The role of dopamine in reward-based motor adaptation, savings, and interference

Abbreviated Title: Dopamine in motor adaptation

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Abstract

Dopamine signaling is thought to mediate reward-based learning. We tested for a role of dopamine in motor adaptation by administering the dopamine precursor levodopa to healthy participants in two experiments involving reaching movements. Levodopa has been shown to impair reward-based learning in cognitive tasks. Thus, we hypothesized that levodopa would selectively impair aspects of motor adaptation that depend on reinforcement of rewarding actions.

In the first experiment, participants performed two separate tasks in which adaptation was driven either by visual feedback of the hand position or binary reward feedback. We used EEG to measure event-related potentials evoked by task feedback. We hypothesized that levodopa would specifically diminish adaptation and the neural responses to feedback in the reward learning task. However, levodopa did not affect motor adaptation in either task nor did it diminish event-related potentials elicited by reward outcomes.

In the second experiment, participants learned to compensate for mechanical force field perturbations applied to the hand during reaching. Previous exposure to a particular force field can result in savings during subsequent adaptation to the same force field and interference during adaptation to an opposite force field. We hypothesized that levodopa would diminish savings and anterograde interference, as previous work suggests that these phenomena result from a reinforcement learning process. However, we found no reliable effects of levodopa.

These results suggest that reward-based motor adaptation, savings, and interference may not depend on the same dopaminergic mechanisms which have been shown to be disrupted by levodopa during various cognitive tasks.

New and Noteworthy

Motor adaptation relies on multiple processes including reinforcement of successful actions. Cognitive reinforcement learning is impaired by levodopa-induced disruption of dopamine function. We administered levodopa to healthy adults who participated in multiple motor adaptation tasks. We found no effects of levodopa on any component of motor adaptation. This suggests that motor adaptation may not depend on the same dopaminergic mechanisms as cognitive forms or reinforcement learning which have been shown to be impaired by levodopa.

Introduction

Human motor control is adaptive to changes of the environment and the body through multiple mechanisms including reinforcement of successful actions and recalibration of internal mappings between motor commands and sensory outcomes (Taylor and Ivry 2014; Huang et al. 2011; Wolpert, Ghahramani, and Jordan 1995). Two prominent experimental models of motor learning have been used in recent work in this area: force field adaptation and visuomotor rotation (VMR) tasks. In studies of force field adaptation a robot applies velocity-dependent forces to the hand during reaches to targets. In visuomotor rotation tasks, a cursor on a digital display represents the position of the hand, and the mapping between the actual reach angle and the position of the cursor is rotated to induce errors. In both tasks participants quickly adapt their movements to compensate for the experimentally induced perturbations (i.e., external forces or visual feedback rotation, respectively). Learning is thought to rely primarily on circuits involving the cerebellum, and parietal, sensory, and motor cortical areas (Tanaka, Sejnowski, and Krakauer 2009; Diedrichsen et al. 2005; Mathis, Mathis, and Uchida 2017; Kumar, Manning, and Ostry 2019; Ostry and Gribble 2016; Wong et al. 2019; Taylor, Klemfuss, and Ivry 2010; Smith and Shadmehr 2005; Ito 2000; Krakauer et al. 2004). Theories of adaptation state that activity within these neural circuits guides movement by representing a predictive mapping between motor commands and sensory consequences in visual or proprioceptive space (Miall et al. 2007; Wolpert, Ghahramani, and Jordan 1995; Bhanpuri, Okamura, and Bastian 2013). When experimental perturbations produce unexpected sensory consequences, it is thought that a sensory prediction error is computed that drives updating of the sensory-motor mapping to produce adaptation (Tseng et al. 2007; Therrien and Bastian 2015; Adams, Shipp, and Friston 2013; Izawa and Shadmehr 2011; Shadmehr, Smith, and Krakauer 2010; Synofzik, Lindner, and Thier 2008).

While sensory error-based learning mechanisms are dominant in typical motor adaptation paradigms, influences of reinforcement learning processes are increasingly recognized as important (Izawa and Shadmehr 2011; Cashaback et al. 2019; Palidis, Cashaback, and Gribble 2019; Nikooyan and Ahmed 2015; van der Kooij and Smeets 2019; van der Kooij et al. 2018; Kim, Parvin, and Ivry 2018, 2019; McDougle et al. 2016; Bernardi, Darainy, and Ostry 2015; Sidarta et al. 2016; Sidarta, van Vugt, and Ostry 2018). In some cases, sensory error-based learning is influenced by reinforcement outcomes. Explicit reward feedback has been shown to enhance the retention of error-based learning, while punishment feedback accelerates acquisition (Shmuelof et al. 2012; Galea et al. 2015; Kuling et al. 2019). Sensory error-based learning can also be modulated by implicit reward or task errors related to whether feedback hits or misses visual targets (Kim, Parvin, and Ivry 2019; Leow et al. 2018). Reinforcement learning and sensory error-based learning can also contribute to adaptation as separable processes. Adaptation to sensory error has been shown to occur automatically even when it interferes with the instrumental goals of the task, supporting a distinction between reinforcement of successful actions and sensory error-based learning (Mazzoni and Krakauer 2006). Reward-based adaptation can be isolated experimentally by providing only binary reinforcement feedback, which indicates success or failure. This produces learning with perceptual and behavioral signatures that are different from those observed during visuomotor adaptation (Izawa and

Shadmehr 2011; Shmuelof et al. 2012). When sensory error-based learning cannot occur due to impoverished sensory feedback or cerebellar damage, reward-based learning can produce comparable behavioral adaptation (Izawa and Shadmehr 2011; Cashaback et al. 2017; Therrien, Wolpert, and Bastian 2016). Although sensory error-based learning can correct biases that affect average motor error, a reinforcement learning process may be necessary to discover motor solutions that minimize the variance of motor error, a hallmark of motor skill acquisition (Mehler et al. 2017).

Dopamine plays a nearly ubiquitous role in reward-based learning across species and behaviours. In formal models of reinforcement learning, the difference in reward between expected and received outcomes is known as reward prediction error (Daw and Tobler 2014; Walsh and Anderson 2012; Sambrook and Goslin 2015). When an action results in an outcome that is better or worse than expected, reward prediction error serves to update a representation of that action's value accordingly. Phasic changes in the firing rate of midbrain dopamine neurons show concordance with reward prediction error signals predicted by computational models of reinforcement learning (Schultz, Dayan, and Montague 1997; García-García, Zeighami, and Dagher 2017; Watabe-Uchida, Eshel, and Uchida 2017; Jocham and Ullsperger 2009; Bayer and Glimcher 2005). These dopaminergic signals are thought to mediate synaptic plasticity in the striatum and frontal cortex, which underlies reward-based learning (Otani et al. 2003; Wang et al. 2018; Reynolds and Wickens 2002).

Levodopa is a dopamine precursor commonly used to treat Parkinson's disease. In experimental studies of reinforcement learning, levodopa often impairs reward-based learning in both patients and healthy participants (Vo, Seergobin, and MacDonald 2018; R. Cools et al. 2001; Roshan Cools et al. 2003; Roshan Cools, Altamirano, and D'Esposito 2006; Roshan Cools et al. 2007; Feigin et al. 2003; Frank, Seeberger, and O'reilly 2004; Graef et al. 2010; Hiebert et al. 2014; Jahanshahi et al. 2010; Kwak et al. 2010; MacDonald et al. 2011; Swainson et al. 2000; Torta et al. 2009; Vo et al. 2014). According to the "dopamine overdose" hypothesis, dopamine levels affect performance in tasks which depend on the ventral striatum according to an inverted-u function (Roshan Cools, Altamirano, and D'Esposito 2006). In Parkinson's disease, the dorsal striatum is significantly depleted of dopamine whereas the ventral striatum is comparatively spared, particularly at earlier disease stages. Dopaminergic therapy is predicted to ameliorate deficits caused by dopamine-depletion in the dorsal striatum but to worsen functions ascribed to the less-affected ventral striatum. In line with this view, reward-based learning is thought to rely on dopamine signaling in ventral striatum and is impaired by levodopa in both healthy participants and patients with early stage Parkinson's disease.

Dopamine is widely implicated in biological reinforcement learning, and reward-based motor adaptation has been successfully modeled as a reinforcement learning process (Izawa and Shadmehr 2011; Dhawale et al. 2019). However, it is unknown whether the general role of dopamine in learning extends to human motor adaptation. Here we administered levodopa to healthy young participants to manipulate dopamine function and test for effects on motor adaptation. In our first experiment, participants received levodopa and placebo in separate sessions using a repeated measures design. Both sessions included a reward-based learning

task and a sensory error-based VMR task, similar to those used in a previous experiment (Palidis, Cashaback, and Gribble 2019). In the reward-based learning task, adaptation was induced through binary reinforcement feedback at the end of each movement. We measured changes in the mean reach angle due to reinforcement as well as modulations in trial-by-trial variability of reach angle as a response to reward outcomes. Previous research has shown that motor variability is larger following unrewarded outcomes compared to rewarded outcomes (Pekny, Izawa, and Shadmehr 2015; Dhawale et al. 2019; van Mastrigt, Smeets, and van der Kooij 2019; van der Kooij and Smeets 2019; Holland, Codol, and Galea 2018). Reinforcement of successful actions should be reflected in reduced variability following reward (Cashaback et al. 2019). Following non-reward, an increase in variability is linked to motor exploration in search of more rewarding actions (Dhawale, Smith, and Ölveczky 2017). This exploratory modulation of variance has been shown to be impaired in individuals with Parkinson's Disease who are medicated, but it remains unclear whether this deficit is caused by the disease process itself or off-target effects of dopaminergic medication (Pekny, Izawa, and Shadmehr 2015). We hypothesized that reward-based motor adaptation relies on dopaminergic signaling of reward prediction error. We predicted that levodopa would impair reward-based motor adaptation and modulation of trial-by-trial variability in accordance with the "dopamine overdose hypothesis".

In the sensory error-based learning task, participants adapted to visuomotor rotation perturbations which were designed to produce sensory prediction error while minimizing reward prediction error. We hypothesized that sensory error-based learning would be unaffected by levodopa, as it is thought to be mediated by non-dopaminergic mechanisms dependent primarily on the cerebellum.

In experiment 1, we recorded EEG to measure the neural event-related potential (ERP) correlates of reward and sensory error processing. We were particularly interested in a medial frontal ERP component called the feedback related negativity, or alternatively the reward positivity (FRN/RP). In a previous experiment, we found that the FRN/RP was modulated by reward feedback but not sensory error feedback during motor adaptation (Palidis, Cashaback, and Gribble 2019). This is consistent with the "reinforcement learning theory of the FRN/RP", which suggests that it reflects reward prediction error signals in the anterior cingulate cortex driven by dopamine release (Walsh and Anderson 2012; Sambrook and Goslin 2015, 2016; Holroyd and Coles 2002; Warren et al. 2015; Becker et al. 2014; Vezoli and Procyk 2009; Miltner, Braun, and Coles 1997; Emeric et al. 2008; Hauser et al. 2014; Gehring and Willoughby 2002; Mathewson et al. 2008; Carlson et al. 2011; Foti et al. 2011; Holroyd, Pakzad-Vaezi, and Krigolson 2008). Previously, some studies using pharmacological and genetic techniques have supported a dopaminergic basis for the FRN/RP (Schutte et al. 2020; Santesso et al. 2009; Enge et al. 2017; Mueller et al. 2014; Marco-Pallarés et al. 2009). However, at least one study failed to detect effects of dopaminergic manipulation on the FRN (Forster et al. 2017). Overall, direct evidence for a link between dopamine and the FRN/RP is limited, and no studies have investigated this link in the context of motor adaptation. We hypothesized that levodopa would diminish the magnitude of the FRN/RP along with behavioral expression of reward-based learning in accordance with the "dopamine overdose" hypothesis.

In experiment 2, participants ingested either levodopa or placebo prior to undergoing a force field adaptation paradigm. Our paradigm was designed to test for effects of levodopa on savings, in which adaptation is facilitated when a particular perturbation is encountered a second time after washout of initial learning. We also tested for effects of levodopa on anterograde interference, in which adaptation to a force field in a particular direction causes interference with subsequent adaptation to an opposite-direction force field (Huang et al. 2011; Leow et al. 2013; Krakauer, Ghez, and Ghilardi 2005; Sing and Smith 2010; Miall, Jenkinson, and Kulkarni 2004; Bock, Schneider, and Bloomberg 2001). While force field adaptation is thought to rely primarily on sensory error-based learning mechanisms, savings and anterograde interference can be accounted for by additional influences of a reinforcement learning process (Huang et al. 2011). Individuals with Parkinson's disease often exhibit deficits in operant reinforcement and show reduced savings and interference despite intact initial adaptation (Leow et al. 2013; Leow, Loftus, and Hammond 2012; Bédard and Sanes 2011). While these results suggest a role of dopamine in savings and interference, they cannot distinguish between effects of Parkinson's disease and "dopamine overdose" effects of medication. We used pharmacological manipulation in healthy participants to provide a more specific and controlled test for a role of dopamine in savings and interference. We predicted that levodopa would impair savings and interference while leaving initial adaptation unaffected, as levodopa has been shown to impair reinforcement learning processes in healthy participants.

We tested for effects of levodopa using a comprehensive battery of motor adaptation tasks which rely on various behavioral processes including reward-based learning, motor exploration, sensory error-based learning, savings, and anterograde interference. This allowed us to test the hypotheses that dopaminergic mechanisms specifically underlie adaptive motor responses to reward outcomes as well as the formation of motor memories that produce savings and interference effects. We also measured the FRN/RP using EEG, which is a common neural correlate of reward prediction error. This allowed us to test the hypothesis that dopaminergic signaling of reward prediction error in the medial frontal cortex drives reward-based motor adaptation.

Methods

Experiment 1

Participants

A total of *n=21* [12 female, Age: 20.99 years (SD 3.26)] healthy, right-handed participants were included in experiment 1. All participants were screened for neurological and psychiatric illness, history of drug or alcohol abuse, and contraindications for levodopa. Two participants were excluded due to malfunction of the robot that prevented the experiment from being completed, and two participants were excluded who did not return for the second testing session. Participants provided written informed consent to experimental procedures approved by the Research Ethics Board at Western University.

Experimental design

Drug administration: All participants underwent two experimental sessions, with levodopa and placebo being administered in separate sessions using a randomized, double blind, crossover design. In one session, a capsule was ingested which contained 100 mg of levodopa (L-3,4-dihydroxyphenylalanine) and 25 mg of carbidopa. Levodopa is a dopamine precursor, and carbidopa is a decarboxylase inhibitor given to reduce conversion of levodopa to dopamine in the periphery. This dose has been shown to produce various behavioral effects in healthy young adults (Vo, Seergobin, and MacDonald 2018; Flöel et al. 2005; Knecht et al. 2004; Onur et al. 2011; Vo et al. 2016; Vo, Seergobin, and MacDonald 2017). In the other session, an equal volume of placebo was administered in an identical capsule. The order of administration was counterbalanced. After administration of the capsule, the robot was calibrated, the EEG cap was placed on the participant's head, and participants performed a practice block of the behavioral task (see below). Subsequently, the experimental tasks began 45 minutes after ingestion of the capsule to coincide with peak plasma levels of levodopa (Olanow, Schapira, and Rascol 2000). We measured subjective alertness using the Bond-Lader visual analog scale (Bond and Lader 1974), as well as heart rate and blood pressure, immediately prior to ingesting the capsule and again at the end of each session.

Overview of behavioral tasks: Each participant underwent the same experimental tasks in both sessions. Participants made reaching movements toward a visual target and received visual feedback pertaining to reach angle only at movement end point. Neural responses to feedback were recorded by EEG. Participants were instructed that each reach terminating within the target would be rewarded with a small monetary bonus. Participants first performed a block of 50 practice trials. The subsequent behavioral procedure consisted of two blocks of a reward learning task and two blocks of a visuomotor rotation (VMR) task. The order of the blocks alternated between the two task types but was otherwise randomized. Participants took self-paced rests between blocks.

In the VMR task, a cursor appeared at movement end point to represent the position of the hand. In randomly selected trials, cursor feedback indicated a reach angle that was rotated relative to the true angle of the hand position. This was intended to produce sensory prediction error and trial-by-trial compensatory changes in reach angle opposite the direction of the rotations. The rotations were small relative to the size of the target, such that participants nearly always landed in the target, fulfilling the goal of the task and earning a monetary reward (the cursor feedback was within the target on 95.5% of trials, SD: 2%). Thus, reward and task error were constant between perturbed and unperturbed feedback, and by comparing the two conditions we could isolate the neural correlates of sensory error processing.

In the reward learning task, no cursor appeared to indicate the position of the hand. Instead, binary feedback represented whether or not participants succeeded in hitting the target. This allowed us to assess reward-based learning in isolation from sensory error processing, as visual information revealing the position of the hand was not provided. In separate blocks, reward feedback was tailored to produce adaptation towards increasingly clockwise and

counterclockwise reach angles. Reward was delivered when the difference between the current reach angle and the median of the previous 10 reach angles was in the direction of intended learning. We compared the neural responses to reward and nonreward feedback to assess the neural correlates of reward processing during adaptation.

Apparatus/Behavioral Task

Participants produced reaching movements with their right arm while holding the handle of a robotic arm (InMotion2; Interactive Motion Technologies). Position of the robot handle was sampled at 600 Hz. A semi-silvered mirror obscured vision of the arm and displayed visual information related to the task. An air sled supported each participant's right arm. Participants reached towards a white circular target 14 cm away from a circular start position in front of their chest. The start position turned from red to green to cue the onset of each reach once the handle had remained inside it continuously for 750 ms. Participants were instructed that they must wait for the cue to begin each reach but that it was not necessary to react quickly upon seeing the cue. Participants were instructed to make forward reaches and to stop their hand within the target. An arc-shaped cursor indicated reach extent throughout each movement without revealing reach angle. In only the first five baseline trials of each block, an additional circular cursor continuously indicated the position of the hand throughout the reach. A viscous force field assisted participants in braking their hand when the reach extent was 14 cm. The robot ended each movement by fixing the handle position when the hand velocity decreased below 0.03 m/s. The hand was fixed in place for 700 ms, during which time visual feedback of reach angle was provided. Feedback indicated either reach end point position, a binary reward outcome, or feedback of movement speed (see below). Visual feedback was then removed, and the robot guided the hand back to the start position. Reach end point was defined as the position at which the reach path intersected the perimeter of a circle (14-cm radius) centered at the start position. Reach angle was calculated as the angle between vectors defined by reach end point and the center of the target, each relative to the start position, such that reaching straight ahead corresponds to 0° and counterclockwise reach angles are positive.

Feedback about reach angle was provided either in the form of end-point position feedback or binary reward feedback. The type of feedback, as well as various feedback manipulations, varied according to the assigned experimental block type (see Reward Learning Task and Visuomotor Rotation Task). Participants were told that they would earn additional monetary compensation for reaches that ended within the target, up to a maximum of CAD$10. Movement duration was defined as the time elapsed between the hand leaving the start position and the moment hand velocity dropped below 0.03 m/s. If movement duration was >700 ms or <450 ms, no feedback pertaining to movement angle was provided. Instead, a gray arc behind the target turned blue or yellow to indicate that the reach was too slow or too fast, respectively. Participants were informed that movements with an incorrect speed would be repeated but would not otherwise affect the experiment. To minimize the impact of eyeblink-related EEG artifacts, participants were asked to fixate their gaze on a black circular target in the center of the reach target and to refrain from blinking throughout each arm movement and subsequent presentation of feedback.

Practice block: Each participant first completed a block of practice trials that continued until they achieved 50 movements within the desired range of movement duration. Continuous position feedback was provided during the first 5 trials, and only end-point position feedback was provided for the following 10 trials. Subsequently, no position feedback was provided outside the start position.

Reward Learning task: Binary reward feedback was provided to induce adaptation of reach angle. Each session included two blocks in the reward learning condition. The direction of intended learning was clockwise in one block and counterclockwise in the other. Each block continued until the participant completed 125 reaches with acceptable movement duration. Participants reached toward a circular target 1.2 cm in diameter. The first 11 reaches were baseline trials during which continuous position feedback was provided during the first 5 trials, followed by 6 trials with only end-point cursor feedback. After these baseline trials no cursor feedback was provided, and binary reward feedback was instead provided at the end of the movement. Target hits and misses were indicated by the target turning green and red, respectively. Unbeknownst to participants, reward feedback did not necessarily correspond to the visual target. Instead, reward was delivered if the difference between the current reach angle and the median angle of the previous 10 reaches was in the direction of intended learning. When the running median was at least 6° away from zero in the direction of intended learning, reward was delivered at a fixed probability of 50%. This was intended to minimize conscious awareness of the manipulation by limiting adaptation to 6°. Reward was never delivered when the absolute value of the reach angle was greater than 10°, for the same reason. We employed this adaptive, closed-loop reward schedule so that the overall frequency of reward was controlled.

Visuomotor rotation task: End-point feedback was rotated relative to the actual reach angle to induce sensory error-based adaptation. Each session included two blocks in the VMR condition. Each block continued until participants completed 124 reaches within acceptable movement duration limits. Participants reached toward a circular target 3.5 cm in diameter. Participants first performed baseline reaches during which cursor feedback reflected veridical reach angle continuously for the first 5 trials and only at movement end point for the subsequent 5 trials. After the baseline reaches the adaptation portion of each block began, unannounced to participants. During the adaptation trials, end-point position feedback was provided indicating a reach angle that was rotated relative to the true reach angle. There were 114 total experimental trials (38 with 0° rotation, and 19 each with ±2° and ±4° rotations). Participants were instructed that end-point feedback within the target would earn them bonus compensation, but no explicit reward feedback was provided.

EEG data acquisition

EEG data were acquired from 16 cap-mounted electrodes with an active electrode system (g.GAMMA; g.tec Medical Engineering) and amplifier (g.USBamp; g.tec Medical Engineering). We recorded from electrodes placed according to the 10-20 System at sites Fp1, Fp2, F3, F4,

F7, F8, FT9, FT10, FCz, Cz, C3, C4, CPz, CP3, CP4, and Pz referenced to an electrode placed on participants' left earlobe. Impedances were maintained below 5 kΩ. Data were sampled at 4,800 Hz and filtered online with band-pass (0.1–1,000 Hz) and notch (60 Hz) filters. A photodiode attached to the display monitor was used to synchronize recordings to stimulus onset.

Behavioral data analysis

Reward learning task. To analyze reward-based motor adaptation, we first averaged reach angles in each block within three bins of 38 trials. We excluded baseline trials and trials that did not meet the movement duration criteria, as no feedback related to reach angle was provided on these trials. Each block continued until 114 trials after the baseline period met the movement duration criteria, so equal numbers of trials were analyzed for each participant. We then performed 2x2x3 repeated measures ANOVA on reach angle. The factors were bin (levels: early, middle, late), direction of intended learning (levels: clockwise, counterclockwise), and drug (levels: placebo, levodopa).

We also analyzed trial-by-trial variability in reach angle in response to reinforcement feedback using an approach similar to (Pekny, Izawa, and Shadmehr 2015). First, we calculated trial-by-trial changes in reach angle as in *Eq. 1:*

$$\Delta\theta_i = \theta_{i+1} - \theta_i \quad (1)$$

We then multiplied $\Delta\theta_i$by -1 for trials in the clockwise learning condition, so that positive values for $\Delta\theta_i$corresponded to changes in reach angle in the direction of intended learning, and any biases in $\Delta\theta$ related to the direction of intended learning would have the same sign in the CW and CCW learning conditions. Next we conditioned $\Delta\theta_i$ on the reinforcement outcome of trial i and the drug condition to obtain trial-by-trial changes in reach angle following reward and non-reward after both placebo and levodopa administration. Next, we quantified trial by trial variability in each condition as the natural logarithm of the sample variance of $\Delta\theta_i$. Our dependent variable is an estimate of variance. This estimate of variance itself has variance due to sampling. For a normal distribution, the variance of a sample variance is proportional to the square of the true population variance. A log transformation is appropriate for linear modeling when the variance of the dependent measure is proportional to the square of its expectation (Montgomery, Peck, and Geoffrey Vining 2015).

We then performed 2x2 repeated measures ANOVA on Log(var($\Delta\theta_i$)). The factors were drug (levels: placebo,levodopa), and reward outcome on trial i (levels: non-reward, reward.)

Visuomotor rotation task. To quantify trial-by-trial learning we first calculated the change in reach angle between successive trials, as in *Eq. 1.* We then performed a linear regression on $\Delta\theta_i$ with the rotation imposed on trial i as the predictor variable. The rotation was 0°, ±2°, or ±4°. This regression was performed on an individual participant basis, separately for placebo and levodopa conditions. We excluded trials that did not meet the duration criteria as no visual

feedback was provided on these trials. We took the average of the resulting slope estimates across blocks, multiplied by 1, as a metric of learning rate for each participant, as it reflects the portion of visual errors that participants corrected with a trial-by-trial adaptive process. We tested for the presence of adaptation in each condition by submitting learning rates to 1-sample t-tests against zero. We tested for an effect of levodopa vs placebo on learning rates using a paired t-test.

EEG preprocessing

EEG data were resampled to 480 Hz and filtered off-line between 0.1 and 35 Hz with a second-order Butterworth filter. Continuous data were segmented into 2-s epochs time-locked to feedback stimulus onset at 0 ms (time range: -500 to +1,500 ms). Epochs flagged for containing artifacts as well as any channels with bad recordings were removed after visual inspection. Subsequently, extended infomax independent component analysis was performed on each participant's data (Delorme and Makeig 2004). Components reflecting eye movements and blink artifacts were identified by visual inspection and subtracted by projection of the remaining components back to the voltage time series.

EEG data analysis

After artifact removal, we computed ERPs by trial averaging EEG time series epochs for various feedback conditions described in the sections below. ERPs were computed on an individual participant basis separately for recordings from channels FCz and Pz. We selected FCz and Pz a priori because these electrodes typically correspond to the peaks of the scalp distributions for the feedback related negativity/reward positivity and the P300 ERP components, respectively. We found this to be true in a previous experiment using a very similar paradigm (Palidis, Cashaback, and Gribble 2019). All ERPs were baseline corrected by subtracting the average voltage in the 75-ms period immediately following stimulus onset. We used a baseline period following stimulus onset because stimuli were presented immediately upon movement termination and the period before stimulus presentation was more likely to be affected by movement related artifacts. Trials in which reaches did not meet the movement duration criteria were excluded, as feedback relevant to reach adaptation was not provided on these trials. Finally, ERPs were low-pass filtered with a cutoff frequency of 30 Hz.

We computed ERPs separately following administration of placebo and levodopa. In the reward learning task, we computed ERPs separately for feedback indicating non reward (placebo: 107.1 ±9.4 trials, levodopa: 104.1 ±8.3 trials) and feedback indicating reward (placebo: 118.5 ±9.4 trials, levodopa: 117.9 ±7.9 trials). In the visuomotor rotation task, we computed ERPs separately for veridical endpoint feedback (placebo: 72.7 ± 3.4 trials, levodopa: 73.0 ± 3.1 trials), ±2° rotated feedback (placebo: 71.0 ± 5.2 trials, levodopa: 72.2 ± 3.7 trials), and ±4° rotated feedback (placebo: 64.7 ± 4.7 trials, levodopa: 66.6 ± 4.2 trials). We excluded trials in which the cursor did not land within the target.

We analyzed ERPs in both the reward learning task and the visuomotor rotation task using repeated measures ANOVA on ERP voltage separately for each sample between 100-600 ms after feedback onset. We corrected significance values for multiple comparisons across time using the Benjamini-Hochberg procedure for estimating the false discovery rate, or FDR, implemented by the MATLAB *mafdr* function. For the reward learning task, we used 2x2 repeated measures ANOVA with factors drug (levels: placebo, levodopa) and reinforcement outcome (levels: reward, non-reward). For the visuomotor rotation task, we used 2x3 repeated measures ANOVA with factors drug (levels: placebo, Levodopa), and rotation (levels: 0°, ±2°, ±4°). In order to better characterize effects of the rotation factor, we performed post hoc t-tests comparing ERPs elicited by rotated feedback to those elicited by unrotated feedback, separately for the ±2° and ±4° rotation conditions. We perform these tests on all time points with a significant main effect or interaction involving the rotation factor, and report time points with $p < 0.05$ as significant, uncorrected for multiple comparisons.

Statistics

Repeated measures ANOVAs were performed using the MATLAB *ranova* function. The Greenhouse–Geisser method was used to correct *p*-values for violations of sphericity.

Experiment 2

Participants

A total of 38 participants were included in experiment 2 (Table 2). All participants were screened for neurological and psychiatric illness, history of drug or alcohol abuse, and contraindications for levodopa. Participants provided written informed consent to experimental procedures approved by the Research Ethics Board at Western University.

Procedure

Drug administration: Participants were administered either levodopa or placebo in a randomized double blind design. A capsule was ingested which contained 100 mg of levodopa (L-3,4-dihydroxyphenylalanine) and 25 mg of carbidopa or an equal volume of placebo. The experimental tasks began 45 minutes after ingestion of the capsule to coincide with peak plasma levels of levodopa. We measured subjective alertness using the Bond-Lader visual analog scale (Bond and Lader 1974) as well as heart rate and blood pressure immediately prior to ingesting the capsule and again at the end of each session.

Force field adaptation task: Participants produced reaching movements with their right arm while holding the handle of a robotic arm (InMotion2; Interactive Motion Technologies). The position of the robot handle was sampled at 600 Hz. A semi-silvered mirror obscured vision of the arm and displayed visual information related to the task. An air sled supported each participant’s right arm.

On each trial, participants reached from a central home position (blue circle 20 mm in diameter) to one of 8 circular targets (24 mm in diameter) arranged around the home position at a distance of 10 cm. The target angles were 0°, 45°, 90°, 135°, 180°, 225°, 270°, and 315°. A 5-mm pink circular cursor represented the position of the robot handle. When the cursor reached the target on each trial, the target either turned blue to indicate that the movement duration was satisfactory (375 ± 100 ms), green to indicate that the movement was too slow, or red to indicate that the movement was too fast. The subject moved the robot handle back to the home position at the end of each reach.

In null field blocks, the robot motors did not apply any external forces to the hand. In force field blocks, the robot applied forces to the hand that were perpendicular to the direction of movement and proportional to the velocity of the hand (*eq. 2)*. The direction of the force field was either clockwise or counterclockwise, in separate blocks.

$$\begin{bmatrix} F_x \\ F_y \end{bmatrix} = b \begin{bmatrix} 0 & d \\ -d & 0 \end{bmatrix} \begin{bmatrix} v_x \\ v_y \end{bmatrix} \quad (2)$$

x and y correspond to the lateral and sagittal directions.F_x and F_y describe the forces applied to the hand, v_x and v_y describe the velocity of the hand, b is the field constant, and d corresponds to the direction (d = 1 for a clockwise force field (CWFF), -1 for a counterclockwise force field (CCWFF) or 0 for a null field (NF)).

All participants completed five blocks of 96 trials. Each block consisted of 12 reaches to each of the 8 targets presented in random order. The five blocks occurred in the following order: NFa (null field), FF1a (CWFF), NFb (null field), FF1b (CWFF), FF2 (CCWFF). Trials 6, 24, 35, 50, 71, and 91 of each block were “catch trials”, during which reaches occurred in a null field. When the force field is suddenly removed in catch trials, errors occur in the opposite direction of the force field. A reduction in reach error during force field trials may reflect either adaptation to the force field, stiffening of the arm, or changes in feedback corrections. The magnitude of errors opposite the force field in catch trials is thought to better capture adaptation of feedforward control. Similar to catch trials, we expected after-effects at the beginning of NFa in the form of counterclockwise reach errors after the sudden removal of the clockwise force field in FF1a.

Data analysis

Robot handle positional data were low-pass filtered with a 40 Hz cutoff frequency and differentiated to yield instantaneous velocity and acceleration. On each trial, movement onset and end of movement were defined according to a velocity threshold set at 5% of the maximum tangential velocity of the robot endpoint. Our behavioral measure of interest was the lateral deviation of the hand at the time of peak tangential velocity. Perpendicular deviation (PD) was calculated relative to a line drawn from the position of movement onset in the direction of the target angle (either 0°, 45°, 90°, 135°, 180°, 225°, 270°, or 315°). PD was calculated for each trial as the perpendicular distance between the position of the hand at peak velocity and this

line, with positive PD corresponding to clockwise deviations. To analyze kinematic data from the force field and null field trials, we segmented each block into 4 bins each consisting of 24 trials. We computed the average PD across trials within each bin. We submitted the average PD for each bin to mixed ANOVAs (detailed below).

Adaptation/Savings: We used the data from force field trials in FF1a and FF1b blocks to test for adaptation and savings effects using a single ANOVA. Within-subject factors were bin (levels: trials 1-24, 25-48, 49-72, 73-96), and block (levels: FF1a, FF1b). Drug condition was included as a between-subjects factor (levels: placebo, levodopa). Participants encountered the same CWFF in FF1a and FF1b, separated by a null field block to produce washout of initial learning. We expected adaptation to result in decreasing PD over the course of each block, reflected in a main effect of bin. We expected savings to result in a faster reduction of PD during FF1b compared to FF1a, reflected in a bin*block interaction effect. Potential effects of levodopa on adaptation and savings were assessed by testing for drug*bin and drug*bin*block interaction effects, respectively.

We used a similar approach to analyze adaptation and savings in catch trials from FF1a and FF1b, using a separate mixed ANOVA. Within-subject factors were trial (levels: 6,24,35,50,71,91) and block (levels: FF1a, FF1b). Drug condition was included as a between-subjects factor (levels: placebo, levodopa). When the force field is unexpectedly removed on catch trials, adaptation produces errors in the direction opposite the force field (negative PD). We expected adaptation to result in increasing PD opposite the force field over the course of each block, reflected in a main effect of trial. We expected savings to result in a faster increase in PD in FF1b than FF1a, reflected in a trial*block interaction effect. Potential effects of levodopa on adaptation and savings were assessed by testing for drug*trial and drug*trial*block interaction effects, respectively.

After-Effects/Deadaptation: We performed mixed ANOVA on PD in NFb with bin as a within subject factor and drug condition as a between-subjects factor. At the onset of NFb, the CWFF to which participants had adapted in FF1a was suddenly removed. We expected adaptation to the CWFF to produce after-effects in the form of reach errors in the direction opposite the force field (negative PD). Over the course of NFb, we expected these after-effects to decrease through deadaptation. We assessed deadaptation by testing for a main effect of bin. We expected any effects of levodopa on after-effects or deadaptation to be reflected in a drug*bin interaction effect. We did not separately assess null field trial data in NFb as all trials occurred in a null field.

Interference: We performed mixed ANOVA on PD in FF2 with bin as a within subject factor and drug condition as a between-subjects factor. In FF2, participants were exposed to a CCWFF immediately after adapting to a CWFF in FF1b. We expected initially large counterclockwise reach errors (negative PD) as a consequence of the CCWFF in combination with after-effects from adaptation to the CWFF in the previous block. We assessed adaptation in the form of a reduction in these errors by testing for a main effect of bin. Typically, adaptation to a force field proceeds more slowly after previously learning an opposite force field due to anterograde

interference effects. We assessed effects of levodopa on interference by testing for a drug*bin interaction effect.

We used a similar approach to analyze interference effects using the catch trial data from FF2, using a separate mixed ANOVA. Trial was used as a within subject factor (levels: 6,24,35,50,71,91) and drug condition was a between-subjects factor (levels: placebo, levodopa). We expected to observe after-effects from FF1b in the form of negative PD in early catch trials, and an increase in catch trial PD values throughout the block as an indication of adaptation to the CCWFF. We assessed adaptation by testing for a main effect of trial. We assessed effects of levodopa on interference by testing for a drug*trial interaction effect.

Statistics

Mixed ANOVAs were performed using IBM SPSS Statistics version 25. The Greenhouse–Geisser method was used to correct *p*-values for violations of sphericity.

Results

Experiment 1

Control measures: Participants' judgments at the end of the second session as to whether they received placebo or drug were correct at near chance level (47.62%). Table 1 shows the values for heart rate, blood pressure, and alertness recorded at the beginning and end of each experimental session for both the placebo and levodopa conditions. We computed the percent change in heart rate and blood pressure recorded at the beginning and end of each session. There were no reliable differences between the levodopa and placebo conditions in the percent change of heart rate ($t(17) = 0.35$, $p=0.73$), systolic blood pressure ($t(17) = -1.17$, $p=0.26$), or diastolic blood pressure ($t(17) = -0.82$, $p=0.42$). We did observe a significant difference between levodopa and placebo in the percent change of alertness ($t(20) = 2.46$, $p=0.023$). However, this effect was likely due to chance as alertness was only different between the two drug conditions at the time point pre-administration of the capsule ($t(20) = 2.18$, $p=0.042$), but not post-administration ($t(20) = -0.068$, $p=0.95$)

Behavioral results

Reward learning task. Reach angles averaged across participants are shown in Figure 1. We analyzed reach angles averaged into bins corresponding to early, middle, and late portions of each block. We found a statistically reliable effect of intended learning direction on reach angle ($F(1,20) = 72.58$, $p = 4.35e-8$), indicating that participants adapted their reach angle in accordance with the reward feedback. We also observed a reliable interaction effect between direction of intended learning and bin ($F(2,40) = 55.18$, $p = 1.03e-8$), as behavioral adaptation accumulated over the course of each block. We did not observe reliable main effects of bin ($F(2,40) = 2.42$, $p = 0.113$) or drug ($F(1,20) = 2.23$, $p = 0.151$). Nor did we observe reliable

interaction effects for bin*drug ($F(2,40) = 1.02$, $p = 0.366$), drug*direction ($F(1,20) = 2.49$, $p = 0.130$), or bin*drug*direction ($F(2,40) = 0.14$, $p = 0.798$).

The variance of trial-by-trial changes in reach angle following reward and non-reward outcomes is shown in Figure 2. We found a reliable main effect of reinforcement outcome on the log transformed variance of trial-by-trial changes in reach angle ($F(1,20) = 74.84$, $p = 3.41e-8$). This indicates an increase in trial-by-trial variance of reach angle following non-reward outcomes relative to reward. We did not find a reliable effect of drug condition ($F(1,20) = 0.0077$, $p = 0.931$) or reward*drug interaction ($F(1,20) = 0.0478$, $p = 0.829$).

Visuomotor rotation task. Mean trial-by-trial changes in reach angle after the different feedback rotations are shown in Figure 3. Learning rates were reliably greater than zero following administration of both placebo (mean: 0.313, SD: 0.133, $t(20) = 10.77$, $p = 8.93e-10$) and levodopa (mean: 0.294, SD: 0.102, $t(20) = 13.18$, $p = 2.54e-11$). Learning rates were not reliably different in the two conditions ($t(20) = 0.703$, $p=0.491$).

Event-related potential results

Reward learning task.

Electrode FCz: Event-related potentials (ERPs) elicited by reinforcement feedback at electrode FCz are shown in Figure 4a. We found reliable main effects of reinforcement outcome between 197 - 600 ms after feedback onset (Figure 4c, ranges for significant time points: F = [5.50 47.82], p = [0.047 <0.000], uncorrected p = [.029 <0.000]). Reward feedback resulted in increased ERP voltage relative to non-reward feedback between 197-346 ms after feedback. Reward feedback resulted in decreased ERP voltage relative to non-reward feedback between 383-473 ms and 531-600 ms after feedback. We did not find reliable main effects of levodopa at any time point (ranges for all timepoints between 100-600 ms: F = [0.00 1.92], uncorrected p = [1.00 0.18]). Nor did we find any reliable interaction effects between reinforcement outcome and levodopa (ranges for all timepoints between 100-600 ms: F = [0.00 1.75], uncorrected p = [1.00 0.20]).

Electrode Pz: ERPs elicited by reinforcement feedback at electrode Pz are shown in Figure 4b. We found reliable main effects of reinforcement outcome between 220 - 600 ms after feedback onset (Figure 4d, ranges for significant time points: F = [6.06 75.38], p = [0.049 <0.000], uncorrected p = [.023 <0.000]). Reward feedback resulted in increased ERP amplitude relative to non-reward feedback between 220-359 ms after feedback. Reward feedback resulted in decreased ERP amplitude relative to non-reward feedback at between 468-496 ms and 533-600 ms after feedback. We did not find reliable main effects of levodopa at any time point (ranges for all timepoints between 100-600 ms: F = [0.00 2.16], uncorrected p = [0.96 0.16]). Nor did we find any reliable interaction effects between reinforcement outcome and levodopa (ranges for all timepoints between 100-600 ms: F = [0.00 4.33], uncorrected p = [0.99 0.05]).

Visuomotor rotation task.

Electrode FCz: ERPs elicited by endpoint cursor feedback at electrode FCz are shown in Figure 5a. We found reliable main effects of feedback rotation between 181 - 230 ms after feedback onset (Figure 5c, ranges for significant time points: F = [6.32 9.50], p = [0.041 0.0178], uncorrected p = [0.0041 0.0004]). In all significant timepoints and for both rotation magnitudes, the ERP voltage was lower for rotated feedback compared to unperturbed feedback in the respective drug condition. Post-hoc t-tests revealed ±2° rotated feedback caused decreased voltage relative to unrotated feedback between 181-203 ms after feedback in the levodopa condition ($p<0.05$ uncorrected). ±4° rotated feedback caused decreased voltage relative to unrotated feedback between 181-230 ms after feedback in the levodopa condition and 210-230 ms after feedback in the placebo condition ($p<0.05$ uncorrected).

We did not find reliable main effects of levodopa at any time point (ranges for all timepoints between 100-600 ms: F = [0.024 4.38], uncorrected p = [0.878 0.049]). Nor did we find any reliable interaction effects between reinforcement outcome and levodopa (ranges for all timepoints between 100-600 ms: F = [0.25 5.29], uncorrected p = [0.781 0.0092]).

Electrode Pz: ERPs elicited by endpoint cursor feedback at electrode Pz are shown in Figure 5b. We found reliable interaction effects between feedback rotation and levodopa 145-213 ms, and 220-350 ms after feedback (Figure 5d, ranges for significant time points: F = [4.33 11.19], p = [0.0497 0.0070], uncorrected p = [.0198 0.0001]). The earlier cluster occurred near the onset of the P300 deflection and appear to primarily reflect a delaying of P300 onset by feedback rotation after levodopa administration but not placebo. This was supported by post hoc testing. ERP voltage was lower in ±2° rotated feedback relative to unrotated feedback 156-161 ms and 193-198 ms in the levodopa condition. ERP voltage was lower in the ±4° rotated feedback relative to unrotated feedback between 145-169, 179-213, and 220-275 ms in the levodopa condition. In the placebo condition, voltage was larger after ±2° rotated feedback relative to unrotated feedback 145-159 ms after feedback. Later time points with significant interaction effects between rotation and drug spanned the peak of the P300 in all conditions, and appeared to reflect an increase in P300 peak amplitude by feedback rotation after placebo but not levodopa, which was supported by post hoc tests. ±2° rotated feedback elicited larger ERP voltage than unperturbed feedback in the placebo condition between 256-304 ms. ±4° rotated feedback elicited larger ERP voltage than unperturbed feedback in the placebo condition between 270-334 ms.

We did not find reliable main effects of levodopa at any time point (ranges for all timepoints between 100-600 ms: F = [0.000 0.289], uncorrected p = [0.996 0.597]). Nor did we find any reliable main effects of feedback rotation (ranges for all timepoints between 100-600 ms: F = [0.034 6.37], uncorrected p = [0.967 0.0040]).

Experiment 2

Control measures: Participants' judgment as to whether they received placebo or drug was near chance level (52.63%) and only 13.16% of participants responded that they thought they had received the drug. The values for heart rate, blood pressure, and alertness are reported in Table 2 for both the placebo and levodopa groups at the beginning and end of each experimental session. There were no reliable differences between the levodopa and placebo conditions in the percent change of heart rate ($t(36) = -1.09$, $p=0.282$), systolic blood pressure ($t(36) = 1.37$, $p=0.18$), diastolic blood pressure ($t(36) = 1.37$, $p=0.18$), or alertness ($t(36) = 0.88$, $p=0.39$).

Force field adaptation results

In each trial, we measured the perpendicular deviation (PD) of the reach trajectory at peak tangential velocity. PD data from throughout each force field and null field block, excluding catch trials, are shown in Figure 6. PD data from catch trials are shown in Figure 7.

Adaptation and savings: We analyzed learning and savings effects using PD data from FF1a, when participants first encountered a CW force field, and FF1b, when participants encountered the same CW force field again after a washout block. We used mixed ANOVA with bin (trials 1-24, 25-48, 49-72, 73-96) and block (FF1a, FF1b) as within-subject factors and drug condition (placebo, levodopa) as a between-subjects factor. We observed a reliable effect of bin on PD ($F(3,108) = 187.18$, $p < 0.001$) which reflected a decrease in PD over the course of each block, indicating adaptation. Adaptation is often facilitated when a force field is encountered a second time after washout of initial learning. This phenomenon, known as savings, would be reflected in a block*bin interaction effect. However, we did not observe a block*bin interaction($F(3,108) = 2.006$, $p=0.130$). We also found no reliable effects of block ($F(1,36) = 2.123$, $p = 0.154$), block*drug ($F(1,36) = 0.139$, $p = 0.712$), bin*drug ($F(3,108) = 0.702$, $p=0.513$), or block*bin*drug ($F(3,108) = 1.527$, $p=0.219$), or drug ($F(1,36) = 0.026$, $p = 0.872$).

We performed a similar analysis on the catch trial data from FF1a and FF1b, using trial (6,24,35,50,71,91) and block (FF1a, FF1b) as within-subject factors and drug condition (placebo, levodopa) as a between-subjects factor. We observed a significant main effect of trial on PD ($F(5,175) = 20.469$, $p<0.001$), indicating that the PD opposite the direction of the force field increased in catch trials throughout each block. We also observed a marginally significant trend towards a block*trial interaction effect ($F(5,175) = 2.381$, $p = 0.055$), which may indicate some occurrence of savings. We observed no reliable effect of block ($F(1,35) = 1.551$, $p = 0.221$), block*drug ($F(1,35) = 0.528$, $p=0.472$), trial*drug ($F(5,175) = 1.111$, $p = 0.354$), block*trial*drug ($F(5,175) = 0.784$, $p=0.536$), or drug ($F(1,35) = 0.665$, $p = 0.420$).

After-effects / Deadaptation: We analyzed deadaptation effects using PD data from NFb, when participants reached in a null force field after adapting to a CW field in FF1a. We used mixed ANOVA with bin (trials 1-24, 25-48, 49-72, 73-96) as a within-subject factor and drug condition (placebo, levodopa) as a between-subjects factor. We found a significant effect of bin ($F(3,108) = 84.388$, $p<0.001$), indicating that PD decreased over the course of the block as participants de-adapted to the previously encountered force field. We found no reliable effect of bin*drug ($F(3,108) = 0.503$, $p = 0.639$). We found no reliable effect of drug ($F(1,36) = 1.681$, $p = 0.203$).

Interference: We analyzed interference effects using PD data from FF2, when participants reached in a CCW force field after adapting to a CW field in FF1b. We used mixed ANOVA with bin (trials 1-24, 25-48, 49-72, 73-96) as a within-subject factor and drug condition (placebo, levodopa) as a between-subjects factor. We found a significant effect of bin ($F(3,108) = 217.532$, $p<0.001$). We found no reliable effect of bin*drug ($F(3,108) = 0.876$, $p = 0.445$). We found no reliable effect of drug ($F(1,36) = 0.603$, $p = 0.443$).

We analyzed the catch trial data from FF2 using trial (6,24,35,50,71,91) as a within-subject factor and drug condition (placebo, levodopa) as a between-subjects factor. We found a reliable effect of trial ($F(5,180) = 38.111$, $p < 0.001$). We did not find reliable effects of trial*drug ($F(5,180) = 0.810$, $p = 0.517$), or drug ($F(1,36) = 0.690$, $p = 0.412$).

Discussion

We tested for effects of levodopa, a dopamine precursor, in three different motor adaptation tasks across two experiments. In the first experiment we recorded EEG during a reward-based motor adaptation task and a sensory error-based visuomotor rotation (VMR) adaptation task. In the second experiment, we used a force field adaptation paradigm to test for effects of levodopa on initial adaptation, savings, and anterograde interference. We hypothesized that levodopa would selectively impair neural and behavioral responses to reinforcement feedback in the reward-based learning task as well as savings and interference. However, the only reliable influence of levodopa was in modulating the effect of visuomotor rotation on the P300 event-related potential component.

Visuomotor rotation task: During the VMR task included in experiment one, a cursor appeared at the endpoint of each reach to represent the position of the hand. In randomly intermixed trials, the cursor indicated a reach angle which was rotated relative to the true reach angle by either 0°, ±2°, or ±4°. Adaptation was evident in trial-by-trial changes in reach angle opposite the direction of the rotations that scaled linearly with rotation magnitude. We observed no effect of levodopa on adaptation. This was expected, as trial-by-trial error correction induced by relatively small visuomotor rotations is thought to be driven primarily by sensory error-based learning mechanisms as opposed to dopaminergic reinforcement learning circuits (Tanaka, Sejnowski, and Krakauer 2009; Diedrichsen et al. 2005; Wong et al. 2019; Taylor, Klemfuss, and Ivry 2010; Ito 2000; Krakauer et al. 2004).

We previously found that visuomotor rotation caused small but reliable increases in the peak amplitude of the P300 ERP component, a positive ERP deflection which peaked at electrode Pz between 342-350 ms following feedback presentation (Palidis, Cashaback, and Gribble 2019). This is consistent with theoretical interpretations of the P300 as a process of updating neural representations of the stimulus context in response to prediction error (Feldman and Friston 2010; Mars et al. 2008; Bennett, Murawski, and Bode 2015; Polich 2007; Donchin and Coles 1988; Krigolson and Holroyd 2007). We concluded that the neural underpinnings of the P300 may play a role in processing sensory error feedback, which contributes to adaptation. In the

present study, we observed interaction effects between feedback rotation and drug condition on ERPs recorded from electrode Pz beginning near the onset of the P300 and extending beyond its peak. Effects around the P300 peak were characterized by increased P300 amplitude in response to visuomotor rotations in the placebo condition but not in the levodopa condition. This result replicates previous findings that visuomotor rotations increase the amplitude of P300 responses to feedback, and additionally suggests that this effect is dependent on dopaminergic signaling (Palidis, Cashaback, and Gribble 2019; Aziz et al. 2020; MacLean et al. 2015). However, disruption of P300 amplitude modulation by dopaminergic perturbation did not correspond to any behavioral changes, indicating that the modulation of P300 amplitude by sensory error is not essential for adaptation. Nevertheless, we do not rule out a role of the P300 in processing sensory error, as a robust P300 response was still elicited by cursor feedback after levodopa administration that may have been sufficient to produce adaptation. Interaction effects of rotation and levodopa near the onset of the P300 were characterized by increased latency of P300 onset by feedback rotation in the levodopa condition relative to placebo. The effects of levodopa on P300 amplitude and latency are consistent with previous work indicating a relationship between dopamine function and the P300 response, however the neural mechanisms and functional significance of the P300 in relation to motor adaptation remain unclear (Stanzione et al. 1991; Noble et al. 1994; Sohn et al. 1998; Mulert et al. 2006; Pogarell et al. 2011; Stanzione et al. 1990; Hansenne et al. 1995; Takeshita and Ogura 1994; Chu et al. 2018). Variants of the P300 are elicited by many types of task-relevant stimuli, and have been localized to diffuse cortical areas including parietal, frontal, and motor regions, which have been implicated in processing prediction error (Bledowski et al. 2004; Polich 2007; Li, Wang, and Hu 2009; Soltani and Knight 2000; Ragazzoni et al. 2019; Sabeti et al. 2016; Calhoun et al. 2006; Mantini et al. 2009; Johnson et al. 2019).

We also observed a main effect of feedback rotation on ERP voltage between 181-230 ms after feedback onset at electrode FCz, a medial frontal site. This effect was characterized by lower ERP voltage in response to rotated feedback compared to non-rotated feedback, and appears to reflect a modulation of an N200 ERP component, a negative deflection which is typically maximal at electrode FCz and corresponds to activity in the theta frequency band linked to cognitive control over actions, conflict or error monitoring, and mismatch (Holroyd, Pakzad-Vaezi, and Krigolson 2008; Folstein and Van Petten 2008; Cavanagh and Frank 2014; Harper, Malone, and Bernat 2014). Previous studies have demonstrated modulations of medial frontal theta band activity that is not attributable to reward prediction error (Jonker et al., n.d.; Torrecillos et al. 2014; Savoie et al. 2018). This is consistent with our finding that visuomotor rotation produced effects at medial frontal scalp despite our attempts to control for reward prediction error and task success. Meta-analysis has shown that medial frontal ERPs are most sensitive to reward prediction error at latencies between 240-340 ms, while earlier effects of task feedback are more attributable to salience (Sambrook and Goslin 2015). This corroborates our result that sensory error feedback produced medial frontal effects with latencies only up to 230 ms while reinforcement feedback modulated the FRN/RP up to 350 ms.

Reward learning task: Participants adapted reliably to manipulations of binary reinforcement feedback intended to produce either progressively clockwise or counterclockwise reach angles.

Dopaminergic signaling of reward prediction error has proven to be a highly general mechanism for learning through reinforcement feedback, and computational reinforcement learning models using reward prediction error have been used to successfully account for reward-based motor adaptation (Izawa and Shadmehr 2011; Dhawale et al. 2019). Thus, we hypothesized that dopaminergic perturbation through levodopa would impair reward-based motor adaptation in healthy participants, as it has been shown to do in various other reinforcement based learning tasks. However, we found no effects of levodopa on adaptation. One possibility is that levodopa at the dose used in the current study is simply not a powerful enough disruption of dopaminergic function to impair learning in the task we used. Another possibility is that learning in the current task relies on different neural mechanisms than those shown to be impaired by levodopa in other tasks. (Quattrocchi et al. 2018) found no effect of levodopa or a dopamine antagonist haloperidol on modulation of sensory error-based learning by additional reinforcement feedback. (Holland et al. 2019) found no association between dopamine-related gene polymorphisms on adaptation through binary reinforcement feedback in a task similar to that used in the current study. Together, these findings suggest that reward-based motor adaptation may not rely on dopamine function.

The “dopamine overdose” hypothesis states that levodopa impairs learning by disrupting learning processes in the ventral striatum. The ventral striatum may specifically mediate stimulus-based reinforcement learning, while action-based reinforcement learning in the current study may be subserved by the dorsal striatum (Rothenhoefer et al. 2017). Furthermore, levodopa may specifically impair learning from unfavorable outcomes as opposed to rewarding outcomes (Roshan Cools et al. 2007; Roshan Cools, Altamirano, and D’Esposito 2006; Frank, Seeberger, and O’reilly 2004; Vo, Seergobin, and MacDonald 2018). Non-reward outcomes in the current task may not contribute significantly to learning as they do not instruct the correct response, unlike in binary response tasks.

Another important distinction is between model-free and model-based reinforcement learning processes (Babayan, Uchida, and Gershman 2018; Shahar et al. 2019; Daw et al. 2011; Dolan and Dayan 2013; Russek et al. 2017; Deserno et al. 2015; Doll et al. 2016; Gläscher et al. 2010; Sharpe et al. 2017; Gardner Matthew P. H., Schoenbaum Geoffrey, and Gershman Samuel J. 2018; Sambrook et al. 2018). Model-free reinforcement learning is characterized by reinforcement of simple stimulus-response associations that facilitate habitual, reflexive responding. Model-based learning allows for flexible planning according to a mental representation of the task, and can be limited by working memory processes. Levodopa has been shown to impair reward-based learning in healthy controls and Parkinson’s disease patients, but also to improve some cognitive functions in patients such as working memory, cognitive flexibility, and attention, which are related to model-based learning (Torta et al. 2009; Cooper et al. 1992; Costa et al. 2003; Lange et al. 1992; Lewis et al. 2005; Marini et al. 2003; Beato et al. 2008; Moustafa, Sherman, and Frank 2008; Kulisevsky 2000; R. Cools et al. 2001; Roshan Cools et al. 2003). It is possible that “dopamine overdose” by levodopa selectively impairs model-free learning. This is partly supported by one study which specifically probed model-based learning and found that levodopa improved performance in individuals with Parkinson’s disease (Sharp et al. 2016). It may be that reward-based motor adaptation in the

current study relies on model-based learning, which is not vulnerable to “dopamine overdose” in healthy populations. Reward-based motor adaptation tasks similar to that in the current study have been shown to primarily involve strategic aiming which can be influenced by explicit instructions and cognitive load, suggesting a primary role of model-based learning (Codol, Holland, and Galea 2018; Holland, Codol, and Galea 2018).

We also analyzed the variability of trial-by-trial changes in reach angle as a function of reward outcomes. An increase in variability following non-reward may reflect exploration in search of more valuable actions (Cashaback et al. 2017; Dhawale et al. 2019). Reward related modulation of motor variability has been shown to be impaired in medicated Parkinson’s disease in a very similar task (Pekny, Izawa, and Shadmehr 2015). We hypothesized that this effect may be due to off-target effects of dopaminergic medication, and that we would observe similar impairments in healthy participants after levodopa administration. However, we observed no effect of levodopa on reward-related modulation of motor variability. Reward-based modulation of exploratory variance may therefore not depend on the ventral striatum, which is relatively spared in early stage Parkinson’s disease and therefore vulnerable to “dopamine overdose” in patients and healthy controls alike. Instead, it may depend on the dorsal striatum, which is more closely related to movement planning and is primarily impacted by early stage Parkinson’s Disease.

Reinforcement feedback elicited a very reliable FRN/RP ERP component, which was characterized by a relative positivity for reward outcomes compared to non-reward outcomes that was statistically significant at electrode FCz between 197-346 ms after feedback. Meta analyses have shown that the FRN/RP at the same scalp location and similar time ranges encodes a quantitative reward prediction error across multiple different tasks (Sambrook and Goslin 2015; Walsh and Anderson 2012). Reports have linked the FRN/RP signal to behavioral adjustments in response to feedback (Palidis, Cashaback, and Gribble 2019; Arbel, Goforth, and Donchin 2013; Holroyd and Krigolson 2007; van der Helden, Boksem, and Blom 2010; Frank, Woroch, and Curran 2005). These findings support a prominent theory purporting that the FRN/RP is a reflection of reinforcement learning processes in the anterior cingulate cortex driven by phasic dopamine reward prediction error signals (Holroyd and Coles 2002; Walsh and Anderson 2012). We hypothesized that levodopa would reduce the magnitude of the FRN due to increased tonic dopamine release resulting in a reduction of dynamic range for phasic changes in dopamine release. However, we observed no effects of levodopa on the FRN/RP in response to reinforcement feedback. Previous studies have supported a link between dopamine and the FRN/RP, although results have been mixed. FRN/RP amplitude has been shown to be impaired in Parkinson’s disease patients with apathy but normal in nonapathetic patients (Martínez-Horta et al. 2014). (Brown, Pirio Richardso, and Cavanagh 2019) found that the reward positivity was impaired in Parkinson’s disease patients relative to controls ON levodopa but not OFF levodopa, which is consistent with the dopamine overdose hypothesis. However, there was no significant effect of medication condition within patients. In healthy participants, the dopamine antagonist haloperidol has shown mixed results in reducing the amplitude of the reward positivity (Schutte et al. 2020; Forster et al. 2017). (Mueller et al. 2014), found that the D2 receptor dopamine antagonist sulpiride had opposite effects on FRN/RP amplitude

depending on a genotype variant which regulates prefrontal dopamine levels. This result may depend on a u-shaped relationship between dopamine release in the prefrontal cortex and FRN/RP amplitude mediated by the balance between D1 and D2 receptor activation. Because the effect of dopamine manipulation on the FRN/RP seems to depend on genetic differences in baseline dopamine release, one possibility is that levodopa in the current study had inconsistent effects on different subgroups of participants which cancelled each other in the group average.

Force field adaptation task: Participants reliably adapted to the clockwise force field imposed in blocks FF1a and FF1b. This was evidenced by decreasing error in response to the force field perturbations over the course of each block and increasing error opposite the direction of the force field in catch trials. We observed no reliable effects of savings, whereby adaptation is typically facilitated upon encountering a force field a second time after washout of initial adaptation. Only a trend was observed towards an interaction effect between trial bin and block (FF1a, FF1b) on the PD during catch trials ($p=0.056$), indicating that the time course of adaptation may have been affected by savings. We did not observe any reliable effects of levodopa on adaptation or savings. In the final experimental block (FF2), participants adapted to a counterclockwise force field immediately after adapting to a clockwise field in FF1b. This allowed us to test for effects of levodopa on anterograde interference, whereby adaptation to a new force field is impaired by previous adaptation to an opposite perturbation. We observed no effects of levodopa on learning in FF2, suggesting that levodopa did not influence anterograde interference.

Force field adaptation is thought to rely primarily on sensory error-based learning mechanisms involving the cerebellum. Savings and interference effects have been accounted for by additional model-free learning processes including operant reinforcement of adapted motor commands upon repetition of successful reaches (Huang et al. 2011). These distinctions are supported by findings that cerebellar degeneration impairs force field adaptation while Parkinson's disease patients are spared in initial adaptation but display deficient savings and interference (Taylor, Klemfuss, and Ivry 2010; Maschke et al. 2004; Leow et al. 2013; Leow, Loftus, and Hammond 2012; Bédard and Sanes 2011, 2014). Thus, we hypothesized that dopaminergic perturbation by levodopa would impair savings and interference while leaving initial adaptation intact. We found no effect of levodopa on savings or interference. However, the experimental protocol may have been insufficient to produce savings or interference even in the control group, as we observed limited evidence of savings overall. Savings and interference have been shown to depend on sufficient repetition of the adapted movements to produce reinforcement of the adapted movements (Huang et al. 2011; Leow et al. 2016). Because the current study involved reaches to 8 different targets, repetition and each individual target was limited relative to single target experiments.

Conclusions: As we expected, sensory error-based motor adaptation induced by visuomotor rotations and force field perturbations was not vulnerable to disruption of dopamine signaling by levodopa. This supports the notion that sensory error-based learning is driven by circuits involving cerebellar and sensorimotor cortex distinct from dopaminergic reinforcement learning mechanisms. Contrary to our hypotheses, we also failed to detect any effects of levodopa on

reward-based motor learning or the FRN/RP ERP component, which have both been theorized to depend on dopaminergic signaling of reward prediction error. The dopamine overdose hypothesis suggests that levodopa impairs stimulus-response reinforcement learning processes in the ventral striatum. Reward-based motor adaptation may instead depend on distinct reinforcement learning circuits which are not disrupted by levodopa such as cortical reward learning mechanisms or dopaminergic projections to the dorsal striatum.

Tables

Measure	Placebo	Levodopa
HR	Pre: 76.24 (SD: 11.29) Post: 69.60 (SD: 7.27)	Pre: 77.55 (SD: 8.41) Post: 71.53 (SD: 6.92)
Sys	Pre: 104.43 (SD: 9.01) Post: 104.20 (SD: 6.47)	Pre: 103.95 (SD: 8.34) Post: 102.79 (SD: 8.70)
Dia	Pre: 72.14 (SD: 5.14) Post: 73.20 (SD: 4.55)	Pre: 70.55 (SD: 6.81) Post: 69.74 (SD: 6.04)
Alertness	Pre: 64.58 (SD: 8.38) Post: 47.99 (SD: 15.43)	Pre: 58.20 (SD: 11.79) Post: 48.16 (SD: 15.33)

Table 1: Control measurements from experiment 1. HR, heart rate (bpm). Sys, systolic blood pressure (mm Hg). Dia, diastolic blood pressure (mm Hg). Alertness, Bond-Lader visual analog scale alertness measure.

Measure	Placebo	Levodopa
n	19	19
n female	9	10
Age	21.2 (SD: 2.5)	22.2 (SD: 3.4 years)
HR	Pre: 75.1 (SD: 9.5) Post: 66.2 (SD: 10.2)	Pre: 71.6842 (SD: 12.8) Post: 65.7 (SD: 11.3)
Sys	Pre: 109.2 (SD: 15.4) Post: 104.8 (SD: 14.5)	Pre: 108.4 (SD: 11.4) Post: 99.7 (SD: 10.1)
Dia	Pre: 72.0 (SD: 10.2) Post: 70.1 (SD: 10.2)	Pre: 73.2 (SD: 15.5) Post: 67.0 (SD: 8.2)
Alertness	Pre: 31.3 (SD: 15.3) Post: 39.4 (SD: 17.0)	Pre: 27.1 (SD: 11.0) Post: 43.4 (SD: 12.7)

Table 2: Control measurements from Experiment 2. HR, heart rate (bpm). Sys, systolic blood pressure (mm Hg). Dia, diastolic blood pressure (mm Hg). Alertness, Bond-Lader visual analog scale alertness measure.

Figures

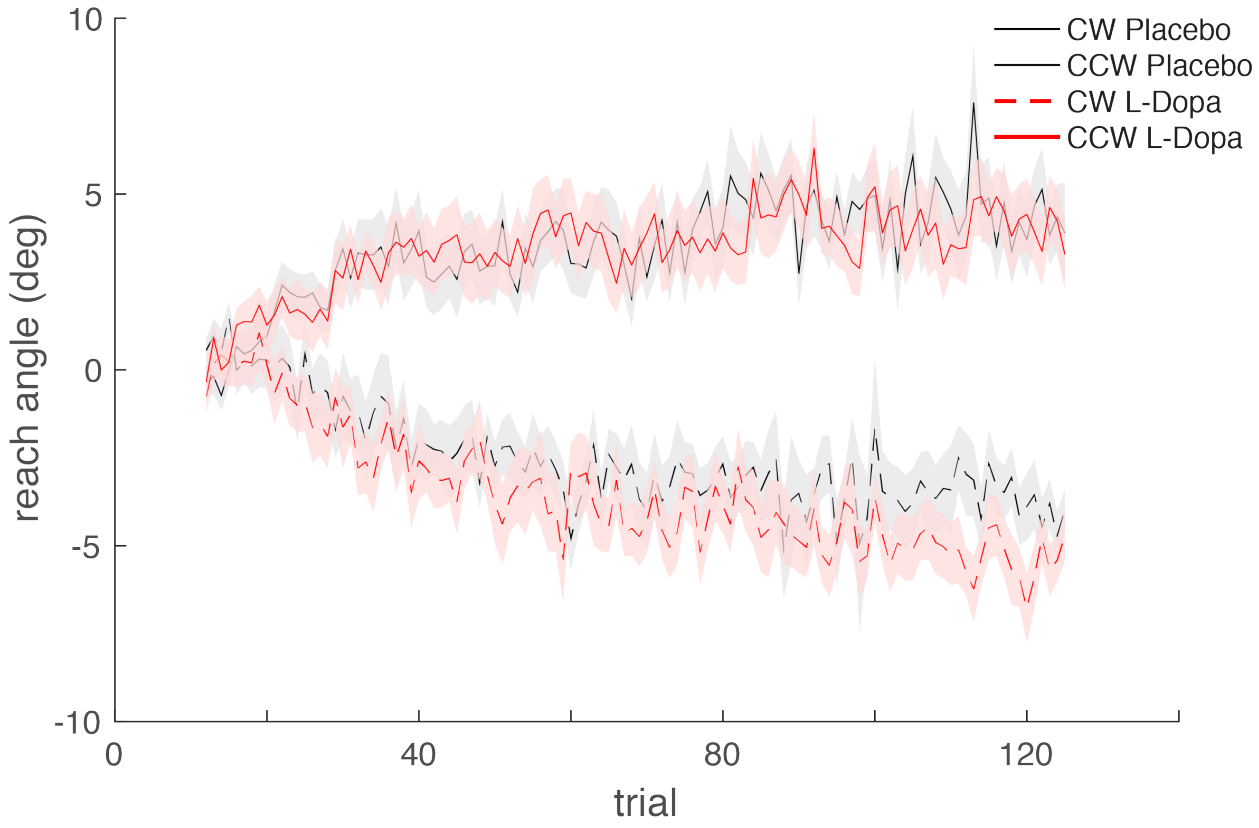

Figure 1. Reward based motor adaptation (n=21). Group average reach angles in the reward learning conditions are plotted (Shaded region: ± SEM). After both placebo and levodopa administration, participants completed a block in each direction of intended learning condition [clockwise (CW) and counterclockwise (CCW)]. Trials 1-11 were baseline trials without reinforcement feedback, and are not shown.

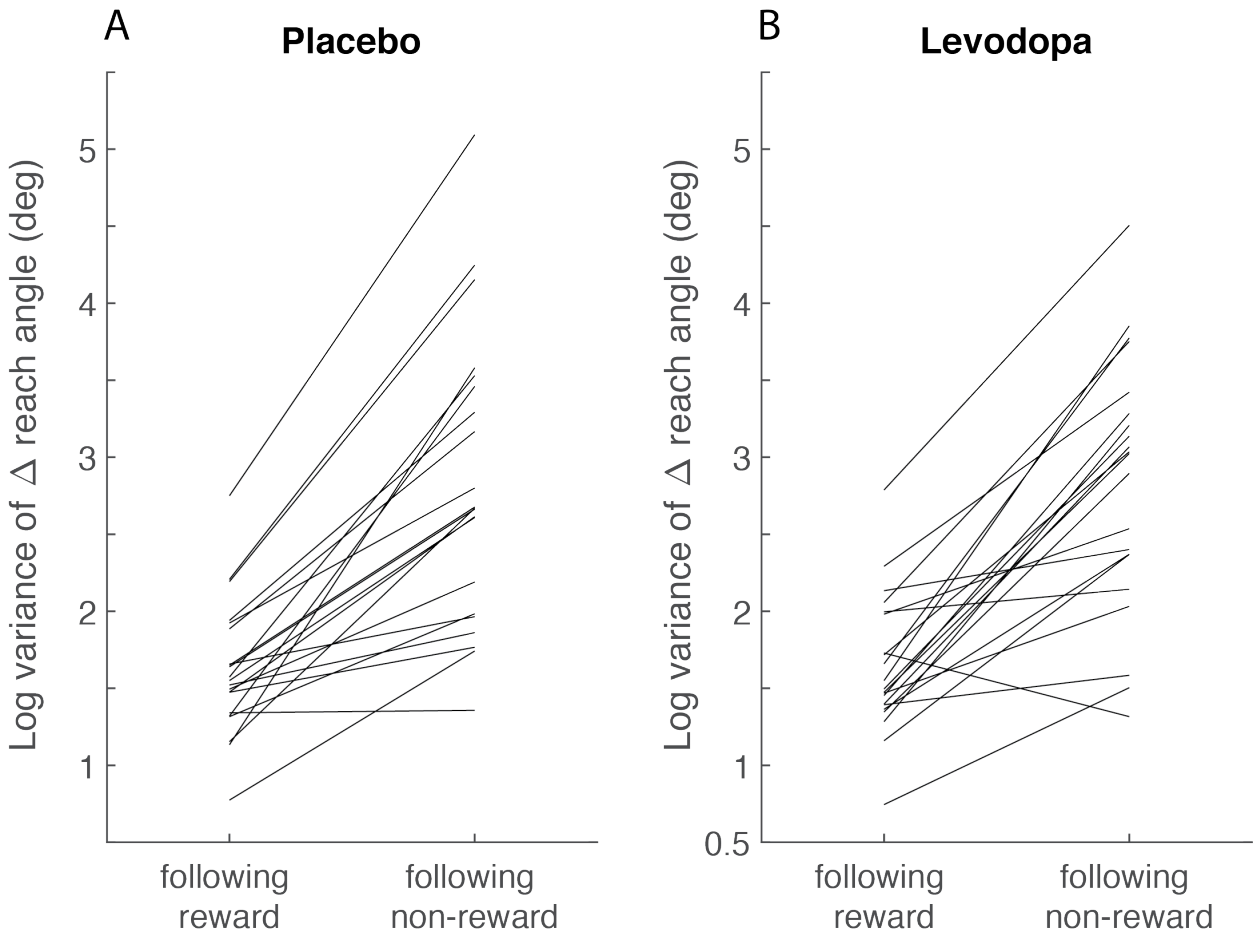

Figure 2. Reward induced modulation of trial-by-trial variability of reach angle (n=21). The log transformed variance of trial-by-trial changes in reach angle (deg) following reward and non-reward are plotted for each participant following administration of levodopa (**A)** and placebo (**B)**.

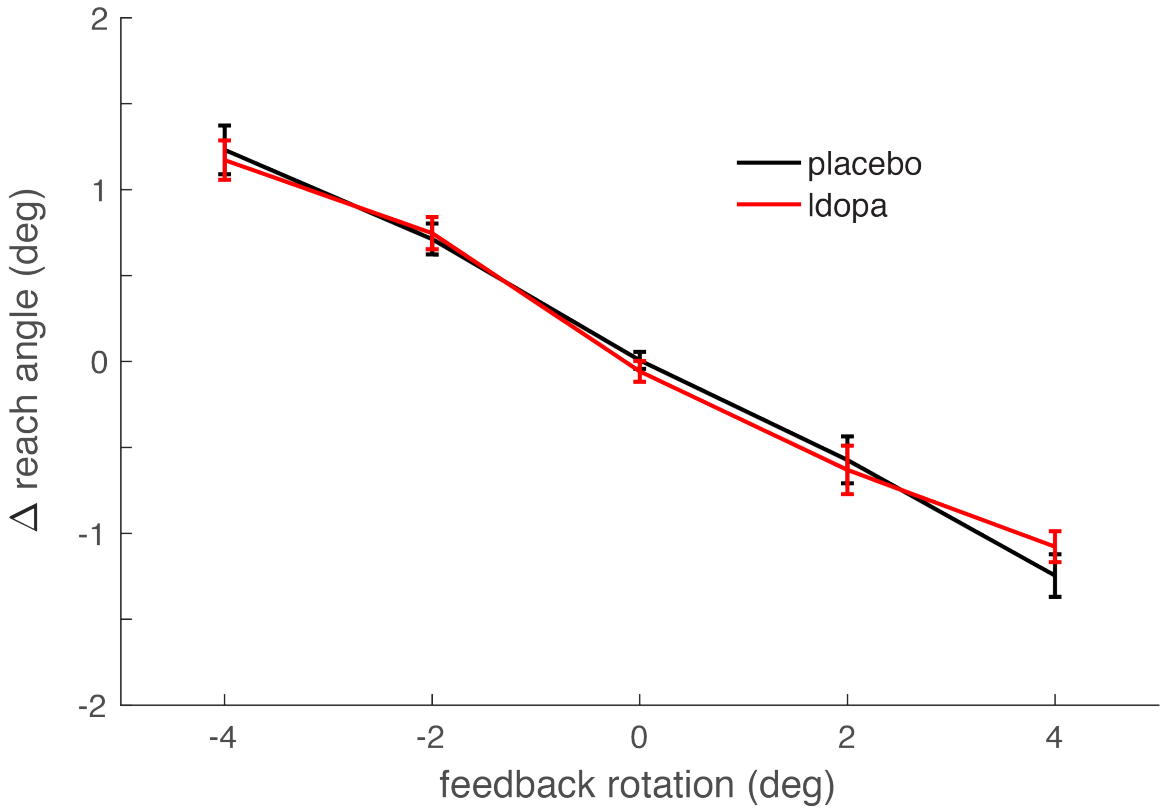

Figure 3. Sensory error-based motor adaptation (n=21). The average change in reach angle between subsequent pairs of trials is plotted for each size and direction of rotation imposed on the preceding trial. The average change in reach angle is in all cases opposite to the rotation, indicating that participants adapted their reaches to counteract the perturbations.

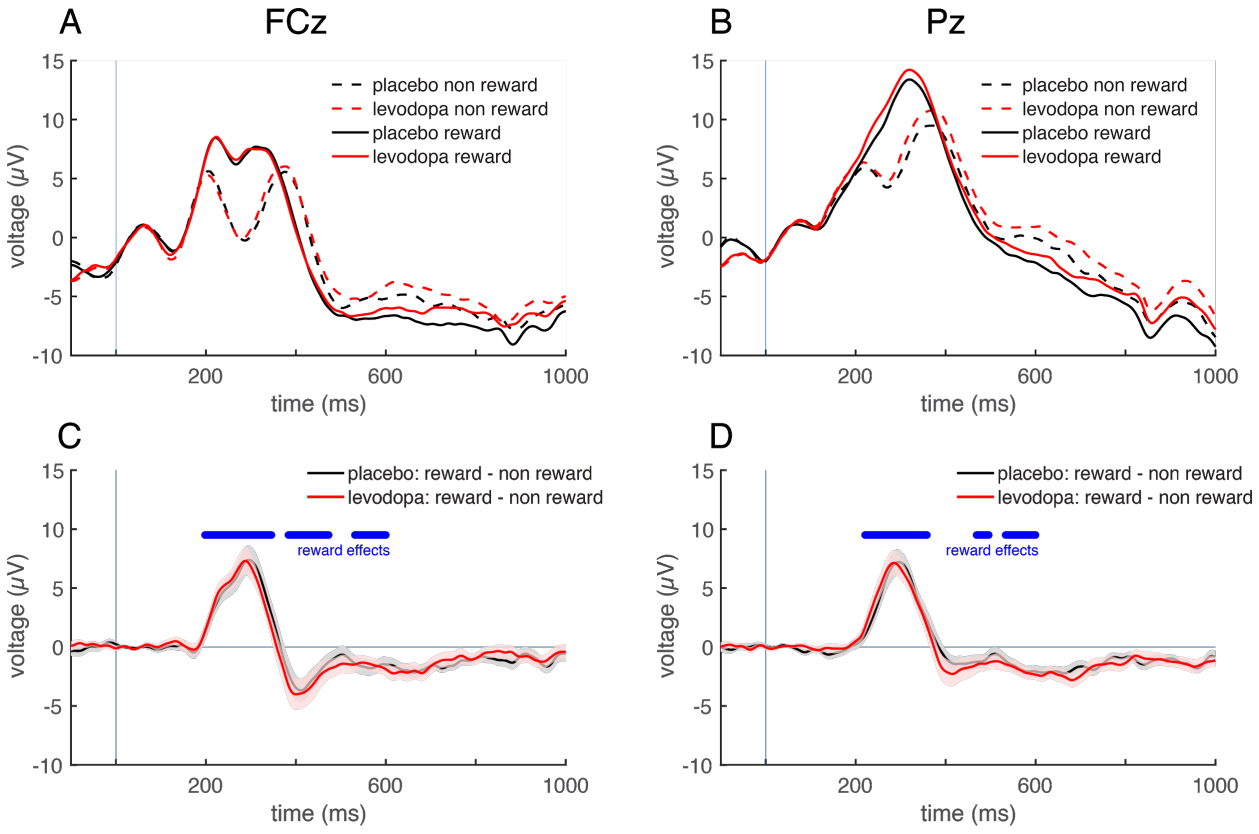

Figure 4. Event-related potentials elicited by reinforcement feedback (n=21). **A,B,** Trial averaged ERPs recorded from electrode FCz and Pz. ERPs are aligned to reinforcement feedback presentation (0 ms: vertical blue line). Trials were selected by reinforcement outcome (reward or non-reward) and drug condition (levodopa or placebo) for averaging. **C,D,** Mean difference waves computed as reward ERP - non reward ERP, separately for the levodopa and placebo conditions (Shaded region: ± SEM). Blue markers indicate time points between 100-600 ms with significant main effect of reward outcome ($p < 0.05$, FDR corrected).

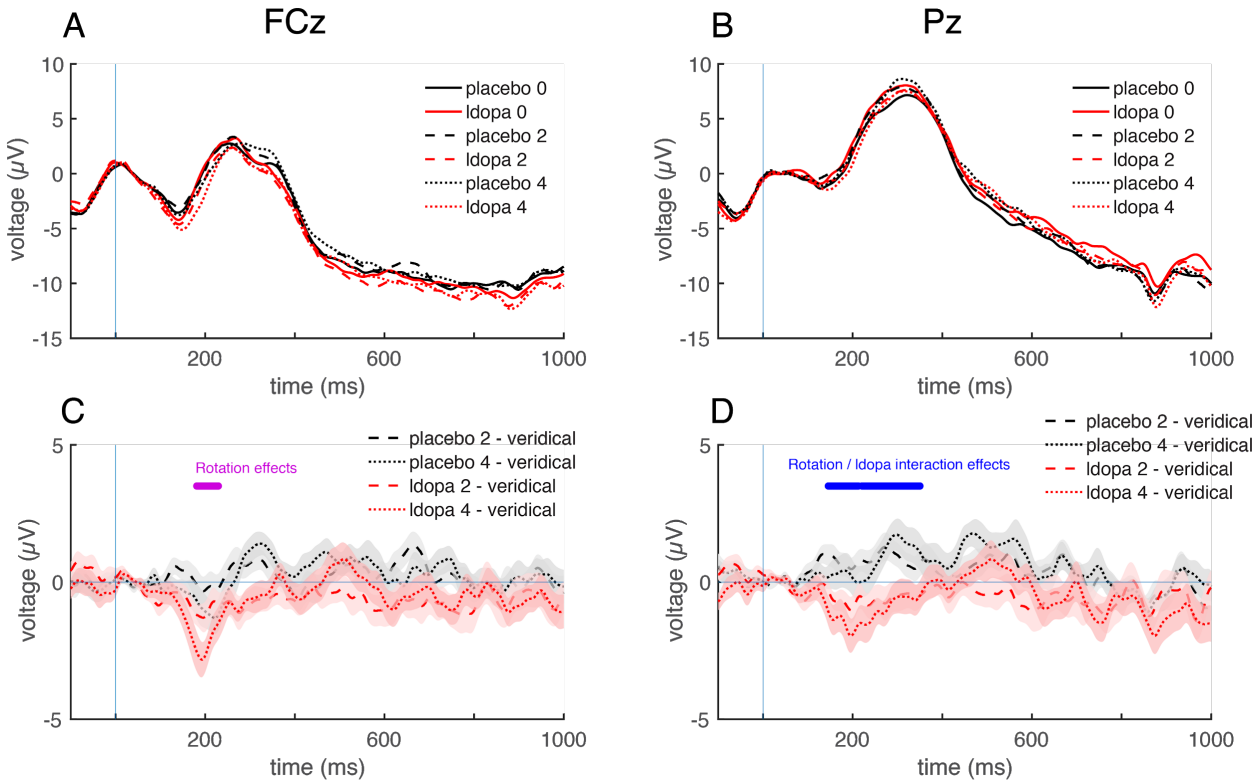

Figure 5. Event-related potentials elicited by endpoint cursor feedback (n=21). **A,B,** Trial averaged ERPs recorded from electrode FCz and Pz. ERPs are aligned to endpoint cursor feedback presentation (0 ms: vertical blue line). Trials were selected for feedback rotation (0°, ±2°, or ±4°) and drug condition (levodopa or placebo) for averaging. **C,D,** Mean difference waves computed as rotated feedback ERP - non rotated feedback ERP, separately for each rotation size and drug condition (Shaded region: ± SEM). Purple markers indicate time points between 100-600 ms with significant main effect of feedback rotation, while blue markers indicate significant rotation by drug interactions ($p < 0.05$, FDR corrected).

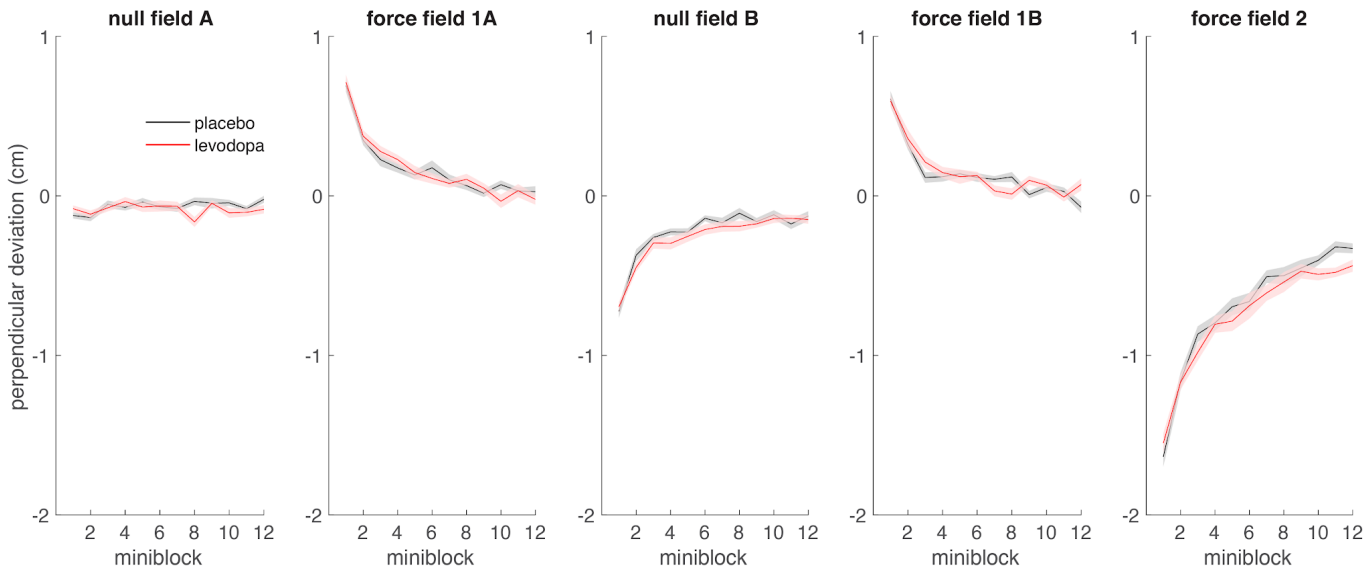

Figure 6. Adaptation effects during force field and null field reaches. Average perpendicular deviation of the hand trajectory within miniblocks consisting of 8 trials each is shown in cm (Shaded region: ± SEM). The placebo condition is shown in black (n=19), and the levodopa condition is shown in red (n=19). Perpendicular deviation was measured on each trial at peak tangential velocity. Trials 6, 24, 35, 50, 71, and 91 of each block were catch trials, and were excluded from the corresponding miniblocks. In *null field A* and *null field B,* the robot did not apply external forces to the hand during reaches. In *force field 1A* and *force field 1B,* participants made reaches in a clockwise force field. In *force field 2* participants made reaches in a counterclockwise force field.

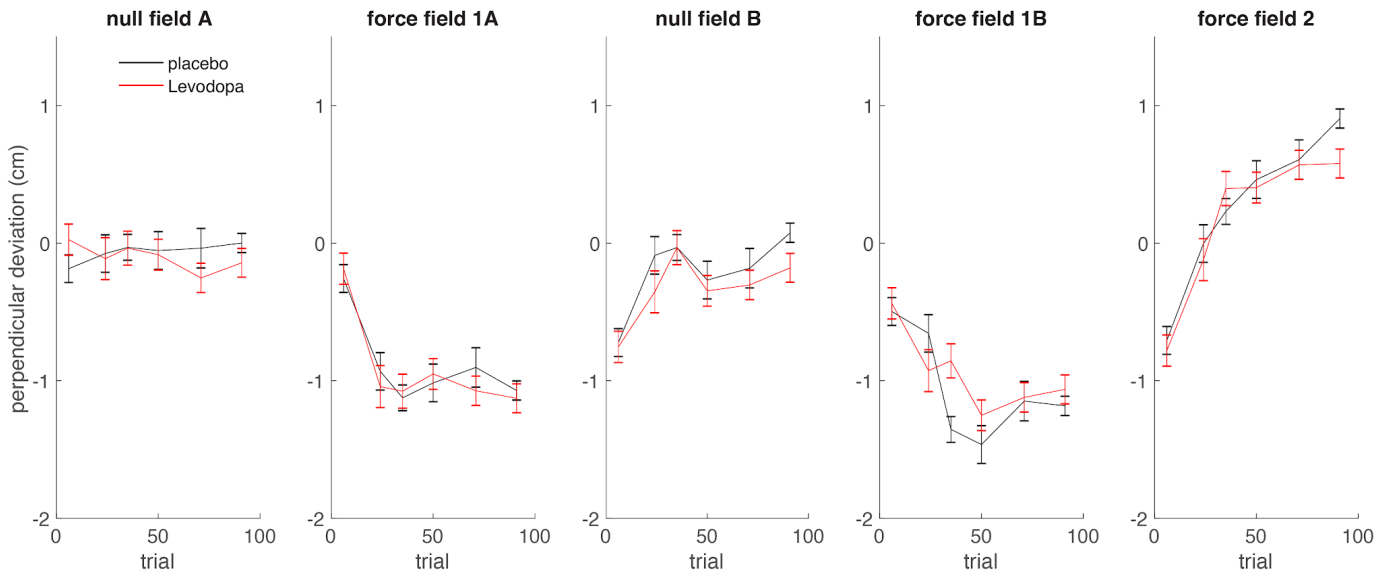

Figure 7. Adaptation effects during catch trials. Perpendicular deviation of the hand trajectory, measured at peak tangential velocity, is shown in cm (Error bars: ± SEM). The placebo condition is shown in black (n=19), and the levodopa condition is shown in red (n=19). Catch trials occurred on trials 6, 24, 35, 50, 71, and 91 of each block. In *null field A* and *null field B,* the robot did not apply external forces to the hand during reaches. In *force field 1A* and *force field 1B,* participants made reaches in a clockwise force field. In *force field 2* participants made reaches in a counterclockwise force field.

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