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TITLE

Left-shifting prism adaptation boosts reward-based learning

Abbreviated title

Prism adaptation boosts learning

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ABSTRACT

Visuospatial cognition has an inherent lateralized bias. Individual differences in the direction and magnitude of this bias are associated with asymmetrical D2/3 dopamine binding and dopamine system genotypes. Dopamine level affects feedback-based learning and dopamine signaling asymmetry is related to differential learning from reward and punishment. High D2 binding in the left hemisphere is associated with preference for reward. Prism adaptation (PA) is a simple sensorimotor technique, which modulates visuospatial bias according to the direction of the deviation. Left-deviating prism adaptation (LPA) induces rightward bias in healthy subjects, it is therefore possible that the right side of space increases in saliency along with left hemisphere dopaminergic activity. Right-deviating prism adaptation (RPA) has been used mainly as a control condition because it does not modulate behavior in healthy individuals. Since LPA induces a rightward visuospatial bias as a result of left hemisphere modulation, and higher dopaminergic activity in the left hemisphere is associated with preference for rewarding events we hypothesized that LPA would increase the preference for learning with reward. Healthy volunteers performed a computer-based probabilistic classification task before and after LPA or RPA. Consistent with our predictions, PA altered the preference for rewarded vs. punished learning, with the LPA group exhibiting increased learning from reward. These results suggest that PA modulates dopaminergic activity in a lateralized fashion.

1. INTRODUCTION

Prism adaptation (PA) is the visuomotor adaptation to displaced vision (Helmholtz, 1867; for review see Redding and Wallace, 2006) and has been shown to modulate a wide range of behaviors, including visuospatial/orienting bias (see Michel, 2016 for review). PA is a promising technique for treating unilateral spatial neglect syndrome (for a review see Newport and Schenk, 2012) and modulates visuospatial cognition in healthy adults (Michel, 2016). Adaptation to right-shifting prisms (RPA) ameliorates the pathological rightward visuospatial bias in patients with unilateral spatial neglect (Rossetti et al., 1998). Whereas, following adaptation to left-shifting prisms (LPA; e.g. Colent et al., 2000; Schintu et al., 2014), healthy individuals show a significant rightward bias (reduction of inherent leftward spatial bias called “pseudoneglect;” Bowers and Heilman, 1980; for a review see Jewell and McCourt, 2000).

There is evidence that the laterality of visuospatial/orienting bias is under dopaminergic control in humans (Tomer, 2008; Slagter et al., 2010) and animals (Zimmerberg et al., 1974), with a preference for the visual space contralateral to the hemisphere with greater dopaminergic activity (Glick et al., 1976; Tomer et al., 2013). In humans, positron emission tomography has shown that the laterality of dopamine (DA) D2/3 receptor binding asymmetries in the putamen and temporal and frontal cortex predicted spatial preference (Tomer et al., 2013). Genetic variations affecting the DA system are also associated with differences in orienting bias (Zozulinsky et al., 2014). The link between DA and attention is further strengthened by the fact that neglect is mitigated by DA receptor agonists (Fleet et al., 1987; Geminiani et al., 1998; Grujic et al., 1998; Gorgoraptis et al., 2012) and changes in orienting attention have been reported in healthy individuals after pharmacological manipulation of central DA transmission (Clark et al., 1989).

DA facilitates attentional shifts and detection of unexpected events. Despite the fact that frontoparietal projections have been found only in non-human animals (Lewis et al.,

2001; Corbetta et al., 2008), a recent fMRI experiment (Krebs et al., 2012) has shown that the cortico-striatal-thalamic circuits, along with the midbrain DA nuclei, integrate expected value and attentional demands, reinforcing the association between DA and attention. Additional support for the role of DA transmission in attention comes from Parkinson disease (Lee et al., 2001) where patients with left-side onset of motor deficits (i.e. right hemisphere-predominant disease) have more severe visuospatial performance deficits than patients with right-side onset (e.g. Levin et al., 1991; Karádi et al., 2015).

DA is known to be crucial in learning, and both DA levels (Frank et al., 2004; Frank, 2005; Bódi et al., 2009; Palminteri et al., 2009) and neurotransmission (Palminteri et al., 2011) affect reward-based learning. Furthermore, recent data show that the degree of hemispheric asymmetry in D2 receptor binding predicts differential sensitivity to reward and punishment in learning tasks (Maril et al., 2013; Tomer et al., 2014; Aberg et al., 2015).

Reward is tightly linked to visual attention (Maunsell, 2004) and the role of reward in directing attention is so strong that stimuli associated with value capture attention independently of the goal of the task and more salient concurrent stimuli (Anderson et al., 2011; Lee and Shomstein, 2014). Therefore, it would be expected that dopaminergic balance between the hemispheres would have an influence on the laterality of attentional preference. However, not only are saliency and reward bound tightly, but saliency increases DA activity even in absence of reward. For instance, the striatum processes salient stimuli independently of their task-determined rewarding value (Zink et al., 2003). It is therefore possible that following LPA, which induces a rightward bias, the right side of space increases its saliency and thus left hemisphere dopaminergic activity.

A direct prediction of this theory is that the change in dopaminergic activity should be detectable in sensitivity to rewarded learning. We hypothesized that LPA would improve learning from reward because higher dopaminergic activity in the left hemisphere is associated with preference for rewarding events during learning. To test this hypothesis, we chose a probabilistic learning task with rewarded and punished learning conditions. In a between-groups design, we administered the task before and either after LPA or RPA (the

control condition). We predicted that LPA would selectively improve learning from rewarding feedback.

2. MATERIALS AND METHODS

2.1. Participants

Fifty healthy volunteers participated in the study. Three were excluded from the analysis due to technical problems and one because of a cataract affecting vision. Participants were assigned either to LPA ($N = 24$, 18 females, mean age = 20.88, SEM = 0.57) or RPA ($N = 22$, 17 females, mean age = 19.77, SEM = 0.38). The LPA and RPA groups did not differ by age [$t(44) = 1.591$, $p = .119$]. All participants had normal or corrected-to-normal vision and were right-handed according to the Edinburgh Handedness Inventory (Oldfield, 1971). Participants gave informed consent and were paid \$15 or given academic credit for participation.

Participants were not compensated based on task performance. The study was approved by the George Washington University Institutional Review Board and was conducted in accordance with the ethical standards of the 1964 Declaration of Helsinki (World Medical Association, 2013).

2.2. Procedure

As shown in Figure 1, the experiment consisted of one session before, and one after, PA. Each session included open-loop pointing (1 min duration) and the feedback-based probabilistic classification learning task (15 min duration). Open loop pointing measurement was repeated at the end of the experiment to assess whether participants were still adapted to the visual displacement. The feedback-learning task started at least 5 minutes after adaptation in order to coincide optimally with the cognitive effect of PA (Schintu et al., 2014).

-Insert Figure 1 about here-

Participants were seated in front of a horizontal wooden board with their heads supported by a chinrest. On the board, three circular targets (8 mm in diameter) were positioned at 0, -10, and +10 degrees from the body midline, approximately 57 cm from participant's nasion.

For both the open-loop pointing and PA procedures (see Sections 2.3 and 2. 2.1), participants rested the left hand on the left thigh and pointed with their right index finger. The right index finger started on a 1.5 cm diameter Velcro® pad, placed close to the midline of the chest. Participants were instructed to point with the index finger perpendicular to the board and to return to the start pad when cued by the experimenter. The experimenter noted the landing position of the participant's finger with a precision of +/- 0.5 cm.

2.2.1. PA Procedure

During PA, participants were fitted with prism goggles with a 15° of-visual-field deviation to the right or left and performed 150 verbally-cued pointing movements to the right and left targets in a pseudorandom order. Participants were instructed to execute a ballistic movement at a fast but comfortable speed. They could see the target, the second half of their pointing movement, and their terminal error.

2.3. Experimental tasks and measurements

2.3.1. Open-loop pointing task

The open-loop pointing task was used to measure the sensorimotor shift produced by PA. Participants performed six pointing movements to the central target (0°) without visual feedback, and were instructed to keep the speed as uniform as possible. The arm movement was concealed. Before each movement, participants were asked to fixate the central target, close their eyes, point at the target while their eyes were closed and then to return the finger to the start pad. To prevent visual feedback on the landing position, the board was hidden by a cardboard baffle after participants looked at the target and closed their eyes. The baffle was removed once the finger was returned to the start pad in order to show the target. The

sensorimotor shift was measured as the mean radial distance in cm of the six landing points from the central target.

2.3.2 Feedback-based probabilistic classification learning task

This two-choice categorization task, based on feedback (adapted from Bódi et al., 2009), was programmed in prime (Psychology Software Tools Inc., Sharpsburg, PA) and designed to measure learning from reward and punishment. Participants learned to identify stimuli as belonging to one of two categories. At the start of the task, participants read the instructions on the screen. They were then walked through an example of a correct and an incorrect response to sample trials in both the punishment-learning task and reward-learning conditions. A practice session of 20 trials then followed. The stimuli employed for the example and practice sessions were different from the ones used in the experiment and data were not analyzed.

Participants categorized one stimulus per trial. The right and left index fingers were placed on the masked keys of a standard keyboard corresponding to the two categories, and participants indicated their choice by responding with their left or right index finger. The assignment of keys to categories was counterbalanced across subjects. Feedback, in the form of points added (rewarded trials) or subtracted (punished trials), appeared under the stimulus and the point total was always visible for each trial. The interval between trials was 2 sec and each stimulus remained on the screen for a maximum of 2 sec or until a response was made. Eight monochrome, abstract figures were used (Figure 2 shows 2 of the 8 stimuli). A randomly chosen subset of four were used in the Pre-PA phase and the remaining four in the Post-PA phase. During each phase, two stimuli were designated as rewarded and two others as punished. Rewarded and punished stimuli were chosen so that one of each pair belonged to Category A on 80% of trials and the other to Category B on 80% of trials. Stimulus assignment to rewarded and punished trials was counterbalanced across participants to avoid stimulus effects. The assignment of stimuli to category was also counterbalanced across

participants. The feedback-learning task consisted of three blocks of 40 trial each for a total of 120 trials.

Participants started with a score of 500 points. On rewarded trials, 25 points were awarded for each correct category guess; whereas incorrect guesses produced no change in points. On punished trials, each incorrect guess resulted in subtraction of 25 points; whereas correct responses resulted in no point change. In order to minimize frustration, if the participant's point total was < 525 after 120 trials, additional trials were added, in which the participant's response was always scored as correct, until the tally was ≥ 525 . Data from these trials were not analyzed.

-Insert Figure 2 about here-

3. RESULTS

Statistical analyses were performed using SPSS (IBM, Version 22.0) and R (R Development, 2010) with alpha set at .05 (two-tailed). All data are presented as means with the standard error of the mean (SEM). Effect sizes are indicated for significant effects. When sphericity was violated Greenhouse-Geisser corrected values are reported.

3.1 Open-loop pointing to measure sensorimotor shift

Figure 3 shows the average landing position for the three open-loop task sessions for 45 participants. One was excluded from this analysis due to a missing data point. The repeated measures analysis of variance (ANOVA), with Phase (pre, post1, and post2) as a within-subjects factor and PA Direction (LPA, RPA) as a between-subjects factor, revealed a main effect of PA Direction [$F(1, 43) = 247.567, p < 0.001, \eta^2_p = 0.0852$], such that pointing was rightward after LPA and leftward of the true center after RPA. There was a Phase by PA Direction interaction [$F(1.643, 70.663) = 214.373, p < 0.001, \eta^2_p = 0.833$], meaning that LPA shifted pointing rightward and RPA shifted it leftward. However, there was no significant main effect of Phase [$F(1.643, 70.663) = 0.572, p = 0.534, \eta^2_p = 0.013$]. A planned,

Bonferroni-corrected, paired t -test revealed that the two post-PA sessions differed significantly from baseline for both PA groups (all $p < 0.001$) and that these effects decayed significantly from post1 to post2 (all $p < 0.001$).

-Insert Figure 3 about here-

To compare the degree of adaptation between the two PA groups, we performed a repeated measures ANOVA on the absolute value of the sensorimotor shift (post-PA – pre-PA) with Phase as a within-subjects factor and PA Direction as a between-subjects factor. This revealed only a main effect of Phase [$F(1, 43) = 117.451$ $p < .001$, $\eta^2_p = 0.732$] (all other $F < 1$), meaning that there was no significant difference in the amount of sensorimotor PA induced in the two groups.

3.2 Feedback-based probabilistic learning task

We chose optimal responding (Knowlton et al., 1994) as the metric for success on the learning task because the optimal response on all trials can result in an accuracy equal to the reinforcement rate of the stimulus (80% in this study); whereas responding at the reinforcement rate—i.e., choosing a response 80% of the time for a given stimulus—leads to suboptimal reinforcement (0.68). Since optimal responses are proportional data, they were logit-transformed. This procedure emphasizes values that are farther from chance (50%), such that improvements in accuracy closer to chance (50-55%) are treated differently from more difficult improvements further from chance (90-95%).

Missed responses occurred infrequently (93 times across participants). The number of omitted responses did not differ between groups ($t(45) = 0.83$, $p = 0.41$), but did differ by phase, with significantly more omissions occurring during pre PA (1.43 ± 2.33) than post PA (0.59 ± 1.29), [$t(45) = 2.47$, $p < 0.05$, $d = 0.45$]. Figure 4 shows logit-transformed optimal responding percentages for each of the PA groups for each phase.

Logit-transformed optimal responses were modeled across blocks using a linear mixed effects model, in which the slope parameter indexed the rate of learning and the quadratic slope indexed the acceleration or deceleration of learning across blocks. After logit transformation, chance performance would be indicated by a score of 0. To improve our ability to model the linear and quadratic slopes, each block was divided into four sub-blocks, for a total of 12 blocks for each phase. The model was fit to a block-specific performance linear mixed-effects (lme4) package (Pinheiro and Bates, 2000). Prior to modeling, block was centered so the intercept corresponded to the halfway point during training. The fixed effects of Reward, Group, and Phase were effect coded (“1” for reward and “-1” for punished; “1” for RPA, and “-1” for LPA; “1” for Post-PA, and “-1” for Pre-PA). Maximum likelihood was used to estimate all fixed and random effects simultaneously. An initial model included 1) fixed-effects for Block, Reward, Group, Phase, and all interactions, and 2) random intercepts and slopes of the linear and quadratic term on Participant. A more complex model, which included random intercepts and slopes on Reward, was also created, but did not converge. Chi-square model comparisons were performed to trim the most complex model but did not indicate the need to eliminate any random effects. The most complex model that converged successfully excluded the random quadratic slope on Participant. Fixed effects for the best-fitting model were then interpreted as described in the results. Confidence intervals around parameter estimates are reported for all significant effects for modeling results using R’s “confint” function.

The analysis revealed a significant effect of Block ($t(44.00) = 8.47, p < 0.001, d = 0.96, 95\% \text{ CI } [0.012 \ 0.021]$) indicating that optimal responding increased across blocks regardless of Phase, Group, or Trial Type (rewarded, punished). A significant main effect of Phase was also detected ($t(2096) = 5.71, p < 0.001, d = 1.21, 95\% \text{ CI } [0.021 \ 0.050]$), indicating that optimal responding was higher during the post-PA, compared to the pre-PA, phase. A marginally significant effect of quadratic slope on optimal responding ($t(76.10) = -1.93, p = 0.057, d = 0.11, 95\% \text{ CI } [-0.0021 \ -0.0002]$) was identified, and indicated a trend of

deceleration in the rise of optimal response across block. No other main effects were significant.

There were several significant interactions including: (1) Group by Trial Type ($t(2096) = -4.02, p < 0.001, d = 0.85, 95\% \text{ CI } [-0.042 -0.012]$) indicating that the LPA group learned more from rewarded trials than the RPA group; (2) Group by Trial Type by Block ($t(2096) = -2.55, p < 0.05, d = 0.24, 95\% \text{ CI } [-0.006 0.00009]$), indicating that the LPA group learned more from rewards than the RPA group in the last two blocks; (3) Group by Phase by Block ($t(2096) = -2.19, p < 0.05, d = 0.20, 95\% \text{ CI } [-0.0056 0.00004]$), indicating that the LPA group was able to increase their optimal responding more than the RPA group during the post adaptation phase; (4) Group by Phase by Trial Type ($t(2096) = -2.57, p < 0.055, d = 0.54, 95\% \text{ CI } [-0.035 -0.006]$), indicating that the LPA group had more optimal responses to rewarded trials during the post adaptation phase than the RPA group; and (5) Group by Trial Type by Phase by Block ($t(2096) = -2.18, p < 0.05, d = 0.20, 95\% \text{ CI } [-0.0058 -0.0002]$), indicating that learning was greater for the LPA group on rewarded trials during post adaptation compared to the RPA group.

-Insert Figure 4 about here-

To follow up the 4-way interaction, we re-ran the model for each PA Direction. The 3-way Block by Reward by Phase interaction was significant for the LPA group ($t(1094) = 2.00, p < 0.05, d = 0.21, 95\% \text{ CI } [0.0003 0.0446]$), but not the RPA group ($t(1023) = -1.13, ns$), and indicates that, only for the LPA group, was optimal responding significantly greater for rewarded trials than punished trials after PA than before PA. To determine when the learning preference for reward over punishment emerged in the LPA group, we performed paired t -tests on all 12 post-PA sub-blocks. Significantly higher optimal responding for rewarded over punished trials was identified on blocks 6, 7, 8, 10, and 12 ($p > 0.048$).

4. DISCUSSION

The aim of the study was to test the hypothesis that LPA modulates DA level, by examining its effect on a feedback learning task. Our hypothesis was based on evidence linking hemispheric asymmetry in DA transmission to the propensity to learn under rewarded vs. punished conditions (Tomer et al., 2013). We hypothesized that LPA would increase dopaminergic activity in the left hemisphere because of the LPA-induced rightward attentional shift (i.e. increased salience in the right hemispace), and thus selectively improve learning from rewarded feedback.

As expected, adaptation to both left and right PA induced a significant sensorimotor aftereffect and this persisted in both groups until the end of the experiment. However, only the LPA group showed a significant effect on learning rate and in the direction of greater preference for reward-based learning. Although the groups did not differ at baseline, the LPA group showed stronger learning on rewarded trials compared to the RPA group.

Because both groups showed a similar magnitude and time course of the sensorimotor aftereffect, the effect on learning cannot be ascribed to a difference in the degree of adaptation or direction of PA. This is similar to our experience with effect of PA on visual bias (e.g. Schintu et al., 2014), which also showed no relationship to the degree of sensorimotor adaption. Therefore, the sensorimotor and visual/cognitive effects of PA likely have different substrata. Unsurprisingly, the RPA group did not show a statistically significant modulation of learning behavior following adaption. RPA does not usually produce significant cognitive changes (see Berberovic and Mattingley, 2003; Goedert et al., 2010 for exception; Schintu et al., 2017 for discussion).

Animals have consistent spatial orienting biases, reflecting asymmetry in dopaminergic pathways (Glick et al., 1977). The link between DA and individual visuospatial bias has been also described in healthy individuals and patients. The laterality of D2 binding in the striatum, frontal and temporal cortex were associated with individual differences in the direction and magnitude of spatial orienting bias (Tomer et al., 2013). Spontaneous eye blinking rate is reduced in Parkinson disease and correlates with disease severity (Karson, Burns, LeWitt, Foster, & Newman, 1984). Healthy individuals with higher resting blink

frequency exhibit a rightward visuospatial bias and indirect evidence suggests that both higher spontaneous blink rate and rightward attentional bias depend on higher DA activity in the left striatum (Slagter et al., 2010).

The link between attention and lateralized DA function is also present in the clinical literature on neglect. However, the reliability of these findings is in question because of small sample sizes, different drugs across studies, and contrasting results. In some studies, DA receptor agonists reorient visual exploration and improve other measures (Fleet et al., 1987; Geminiani et al., 1998) such standard neglect tests (Mukand et al., 2001), whereas others found a worsening of neglect (i.e. increased exploration of the ipsilesional side; Grujic et al., 1998). On the other hand, a double-blind, randomized, placebo-controlled trial in 16 patients (Gorgoraptis et al., 2012) found a beneficial effect of a DA agonist on visual search and selective attention in neglect patients. Finally, a recent multicenter clinical trial (Luauté et al., 2018) found that methylphenidate, an inhibitor of DA reuptake, enhanced the functional outcome of neglect patients treated with PA.

In the present study, despite the behavioral effect induced by PA on a learning task is a straightforward outcome measure, DA changes in the brain can only be inferred and direct measures will be required for confirmation. However, it is possible that DA modulation is modulated by the parieto-cerebellar network, which is active during the spatial realignment (Chapman et al., 2010). The cerebellum might modulate DA activity in superior temporal cortex, which is selectively activated during the later phase of prism exposure and could mediate the effects of prism adaptation (Luauté et al., 2009). It is also one of the cortical area where the D2/3 receptor binding asymmetries predicted spatial preference along with putamen and frontal cortex (Tomer et al., 2013).

Finally, a model based on the shift in hemispheric dominance within the ventral attentional system has been proposed (Crottaz-Herbette et al., 2014, 2017), and offers a parsimonious explanation for the effect of rightward prismatic adaptation on spatial bias in neglect patients and normal subjects.

In conclusion, this is the first study investigating the effect of PA on a no-visuospatial task and precisely on reward-related behavior. Clearly the aftereffects of PA are not limited to sensorimotor coordination or attention and these data add to the growing consensus that adaptation to visual conditions is associated with deep and behaviorally important changes in cognition.

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6. FIGURES

Figure 1

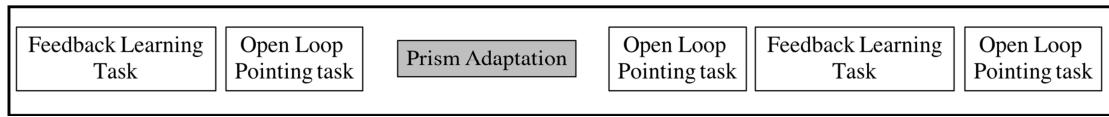


Figure 2

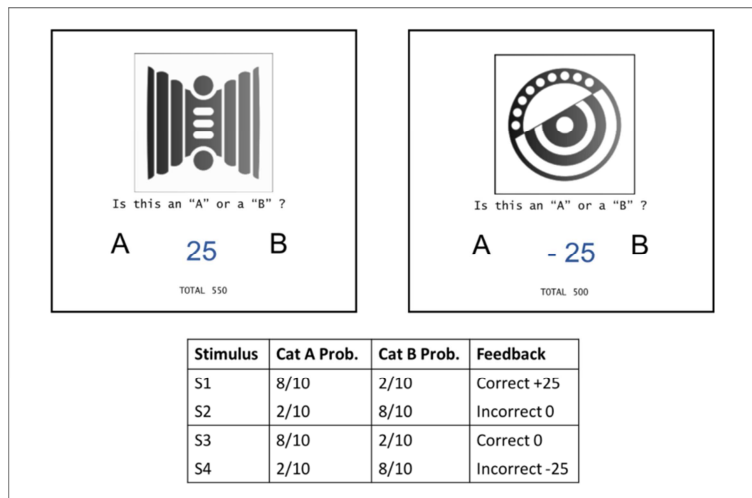


Figure 3

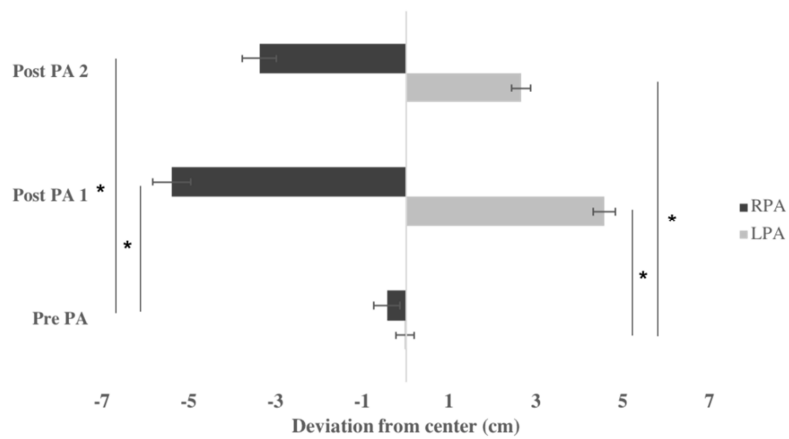
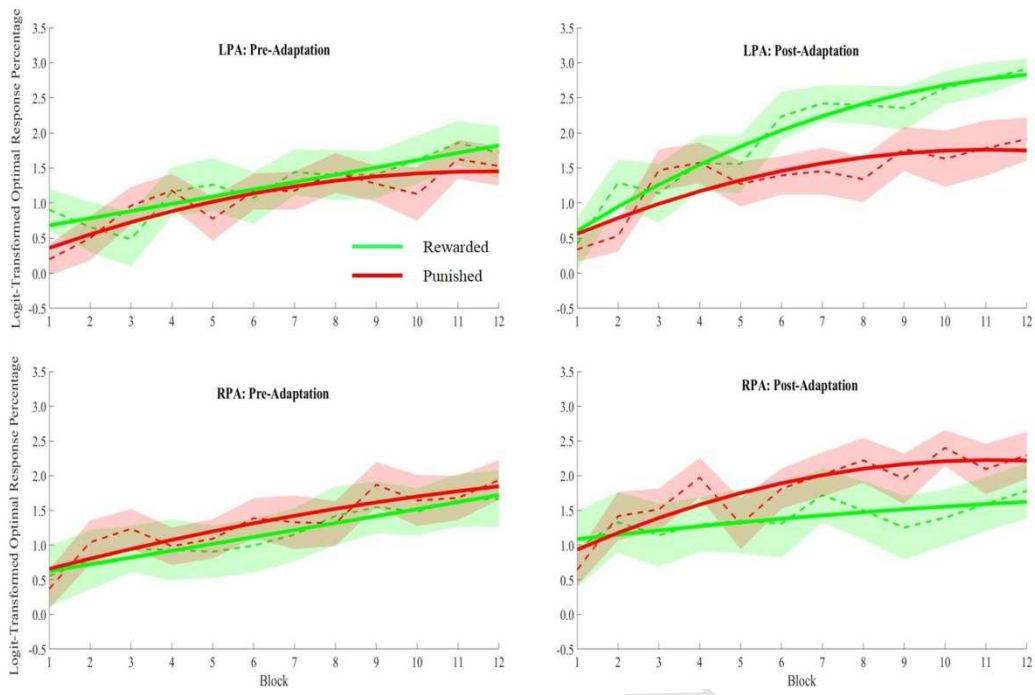


Figure 4



7. LEGENDS

Figure 1: Experimental Design

Figure 2: Feedback-based probabilistic classification task. On each trial, the participant saw one of four stimuli and was asked whether the stimulus belonged to category A or B.) For half of the stimuli, correct responses were rewarded with visual feedback and 25 points winnings (rewarded condition, left upper panel); whereas, for the remaining stimuli, incorrect responses were punished with visual feedback and the loss of 25 points (punished condition, right upper panel). The table (lower panel) reports the proportion of trials that followed the categorical rules and the resulting feedback.

Figure 3: Open-loop pointing. Mean performance of 45 subjects before (Pre PA), after adaptation to leftward (LPA) and rightward-deviating prisms (RPA) (Post PA 1), and at the end of the experiment (Post PA 2, on average 30 minutes after PA). Negative and positive values represent, respectively, leftward or rightward errors/deviation. Error bars represent 1 SEM. * $p < .001$ (Bonferroni-corrected t-test against pre).

Figure 4: Each of the four panels represents the Logit-transformed optimal response for each PA group for each phase. Rewarded learning is represented in green and punished learning in red, and are plotted as a function of the 12 blocks of 10 trials each. Broken lines are the actual performance and solid lines represent the fitted data. Colored ranges around lines are SEM.

LPA = Left Prism Adaptation; RPA = Right Prism adaptation