraker et al., 2007a; Prodoehl et al., 2009). The present results allow us to suggest a more refined role for the basal ganglia in the on-line control of error corrections. While there is growing evidence from patient experiments that online corrections for motor perturbations are impoverished after dopamine depletion (Tunik et al., 2004; Tunik et al., 2007a), perhaps due to the basal ganglia's reliance on an internal model to make corrections, the current results show that this process is intertwined with the precise generation of forces needed as part of the overall correction.

The lack of correlations between GPi/STN activity and submovements in the target challenge task shows that there are different forms of error correction or force production determined by unique task demands. We speculate that in the target challenge task, the main source of detected error is visual rather than proprioceptive or kinesthetic. This would also explain the slower time to first submovement in the target challenge. Even though our task

used only 1-dimensional movements visual information could be used to define a difference vector error that is minimized on-line with motor output that does not require modulation of grip force that is tailored to each submovement, as in the viscous case. Previous studies of visuomotor control support a role for parietal-premotor cortices and cerebellum in visually guided error correction during reaching, consistent with the current results (Desmurget et al., 1999; Desmurget et al., 2001; Diedrichsen et al., 2005).

The second main finding was a correlation between movement amplitude and activity in the putamen and anterior cerebellum. This was true for both the viscous and target challenge task. This finding extends previous studies of movement amplitude based on tomographic blood flow scans (Turner et al., 2003) as well as fMRI studies examining the interaction of movement duration and force (Vaillancourt et al., 2004; Prodoehl et al., 2009). Large amplitude movements require force to be generated for a longer duration. The current results show this is true for all forces, i.e., whether there is a viscous load present or not.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

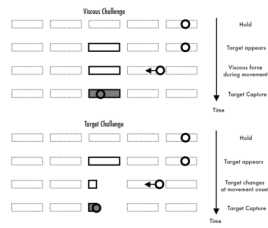
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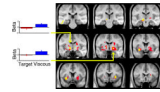
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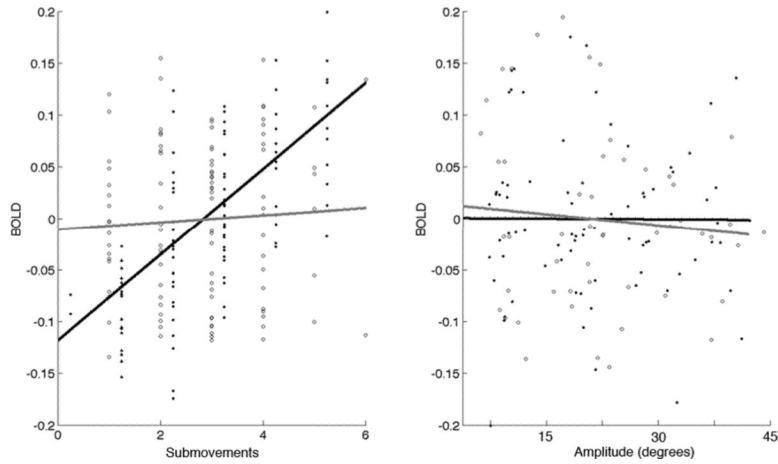
**Figure 1.**

A trial started with the cursor (circle) held stationary in a target (dotted box). Then a new target (solid box) boundary was illuminated and subjects had to shift the cursor into this new position as quickly as possible. Once the cursor was positioned over a target the latter became color filled. Movement direction and amplitude were randomly distributed across trials. In viscous challenge trials a different viscous force was applied on each trial, and the target size was constant. In target challenge trials there was no viscous force but the size of the target varied from trial to trial.

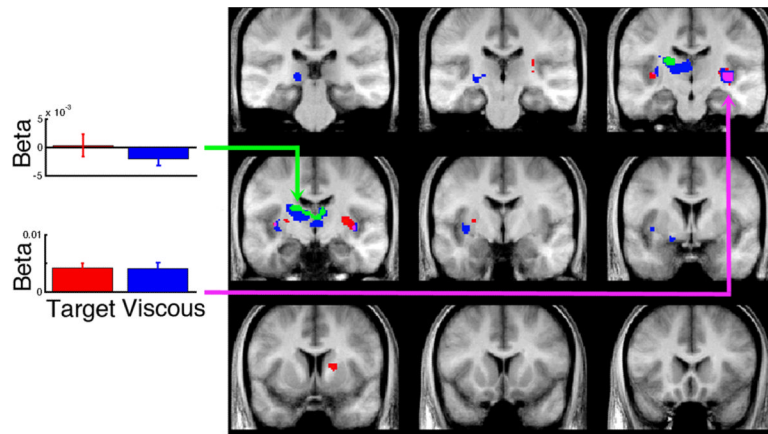


**Figure 2.**

Correlation of trial by trial submovements and BOLD activity in basal ganglia. Significant positive correlations for submovements at the group level, corrected for multiple test comparisons (FDR  $p < 0.05$ ) are shown in red for the viscous trials and blue for the target trials. Significant differences where the correlation with submovements was stronger for viscous than target challenge task are shown in yellow. On the left is plotted the mean beta  $\pm$  SEM for the entire population corresponding to the magnitude of the parameter correlating submovement and BOLD for the left GPi/STN (MNI:  $-14, -18, -6$ ) and right GPi (MNI:  $20, -10, -8$ ). Coronal sections are  $-30, -23, -16, -11, -4, 2, 9, 13, 20$ mm relative to anterior commissure.



**Figure 3.** Correlation of number of submovements (left) and movement amplitude (right) with BOLD signal intensity derived from a .5cm diameter sphere centered in the left GPi/STN (MNI coordinates: 14, -18, -6). BOLD intensity values (% change in signal, center meaned) were derived from model estimates and beta values in one representative subject. Note strong interaction of number of submovements and BOLD in viscous challenge task (black line) but not the target challenge task (grey line).



**Figure 4.**

Correlation of trial by trial movement amplitude and BOLD activity in basal ganglia. Significant positive correlations with amplitude at the group level, corrected for multiple test comparisons (FDR  $p < 0.05$ ) are shown in red for the viscous trials, blue for the target trials and their overlap in purple. Significant task differences where the correlation with amplitude was stronger for target than viscous challenge task are shown in green. On the left is plotted the mean beta  $\pm$  SEM for the entire population corresponding to the magnitude of the parameter correlating amplitude and BOLD for the left caudate (MNI:  $-14, -12, 22$ ) and right putamen/insula (MNI:  $34, -20, 0$ ). Coronal sections are  $-30, -23, -16, -11, -4, 2, 9, 13, 20$ mm relative to anterior commissure.