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Report

Involvement of Human Basal Ganglia In Offline Feedback Control of Voluntary Movement

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Summary

Practice makes perfect, but the neural substrates of trial-to-trial learning in motor tasks remain unclear. There is some evidence that the basal ganglia process feedback-related information to modify learning in essentially cognitive tasks [1–4], but the evidence that these key motor structures are involved in offline feedback-related improvement of performance in motor tasks is paradoxically limited. Lesion studies in adult zebra finches suggest that the avian basal ganglia are involved in the transmission or production of an error signal during song [5–7]. However, patients with Huntington's disease, in which there is prominent basal ganglia dysfunction, are not impaired in error-dependent modulation of future trial performance [8]. By directly recording from the subthalamic nucleus in patients with Parkinson's disease, we demonstrate that this nucleus processes error in trial performance at short latency. Local evoked activity is greatest in response to smallest errors and influences the programming of subsequent movements. Accordingly, motor parameters are least likely to change after the greatest evoked responses so that accurately performed trials tend to precede other accurate trials. This relationship is disrupted by electrical stimulation of the nucleus at high frequency. Thus, the human subthalamic nucleus is involved in feedback-based learning.

Results

Here, we investigate whether the subthalamic nucleus (STN), a pivotal structure in the basal ganglia [9], is involved in the offline feedback control of movement by assessing optimal performance and biasing the selection of parameters for future movement appropriately. The opportunity to record from the STN arises in patients with Parkinson's disease (PD) undergoing ameliorative functional neurosurgery. Local field potentials (LFPs) can be recorded postoperatively from depth electrodes (Figure S1 in the Supplemental Data available online) in the interval between their implantation and subsequent connection to a subcutaneous stimulator. In this interval, patients are alert and can be recorded after treatment with the dopamine precursor levodopa, which improves movement and helps reverse the dopaminergic deficit that is central to this disease. We recorded from the STN bilaterally in six patients (cases 1–6 in Table S1) while they engaged in a PC "game," in which they had to produce a movement under circumstances that require temporal accuracy. In each trial of the game, the subject would start the movement of a spot on a computer screen by pressing a push-button held in one hand and then, as accurately as possible, would stop the spot as it crossed a target line in the middle of the screen by pressing a second push-button held with the other hand (Figure 1A). Data from one STN side were rejected because of suboptimal surgical targeting of the STN (right side in case 3 of Table S1).

The amplitude of evoked STN activity in single trials varied according to trial error in a systematic fashion. By far the biggest potentials were seen in those trials with the smallest error (Figures 1B and 1C). The size of potentials dropped steeply with increasing error, whether the spot was stopped short of or after the target line. Accordingly, the relationship between evoked activity and error was well modeled by taking of the logarithmic transform of the absolute error in each trial and correlation of this with the amplitude of evoked STN activity (Figures 1D and 1E).

To determine when the STN LFP activity best correlated with trial error, we correlated each data point in the 1 s after stopping of the spot with log absolute error for each contact pair. We selected the contact pair exhibiting the highest coefficient of correlation on each side for further analysis. An average of these data across the 11 sides showed two peaks exceeding confidence limits: the first from 115–312 ms and the second from 408–500 ms after the spot was stopped (Figure 2A, black line). To ensure that this result was not dominated by data from a single side, we determined the mean incidence of significant correlations across the best contact pair from each side. This gave a similar picture (Figure 2A, gray line). In addition, the mean number of

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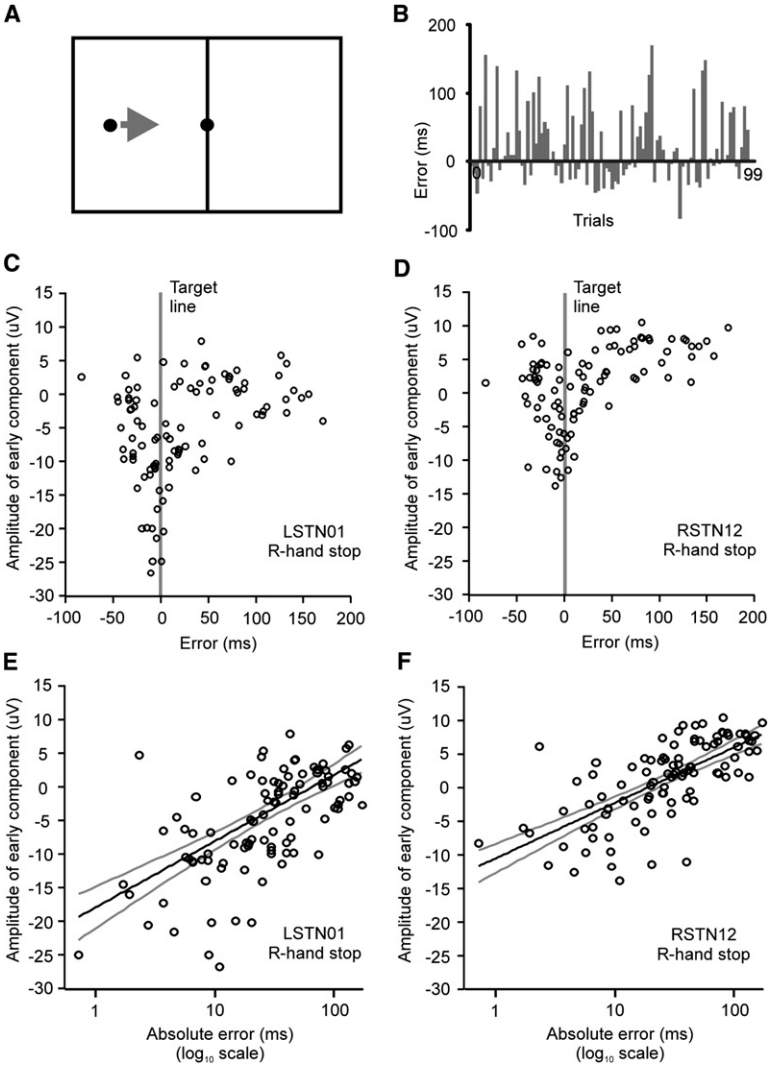

Figure 1. Paradigm and Example Correlations between LFP Activity and Error

(A) Schematic of paradigm. Movement of a spot at constant velocity on screen is started by depression of a button held in one hand and stopped by depression of a second button device held in the other. Aim is for spot to end up bisected by the vertical line in middle of the screen. Two spot velocities were used and changed between unrelated blocks of trials.

(B) Example of errors in stopping spot during each trial. Negative errors mean that spot was stopped before the vertical target line was reached.

(C) Scatter plot of trial error and LFP amplitude for early component recorded at contact pair 01 of left side.

(D) Scatter plot of trial error and LFP amplitude for early component recorded at contact pair 12 of right side.

(E) Scatter plot of trial absolute error (log_{10} axis) and amplitude of evoked early LFP component from data in (C). Regression line is shown in black, and 95% confidence limits (CL) are shown in gray; r = 0.625 and $p < 0.001$.

(F) Scatter plot from data in (D). r = 0.693 and $p < 0.001$. All data from case 1 in whom similar patterns are seen with the left hand stopping spot movement and with late LFP component.

significant correlations, separately averaged for each task (left or right hand stopping the spot trajectory) across these two time periods and the best contact pairs on each side, inversely correlated with median absolute error in each task ($r = -0.583$ and $p = 0.047$). This suggested a relationship between the evoked activity in the STN correlating with accuracy and overall task performance, whereby the evoked activity accounted for 34% of the variance in task performance across subjects and tasks.

Thereafter, individual summary correlations were determined by averaging of the LFP amplitude over the two nonoverlapping sections with the 100 consecutive data points with the highest correlations (Figure 2B) and correlating these with log absolute error. Individual summary correlations were available for all 11 sides. With the exception of the late component on the left side in case 2, all summary correlations were significant. Averaging such correlations across sides suggested that approximately 20% of the variance in the LFP amplitude in single trials could be linearly related to trial error (Figure 2C).

Four patients performed the task without vision-dependant feedback at the end of the recording session. No correlations between LFP amplitude and log absolute error (at $p \leq 0.001$) were detected in averages of these runs, despite matching errors to performance with vision offline. In contrast, averages of the correlations over time at the same contact pairs in the same four patients during performance in corresponding trials with visual feedback demonstrated two peaks of significant bins from 112–292 ms and 376–460 ms. This suggests that the presence of correlations required vision-dependent feedback of error and was not due, for example, to the linear addition of independent potentials, such as any motor potential evoked by each button depression (Figure 3). On the other hand, visual input alone, without self-generated movement, also did not evoke significant correlating LFP activity. This was ascertained when three patients were asked to concentrate on the PC screen while the examiner performed the visuomotor task (Figure 3). No correlations between LFP amplitude and log absolute error (at $p \leq 0.001$) were detected in averages of these runs. In contrast, averages of the correlations over time at the same contact pairs in the same three patients during performance in trials with both self-generated movement and visual feedback of error demonstrated a peak of significant bins from