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Spontaneous eye blink rate predicts learning from negative, but not positive, outcomes

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ABSTRACT

A large body of research shows that striatal dopamine critically affects the extent to which we learn from the positive and negative outcomes of our decisions. In this study, we examined the relationship between reinforcement learning and spontaneous eye blink rate (sEBR), a cheap, non-invasive, and easy to obtain marker of striatal dopaminergic activity. Based on previous findings from pharmacological and patient studies, our main prediction was that in healthy individuals, low blink rates (and concomitant lower striatal dopamine levels) would be associated with better learning from negative choices, while high blink rates (and concomitant higher striatal dopamine levels) would be associated with learning from positive choices. Behavioral analyses showed that in healthy individuals, lower blink rates were indeed associated with greater learning from negative outcomes, indicating that lower dopamine levels per se may enhance avoidance learning. Yet, higher EBR was not associated with better learning from positive outcomes. These observations support the notion that sEBR reflects tonic dopamine levels, and suggest that sEBR may specifically relate to dopamine D2 receptor function, given the importance of the dopaminergic D2 pathway in avoidance learning. More generally, these findings highlight the usefulness of sEBR as a non-invasive and cheap method for assessing the relationship between striatal dopaminergic function and behavior.

1. Introduction

In an ever-changing world, adaptive behavior critically depends on the ability to learn contingencies between actions and positive or negative outcomes. Notably, there are large differences between individuals in the extent to which they learn from the positive compared to negative consequences of their decisions (Cavanagh et al., 2010; Doll et al., 2011; Frank et al., 2009, 2007). While some individuals are more likely to repeat actions that they expect will lead to reward, others are more motivated to avoid negative outcomes. Given that individual differences in reinforcement learning convey vulnerability to specific psychiatric conditions (Maia and Frank, 2011), an important question concerns the neural mechanisms underlying individual differences in reinforcement-based decision making.

A large body of work indicates that the neurotransmitter dopamine in the striatum plays a crucial role in reinforcement learning. Specifically, the extent to which we learn from positive and negative outcomes of decisions is modulated by striatal dopamine in opposite directions; while higher dopamine levels facilitate learning from positive outcomes (Frank and O'Reilly, 2006; Pessiglione et al., 2006), lower dopamine levels seen in Parkinson's disease have been associated with better learning from negative outcomes (Cools et al., 2006; Frank et al., 2004). Of further note, naturally occurring individual differences in the balance of reinforcement learning from positive and negative outcomes have also been related to striatal dopaminergic mechanisms including genetics (Frank et al., 2007) and PET imaging (Cools et al., 2009; Cox et al., 2015). However, PET imaging is quite expensive, reducing the potential to use in large samples.

In the current study, we examined the relationship between reinforcement learning and spontaneous eye blink rate (sEBR), a marker of striatal dopaminergic activity (Karson, 1983), in healthy individuals. sEBR can be obtained by counting the number of eye blinks per minute under resting conditions, which can be measured using facial electrodes or a video camera. As such sEBR may provide a relatively cheap, non-invasive, and simple alternative for assessing the role of striatal dopamine in reinforcement learning.

Convergent evidence shows that sEBR, or the frequency of eye blinks per minute under resting conditions, is regulated at least in part by striatal dopamine. Of particular importance, pharmacological studies in both animals and healthy humans show that sEBR

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is elevated by dopamine agonists and reduced by dopamine antagonists (Cavanagh et al., 2014; Elsworth et al., 1991; Jutkiewicz and Bergman, 2004; Kaminer et al., 2011; Karson, 1988; Kleven and Koek, 1996; Lawrence and Redmond, 1991; Taylor et al., 1999). Moreover, altered blink rates are observed in several neurological and psychiatric disorders that involve disturbances of the dopaminergic system (Karson et al., 1984; Karson et al., 1982b; Lovestone, 1992; Mackert et al., 1991). Most notably, blink rates are significantly decreased in Parkinson's disease, a neurological disorder characterized by depletion of striatal dopamine, even in its early stages (Karson et al., 1984), and are reversed by L-DOPA administration (Karson et al., 1982a). Moreover, monkeys treated with the dopaminergic neurotoxin MPTP, which causes Parkinson-like symptoms, also display reduced blink rates (Lawrence and Redmond, 1991). Furthermore, in another study (Taylor et al., 1999), severity of MPTP-induced Parkinsonism was inversely correlated with blink rates, and blink rates correlated positively with concentration of dopamine in the caudate nucleus post-mortem. Lastly, a recent PET study in monkeys found a strong correlation between sEBR and D2-like receptor availability in the ventral striatum and caudate nucleus (Groman et al., 2014). Furthermore, in this study, D2-like receptor availability correlated with D2-like receptor agonist-induced changes in eye blink rate and the density of D2-like receptors determined in vitro. Thus, convergent evidence from different lines of research indicates that striatal dopamine activity regulates sEBR. The location of the spontaneous blink generator circuit is, however, still unknown, although the spinal trigeminal complex may play a direct role in the circuit (Kaminer et al., 2011). As the basal ganglia regulate spinal trigeminal activity, this would enable dopamine to modify eye blink rate.

We recently found that blink rate was predictive of the modulatory effect of D2 drugs on the aversive cost of cognitive conflict: that is whether it acted to enhance punishment learning or reduce reward learning (Cavanagh et al., 2014). This same measure was sensitive to genetic factors that determine striatal dopamine efficacy. We thus speculated that baseline blink rate reflected individual differences in baseline striatal dopamine levels, which in turn relates to whether subjects learn more from positive or negative outcomes of their decisions. Here we test this link between blink rate and reward vs. punishment learning more directly. Specifically, based on the above summarized literature, we predicted that relatively high sEBR, indicative of high striatal dopamine level, would be associated with greater learning from positive outcomes, while relative low sEBR, indicative of low striatal dopamine level, should be associated with enhanced learning from negative outcomes. Alternatively, sEBR could have similar effects as described above by affecting the degree to which subjects emphasize positive or negative outcomes at the time of choice, rather than learning (see Section 4).

2. Material and methods

2.1. Participants

45 subjects (22 females; mean age 22.6 years) participated in the study. They had normal or corrected-to-normal sight, and no history of neurological or psychiatric disorders. subjects participated for research credit or money (7 euros per hour). The ethical committee of the Department of Psychology of the University of Amsterdam approved the experiment and written consent was obtained from the subjects after the nature and possible consequences of the study were explained to them.

2.2. Procedure and task

After subjects provided written consent, their spontaneous eye blinks were recorded with two vertical Ag–AgCl electrodes above and below the left eye, for 4-min eyes-open segments under resting conditions (cf. Colzato et al., 2008; Colzato et al., 2009a; Slagter et al., 2010). A ground electrode was placed on the forehead. Given that spontaneous EBR is stable during daytime, but increases in the evening (Barbato et al., 2000), data were never collected after 5 p.m. In addition, we asked participants to avoid alcohol and nicotine consumption and to sleep sufficiently the day before the recording. During recordings, participants did not wear contact lenses, were alone in the room, and sat upright and silent. They were asked to look straight ahead at a white wall about 1.5 m in front of them, and were not instructed in any manner about blinking. Participants were not aware of the purpose of the recording.

After the sEBR recordings, subjects were seated approximately 90 cm from a computer screen in a comfortable chair. The 23-inch LCD high-performance gaming monitor was driven by a standard personal computer running the microsoft operating system XP and refreshed at 120 Hz with a resolution of 1920 × 1080 pixels in 16-bit color. Subjects performed a probalistic reinforcement learning task (Frank et al., 2004), programmed in Eprime. This task consists of two phases, a training phase and a transfer phase in which positive/negative learning biases are evaluated. In the training phase, three different visual stimulus pairs (AB, CD, and EF) are presented in random order, and participants have to learn to choose one of the two stimuli (Fig. 1). Visual feedback (the word "Correct!" printed in blue or "Incorrect" printed in red) follows the choice to indicate whether it was correct or incorrect, but this feedback is probabilistic. In AB trials, a choice of stimulus A leads to correct (positive) feedback in 80% of AB trials, whereas a B

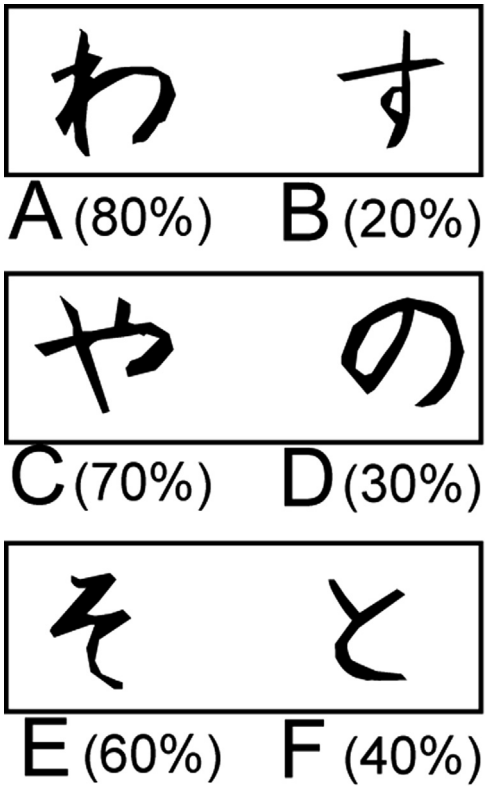

Fig. 1. Example stimulus pairs (Hiragana characters), designed to minimize verbal encoding. In each training trial, one pair is presented and the participant makes a forced choice. The frequency of positive feedback is shown for each choice.

choice leads to incorrect (negative) feedback in these trials (and vice versa for the remaining 20% of trials). CD and EF pairs are less reliable: stimulus C is correct in 70% of CD trials, whereas E is correct in 60% of EF trials. Over the course of training, participants learn to choose stimuli A, C, and E more often than B, D, or F. Note that learning to choose A over B could be accomplished either by learning that choosing A leads to positive feedback, or that choosing B leads to negative feedback (or both). The stimuli were not easy to verbalize Japanese Hiragana characters, presented in black on a white background, in 72 point font. Subjects press a key on the left (i.e., "z") or right (i.e., "m") side of the keyboard depending on which stimulus they choose to be "correct". If no response is made within 4 s, the words "no response detected" are printed in red.

To evaluate whether participants learned more from the positive or negative outcomes of their decisions, we subsequently tested them with additional, novel combinations of stimulus pairs (i.e., AB, CD, EF, AC, AD, AE, AF, BC, BD, BE, BF, CE, CF, DE, and DF), presented in random sequence. Each test pair was presented 4 times. No feedback was provided during this evaluation phase. We predicted that individuals with relatively high sEBR, compared with those with relative low sEBR, would learn more from positive feedback and should, therefore, reliably choose stimulus A in all novel test pairs in which it was present. In contrast, those individuals with relatively low sEBR should learn more from negative feedback and, therefore, reliably avoid stimulus B in all test pairs in which it was present. Subjects were instructed (prior to the evaluation phase) to use "gut instinct" if they did not know how to respond to these novel pairs.

A performance criterion (evaluated after each training block of 60 trials) was enforced to ensure that all participants were at the same performance level before advancing to the evaluation phase (Frank et al., 2004). Because of the different probabilistic structure of each stimulus pair, a different criterion was used for each stimulus pair (65% A in AB, 60% C in CD, 50% E in EF). In the EF pair, stimulus E is correct 60% of the time, but this is particularly difficult to learn. We therefore used a 50% criterion for this pair simply to ensure that if participants happened to "like" stimulus F at the outset, they nevertheless had to learn that this bias was not going to consistently work. The training phase was preceded by 6 practice trials that were not included in the performance evaluation. Prior to the reinforcement learning task, subjects performed an attentional blink task (data reported in Slagter and Georgopoulou (2013)).

2.3. Analysis

2.3.1. EBR analysis

Each individual's sEBR was computed according to automatic and manual procedures using Matlab (Slagter et al., 2010; Slagter and Georgopoulou, 2013). First, a voltage threshold was determined that appeared to capture most blinks, and little artifacts (e.g., muscle-related artifacts) in the data. Then, 20-s epochs were visually inspected for detection accuracy, i.e., the presence/absence of blinks, and counts were updated accordingly. This resulted for each subject in a value reflecting their average spontaneous blink rate per minute (or sEBR). The quality of EBR data was too poor for two subjects to be included in the analyses.

2.3.2. Behavioral analyses

Learning from positive feedback was quantified as the percentage of trials in which a subject chose stimulus A whenever it was present in a novel test pair (i.e., AC, AD, AE, AF; but not the AB pair). Learning from negative feedback was quantified as the percentage of trials in which a subject avoided stimulus B in all test pairs in which it was present, other than AB (i.e., BC, BD, BE, and BF). Seven participants who did not choose A over B more than 50% of the time when the AB pair was presented during the evaluation phase, were excluded from further analyses, reasoning that if they could not reliably choose A/avoid B in this pair, then the results in novel pairs were meaningless (Frank et al., 2004).

2.3.3. Relationship between sEBR and learning from positive and negative outcomes

To examine the relationship between sEBR and reinforcement learning, subjects were divided into a high sEBR group and a low sEBR group using a mean-split. A repeated measures ANOVA with the within-subject factor positive/negative learning and between-subject variable Group (low, high sEBR) was subsequently used to examine our main prediction that the two groups would differ in learning from positive and negative outcomes. Independent sample t tests were used to examine post-hoc whether the predicted interaction effect between Group and positive/negative learning was driven by enhanced learning from negative outcomes in the low (vs. high) sEBR group, by enhanced learning from positive outcomes in the high (vs. low) sEBR group, or both. In case of unequal variances between groups, as indicated by the Levene test, corrected df and t values are reported.

In addition to the categorical split, Pearson correlation tests were used to investigate – across subjects – if individuals with low sEBR learned more from negative outcomes, while individuals with high sEBR learned more from positive outcomes.

3. Results

As in previous studies (e.g., Colzato et al., 2008; Colzato et al., 2009a, 2009b; Doughty, 2001; Slagter et al., 2010), subjects on average blinked 14.3 times per minute (stdev=6.4; range 4.5–30.3). Subjects in the low sEBR group blinked on average 9 times per minute (range 4.5–13.5) while subjects in the high sEBR group blinked on average 19 times per minute (range 14.3–30.3). An independent sample t test confirmed that the low and high sEBR groups differed significantly in their sEBR ($t(34)=-7.43$, $p<.001$).

Critically, statistical tests revealed significant differences between the low and high sEBR group in learning from negative outcomes, but not in learning from positive outcomes. Specifically, the low sEBR group was better at negative vs. positive learning compared to the high sEBR group, as revealed by a significant interaction between Group and positive/negative learning ($F(1,34)=4.11$, $p=.050$) (see Fig. 2). Post-hoc independent t-tests showed that this interaction was driven by enhanced learning from the negative outcomes of decisions in the low (vs. high) EBR group ($t(24.5)=2.64$; $p=.014$). In other words, low EBR individuals displayed a greater tendency towards avoiding stimulus B, in line with our prediction. Yet, the high sEBR group was not better at learning from positive outcomes than the low sEBR group ($t(34)=-0.70$; $p=.49$), contrary to prediction (but see Section 4).

This pattern of findings was further confirmed by cross-subject correlation analyses. Individuals who blinked relatively little generally learned better from negative feedback than individuals who blinked relatively often, as revealed by a significant negative relationship between sEBR and avoiding stimulus B ($r(36)=-.35$; $p=.034$) (see Fig. 3). Yet, no significant cross-subject relationship between sEBR and choosing stimulus A was observed ($r(36)=.01$; $p=.97$). Thus, our data reveal a close association between sEBR and learning from negative, but not positive, outcomes of decisions.

We posthoc explored whether individual differences in sEBR or feedback-related learning were related to individual differences in age or gender. No significant relationship between age and sEBR was observed ($p=.81$), likely due to the relatively restricted age

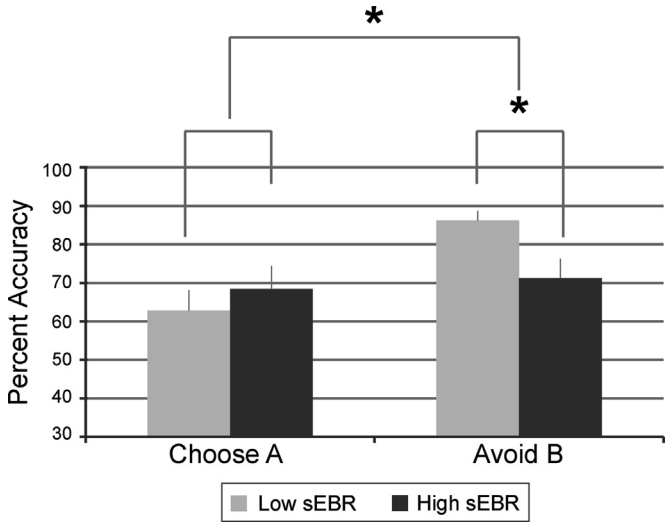

Fig. 2. Low blink rates are associated with better learning from negative outcomes. Displayed is novel test-pair performance, separately for individuals with low spontaneous eye blink rate (sEBR) and high sEBR individuals, and for learning from positive outcomes (choose A) and learning from negative outcomes (avoid B). A significant interaction was observed between group (low, high EBR) and learning from positive vs. negative outcomes (choose A, avoid B). Note that choosing A depends on having learned from positive feedback, while avoiding B depends on having learned from negative feedback.

range of the young adults included in our study. Age also did not predict learning from positive ($p=.63$) or negative ($p=.15$) feedback, as expected. Previous work has shown that old seniors (average age 77 years), but not younger seniors (average age 67 years), display an enhanced tendency to learn from negative compared with positive consequences of their decision (Frank and Kong, 2008). The oldest subject included in our study was 31 years old, which is much younger than this. As to gender, there were no significant differences in spontaneous eye blink rate between men and women. Although numerically women blinked slightly more often (15.2 times per minute vs. 13.3 times per min for men), in line with previous reports (Müller et al., 2007), this difference was not significant ($p=.38$). However, gender was associated with differential learning from negative feedback. That is, men displayed significantly better learning from negative feedback than woman ($p=.01$; but not positive feedback: $p=.63$). Nevertheless, the correlation between spontaneous eye blink rate and learning from negative feedback, when controlling for gender, did not change appreciably ($r= -.35$ when not controlling for gender; $r=-.32$ when controlling for gender). Together these findings indicate that gender may contribute to individual differences in learning from negative information, but does not account for the observed relationship between sEBR and learning from negative information.

4. Discussion

This study examined the relationship between a non-invasive, cheap and easy quantifiable proxy of striatal dopaminergic functioning, namely spontaneous eye blink rate, and the ability to learn from positive and negative outcomes of decisions. While previous studies have shown enhanced learning from negative choices in Parkinson patients (Frank et al., 2004) and in participants with depleted striatal dopamine levels via acute tyrosine depletion (Cox et al., 2015), here we found that lower sEBR in healthy individuals is also associated with enhanced learning from negative outcomes. Thus, lower dopamine levels *per se* may improve learning from negative choices. Yet, higher sEBR was not associated with better learning from positive outcomes.

Notably, a wealth of evidence shows that learning from negative outcomes is mainly related to dopamine D2 receptor functioning, while learning from positive outcomes is mediated by dopamine D1 receptors (Collins and Frank, 2014; Cox et al., 2015; Danjo et al., 2014; Hikida et al., 2010; Kravitz et al., 2012; Tai et al., 2012). Specifically, while phasic dopamine bursts (triggered by unexpected reward) promote learning from positive outcomes by stimulating D1 receptors, dopamine dips (related to absence of expected reward) support learning to avoid negative outcomes through (unbinding of) D2 receptors. This mechanism has been extensively studied with computational models of the basal ganglia in reinforcement learning (Collins and Frank, 2014; Frank, 2005; Wiecki and Frank, 2010). Importantly, in our computational model, these effects of phasic dopamine responses on reinforcement learning are dependent on tonic dopamine levels, with dips in dopamine being more effective at lower levels: a transient cessation in dopamine release is then more likely to allow dopamine levels to drop below a threshold for binding to D2 receptors. This interpretation explains why patients with Parkinson's disease, who have tonically low dopamine levels, can exhibit enhanced learning from negative outcomes. In contrast, it is possible that the lack of association between sEBR and positive learning may result from the fact that phasic dopamine bursts have large dynamic range (Bayer et al., 2007), such that even those with low tonic levels can exhibit sufficiently high phasic increases to bind to

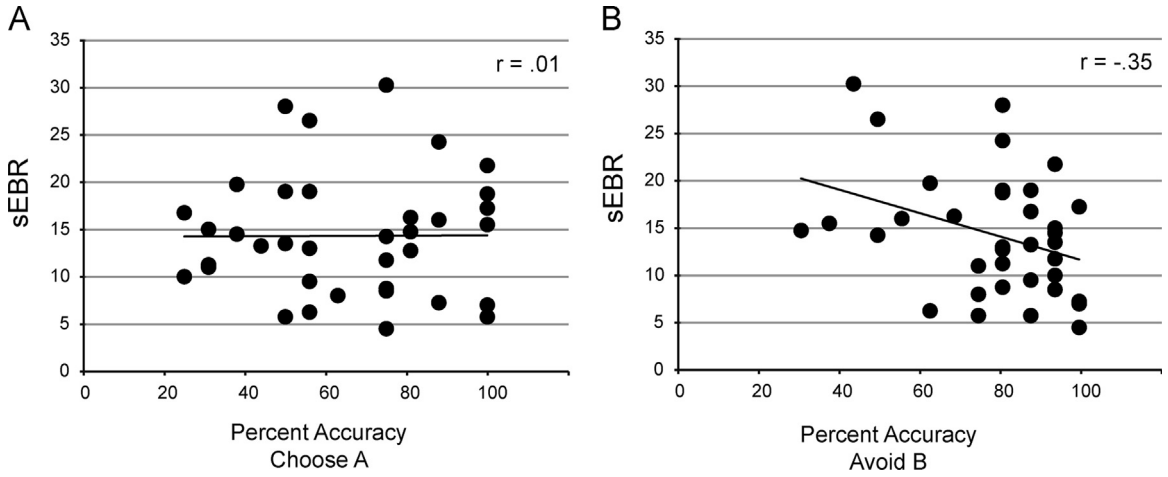

Fig. 3. Individual differences analyses confirm that sEBR is related learning from negative outcomes (B), but not learning from positive outcomes (A). Specifically, across subjects, sEBR correlated negatively with avoid B performance.

(lower affinity) D1 receptors.

Alternatively, another explanation for the selectivity of the association to negative but not positive outcomes is that sEBR appears to relate specifically to striatal D2 receptor function. Indeed, a relationship between sEBR and dopamine D2 receptor functioning is in line with evidence from pharmacological studies showing that D2 agonists enhance sEBR, while D2 antagonist reduce sEBR (Kaminer et al., 2011; Karson et al., 1982; Karson et al., 1981; Kleven and Koek, 1996; Lawrence et al., 1991; Lawrence and Redmond, 1991), as well as results from a recent pharmacological PET study in vervet monkeys (Groman et al., 2014). In this study, sEBR was strongly correlated with D2-like, but not D1-like, receptor availability in the ventral striatum and caudate nucleus. Furthermore, D2-like receptor availability correlated with D2-like receptor agonist-induced changes in eye blink rate and the density of D2-like receptors determined in vitro. These data suggest that sEBR may mainly reflect D2 receptor functioning. However, there are many demonstrations that D1 receptor activity also contributes to sEBR (Elsworth et al., 1991; Jutkiewicz and Bergman, 2004; Kleven and Koek, 1996; Lawrence et al., 1991; Taylor et al., 1999). One study even found no effect of either a D2 agonist (lisuride) or D2 antagonist (sulpride) on sEBR in healthy humans (van der Post et al., 2004), suggesting that sEBR does not (solely) depend on D2 receptor function. Yet, note that in this latter study, eye blinks were recorded while subjects looked at a television monitor displaying a virtual aquarium scene. This visual activity may have affected the spontaneity of eye blinking (Doughty, 2001). Future studies using PET imaging, preferably combined with pharmacological manipulations, are necessary to determine – in humans – to what extent sEBR is linked to tonic dopamine levels and/or dopamine D2 vs. D1 receptor functioning.

These findings provide converging evidence that blink rate is related to baseline striatal dopamine levels which in turn relate to learning from negative outcomes (present study), and our previous observation that the degree to which dopaminergic drugs influence whether other costs (such as cognitive conflict) act to boost learning from negative outcomes (Cavanagh et al., 2014). Yet, Groman et al. (2014) not only reported a relationship in monkeys between D2-like receptor availability in the striatum and sEBR, but also found that D2-like receptor availability in the striatum was associated with sensitivity to positive feedback during reversal learning, which replicates a 2011 finding from the same group (Groman et al., 2011). Moreover, when EBR and positive-feedback sensitivity were regressed against D2-like receptor availability, the two phenotypes accounted for overlapping portions of variance in the PET measure, indicating that the variance they share individually with D2-like receptor availability is also shared with one another. On the surface, these findings appear opposite to those here in healthy humans showing a relationship between sEBR and learning from negative feedback. They are also surprising in light of a large body of research in humans and rodents showing that learning from negative outcomes is mainly related to dopamine D2 receptor functioning, while learning from positive outcomes is mediated by dopamine D1 receptors (Collins and Frank, 2014; Cox et al., 2015; Danjo et al., 2014; Hikida et al., 2010; Kravitz et al., 2012; Tai et al., 2012). Indeed, these rodent studies have established that activity in D2-expressing striatal neurons is both necessary and sufficient for negative but not positive outcome learning, and vice-versa for D1 neurons and positive learning. Although studies in humans sometimes show effects of D2 agents on positive learning (Cavanagh et al., 2014; Cools et al., 2009; Frank and O'Reilly, 2006; Jocham et al., 2011; Pizzagalli et al., 2008; van der Schaaf et al., 2014), it is well known in the animal literature that single low-dose D2 agents have primarily presynaptic autoreceptor effects regulating DA release (and hence would affect phasic DA signals acting on D1 receptors), and these studies have been interpreted with that mechanism, with some evidence from neuroimaging. Indeed the degree to which D2 agents affect positive learning depends on baseline DA levels, consistent with a presynaptic mechanism (Cools et al., 2009). However clearly more research is needed to test this notion. Moreover, using PET imaging, Cox et al. (2015) found in humans that D1 (but not D2) receptor binding related to approach learning, whereas D2 (but not D1) binding related to avoidance learning, and that DA depletion improved avoidance not approach learning, providing empirical support for the association we found in our study. Although the findings by Groman et al. (2011, 2014) seem to be opposite to these on the surface, when their task was simulated with a computational model, it was found that the patterns used to assess "positive feedback sensitivity" in those studies can actually be produced by modulation of learning rates resulting from negative reward prediction error (Piray, 2011). Thus, our findings and those of Groman et al. (2014) might both suggest that EBR is a marker of the ability to learn from negative outcomes of decisions, although of course one should keep in mind that EBR provides an indirect measure of striatal dopaminergic functioning. Future studies using PET imaging combined with learning tasks and sEBR measurements are necessary to provide more direct support for this notion.

While we have primarily focused here on an interpretation in terms of learning, it is also possible that sEBR, as an index of tonic dopamine levels, affects positive vs. negative incentive at the time of choice. In our computational model, tonic dopamine levels affect the degree to which choices are made primarily based on learned weights encoding either the positive or the negative values of each action (Collins and Frank, 2014). Hence, even if learning is symmetric, low tonic dopamine can emphasize the degree to which negative outcomes are represented when making choices. The present findings cannot distinguish between an effect of sEBR on learning vs. choice, and in fact, this same issue pervades the vast majority of reinforcement learning studies (Collins and Frank, 2014; Smittenaar et al., 2012).

Spontaneous eye blink rates were not affected by age or gender. While there is some work relating striatal D2-receptor binding to aging, this work focused on a much wider age range (e.g., in Rinne et al. (1993) 20–81 years old) than our study. We only included young adults included, likely explaining why we did not observe a significant relationship between age and sEBR. As to gender, there were no significant differences in spontaneous eye blink rate between men and women, although women blinked numerically more often (15.2 times vs. 13.3 times per min) than men. Notably, a previous study found no significant difference in striatal dopamine D2-like receptors in male and female subjects although females have numerically lower binding potentials (Brown et al., 2012). Future studies using PET imaging combined with sEBR measurements are necessary to shed more light on how gender and age may affect these different measures of striatal dopaminergic activity.

In summary, spontaneous eye blink rate predicted learning from negative outcomes of decisions, but not learning from positive choices. These observations support the notion that sEBR reflects tonic dopamine levels and relates to dopamine D2 receptor function. They also add to a growing body of work that relates individual differences in sEBR to individual differences in functions known to depend on striatal dopaminergic neurotransmission, such as inhibitory control (Colzato et al., 2009b) and reward-related processing (Pas et al., 2014). Together, these findings highlight the usefulness of sEBR as a non-invasive and cheap method for assessing the relationship between striatal dopaminergic function and behavior.

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References

Barbato, G., Ficca, G., Muscettola, G., Fichele, M., Beatrice, M., Rinaldi, F., 2000. Diurnal variation in spontaneous eye-blink rate. Psychiatry Res. 93, 145–151.
Bayer, H.M., Lau, B., Glimcher, P.W., 2007. Statistics of midbrain dopamine neuron spike trains in the awake primate. J. Neurophysiol. 98, 1428–1439. http://dx.doi.org/10.1152/jn.01140.2006.
Brown, A.K., Mandelkern, M.A., Farahi, J., Robertson, C., Ghahremani, D.G., Sumerel, B., Moallem, N., London, E.D., 2012. Sex differences in striatal dopamine D2/D3 receptor availability in smokers and non-smokers. Int. J. Neuropsychopharmacol. 15, 989–994. http://dx.doi.org/10.1017/S1461145711001957.
Cavanagh, J.F., Frank, M.J., Klein, T.J., Allen, J.J.B., 2010. Frontal theta links prediction errors to behavioral adaptation in reinforcement learning. NeuroImage 49, 3198–3209. http://dx.doi.org/10.1016/j.neuroimage.2009.11.080.
Cavanagh, J.F., Masters, S.E., Bath, K., Frank, M.J., 2014. Conflict acts as an implicit cost in reinforcement learning. Nat. Commun. 5, 5394. http://dx.doi.org/10.1038/ncomms6394.
Collins, A.G.E., Frank, M.J., 2014. Opponent actor learning (OpAL): modeling interactive effects of striatal dopamine on reinforcement learning and choice incentive. Psychol. Rev. 121, 337–366. http://dx.doi.org/10.1037/a0037015.
Colzato, L.S., Slagter, H.A., Spapé, M.M.A., Hommel, B., 2008. Blinks of the eye predict blinks of the mind. Neuropsychologia 46, 3179–3183. http://dx.doi.org/10.1016/j.neuropsychologia.2008.07.006.
Colzato, L.S., Slagter, H.A., van den Wildenberg, W.P.M., Hommel, B., 2009a. Closing one's eyes to reality: evidence for a dopaminergic basis of Psychoticism from spontaneous eye blink rates. Personal. Individ. Differ. 46, 377–380. http://dx.doi.org/10.1016/j.paid.2008.10.017.
Colzato, L.S., van den Wildenberg, W.P.M., van Wouwe, N.C., Pannebakker, M.M., Hommel, B., 2009b. Dopamine and inhibitory action control: evidence from spontaneous eye blink rates. Exp. Brain Res. 196, 467–474. http://dx.doi.org/10.1007/s00221-009-1862-x.
Cools, R., Altamirano, L., D'Esposito, M., 2006. Reversal learning in Parkinson's disease depends on medication status and outcome valence. Neuropsychologia 44, 1663–1673. http://dx.doi.org/10.1016/j.neuropsychologia.2006.03.030.
Cools, R., Frank, M.J., Gibbs, S.E., Miyakawa, A., Jagust, W., D'Esposito, M., 2009. Striatal dopamine predicts outcome-specific reversal learning and its sensitivity to dopaminergic drug administration. J. Neurosci. 29, 1538–1543. http://dx.doi.org/10.1523/JNEUROSCI.4467-08.2009.
Cox, S.M., Frank, M.J., Larcher, K., Fellows, L.K., Clark, C.A., Leyton, M., Dagher, A., 2015. Striatal D1 and D2 signaling differentially predict learning from positive and negative outcomes. NeuroImage 109, 95–101. http://dx.doi.org/10.1016/j.neuroimage.2014.12.070.
Danjo, T., Yoshimi, K., Funabiki, K., Yawata, S., Nakanishi, S., 2014. Aversive behavior induced by optogenetic inactivation of ventral tegmental area dopamine neurons is mediated by dopamine D2 receptors in the nucleus accumbens. Proc. Natl. Acad. Sci. USA 111, 6455–6460. http://dx.doi.org/10.1073/pnas.1404323111.
Doll, B.B., Hutchison, K.E., Frank, M.J., 2011. Dopaminergic genes predict individual differences in susceptibility to confirmation bias. J. Neurosci. 31, 6188–6198. http://dx.doi.org/10.1523/JNEUROSCI.6486-10.2011.
Doughty, M.J., 2001. Consideration of three types of spontaneous eyeblink activity in normal humans: during reading and video display terminal use, in primary gaze, and while in conversation. Optom. Vis. Sci. 78, 712–725.
Elsworth, J.D., Lawrence, M.S., Roth, R.H., Taylor, J.R., Mailman, R.B., Nichols, D.E., Lewis, M.H., Redmond Jr, D.E., 1991. D1 and D2 dopamine receptors independently regulate spontaneous blink rate in the vervet monkey. J. Pharmacol. Exp. Ther. 259, 595–600.
Frank, M.J., 2005. Dynamic dopamine modulation in the basal ganglia: a neurocomputational account of cognitive deficits in medicated and nonmedicated Parkinsonism. J. Cogn. Neurosci. 17, 51–72. http://dx.doi.org/10.1162/0898929052880093.
Frank, M.J., Doll, B.B., Oas-Terpstra, J., Moreno, F., 2009. Prefrontal and striatal dopaminergic genes predict individual differences in exploration and exploitation. Nat. Neurosci. 12, 1062–1068. http://dx.doi.org/10.1038/nn.2342.
Frank, M.J., Kong, L., 2008. Learning to avoid in older age. Psychol. Aging 23, 392–398. http://dx.doi.org/10.1037/0882-7974.23.2.392.
Frank, M.J., Moustafa, A.A., Haughey, H.M., Curran, T., Hutchison, K.E., 2007. Genetic triple dissociation reveals multiple roles for dopamine in reinforcement learning. Proc. Natl. Acad. Sci. USA 104, 16311–16316. http://dx.doi.org/10.1073/pnas.0706111104.
Frank, M.J., O'Reilly, R.C., 2006. A mechanistic account of striatal dopamine function in human cognition: psychopharmacological studies with cabergoline and haloperidol. Behav. Neurosci. 120, 497–517. http://dx.doi.org/10.1037/0735-7044.120.3.497.
Frank, M.J., Seeberger, L.C., O'reilly, R.C., 2004. By carrot or by stick: cognitive reinforcement learning in parkinsonism. Science 306, 1940–1943. http://dx.doi.org/10.1126/science.1102941.
Groman, S.M., James, A.S., Seu, E., Tran, S., Clark, T.A., Harpster, S.N., Crawford, M., Burtner, J.L., Feiler, K., Roth, R.H., Elsworth, J.D., London, E.D., Jentsch, J.D., 2014. In the blink of an eye: relating positive-feedback sensitivity to striatal dopamine D2-like receptors through blink rate. J. Neurosci. 34, 14443–14454. http://dx.doi.org/10.1523/JNEUROSCI.3037-14.2014.
Groman, S.M., Lee, B., London, E.D., Mandelkern, M.A., James, A.S., Feiler, K., Rivera, R., Dahlbom, M., Sossi, V., Vandervoort, E., Jentsch, J.D., 2011. Dorsal striatal D2-like receptor availability covaries with sensitivity to positive reinforcement during discrimination learning. J. Neurosci. 31, 7291–7299. http://dx.doi.org/10.1523/JNEUROSCI.0363-11.2011.
Hikida, T., Kimura, K., Wada, N., Funabiki, K., Nakanishi, S., 2010. Distinct roles of synaptic transmission in direct and indirect striatal pathways to reward and aversive behavior. Neuron 66, 896–907. http://dx.doi.org/10.1016/j.neuron.2010.05.011.
Jocham, G., Klein, T.A., Ullsperger, M., 2011. Dopamine-mediated reinforcement learning signals in the striatum and ventromedial prefrontal cortex underlie value-based choices. J. Neurosci. 31, 1606–1613. http://dx.doi.org/10.1523/JNEUROSCI.3904-10.2011.
Jutkiewicz, E.M., Bergman, J., 2004. Effects of dopamine D1 ligands on eye blinking in monkeys: efficacy, antagonism, and D1/D2 interactions. J. Pharmacol. Exp. Ther. 311, 1008–1015. http://dx.doi.org/10.1124/jpet.104.071092.
Kaminer, J., Powers, A.S., Horn, K.G., Hui, C., Evinger, C., 2011. Characterizing the spontaneous blink generator: an animal model. J. Neurosci. 31, 11256–11267. http://dx.doi.org/10.1523/JNEUROSCI.6218-10.2011.
Karson, C.N., 1988. Physiology of normal and abnormal blinking. Adv. Neurol. 49, 25–37.
Karson, C.N., 1983. Spontaneous eye-blink rates and dopaminergic systems. Brain 106 (3), 643–653, Pt.
Karson, C.N., Bigelow, L.B., Kleinman, J.E., Weinberger, D.R., Wyatt, R.J., 1982a. Haloperidol-induced changes in blink rates correlate with changes in BPRS score. Br. J. Psychiatry 140, 503–507.
Karson, C.N., Burns, R.S., LeWitt, P.A., Foster, N.L., Newman, R.P., 1984. Blink rates and disorders of movement. Neurology 34, 677–678.
Karson, C.N., Lewitt, P.A., Calne, D.B., Wyatt, R.J., 1982b. Blink rates in parkinsonism. Ann. Neurol. 12, 580–583. http://dx.doi.org/10.1002/ana.410120614.
Karson, C.N., Staub, R.A., Kleinman, J.E., Wyatt, R.J., 1981. Drug effect on blink rates in rhesus monkeys: preliminary studies. Biol. Psychiatry 16, 249–254.
Kleven, M.S., Koek, W., 1996. Differential effects of direct and indirect dopamine agonists on eye blink rate in cynomolgus monkeys. J. Pharmacol. Exp. Ther. 279, 1211–1219.
Kravitz, A.V., Tye, L.D., Kreitzer, A.C., 2012. Distinct roles for direct and indirect pathway striatal neurons in reinforcement. Nat. Neurosci. 15, 816–818. http://dx.doi.org/10.1038/nn.3100.
Lawrence, M.S., Redmond Jr., D.E., Elsworth, J.D., Taylor, J.R., Roth, R.H., 1991. The D1 receptor antagonist, SCH 23390, induces signs of parkinsonism in African green monkeys. Life Sci. 49, PL229–PL234. http://dx.doi.org/10.1016/0024-3205(91)90299-Q.
Lawrence, M.S., Redmond, D.E, 1991. MPTP lesions and dopaminergic drugs alter eye blink rate in African green monkeys. Pharmacol. Biochem. Behav. 38, 869–874.
Lovestone, S., 1992. Periodic psychosis associated with the menstrual cycle and increased blink rate. Br. J. Psychiatry 161, 402–404.
Mackert, A., Flechtner, K.M., Woyth, C., Frick, K., 1991. Increased blink rates in schizophrenics. Influences of neuroleptics and psychopathology. Schizophr. Res. 4, 41–47.
Maia, T.V., Frank, M.J., 2011. From reinforcement learning models to psychiatric and neurological disorders. Nat. Neurosci. 14, 154–162. http://dx.doi.org/10.1038/nn.2723.
Müller, J., Dreisbach, G., Brocke, B., Lesch, K.-P., Strobel, A., Goschke, T., 2007. Dopamine and cognitive control: the influence of spontaneous eyeblink rate, DRD4 exon III polymorphism and gender on flexibility in set-shifting. Brain Res. 1131, 155–162. http://dx.doi.org/10.1016/j.brainres.2006.11.002.
Pas, P., Custers, R., Bijleveld, E., Vink, M., 2014. Effort responses to suboptimal reward cues are related to striatal dopaminergic functioning. Motiv. Emot. 38, 759–770. http://dx.doi.org/10.1007/s11031-014-9434-1.
Pessiglione, M., Seymour, B., Flandin, G., Dolan, R.J., Frith, C.D., 2006. Dopamine-dependent prediction errors underpin reward-seeking behaviour in humans. Nature 442, 1042–1045. http://dx.doi.org/10.1038/nature05051.
Piray, P., 2011. The role of dorsal striatal D2-like receptors in reversal learning: a reinforcement learning viewpoint. J. Neurosci. 31, 14049–14050. http://dx.doi.org/10.1523/JNEUROSCI.3008-11.2011.
Pizzagalli, D.A., Evins, A.E., Schetter, E.C., Frank, M.J., Pajtas, P.E., Santesso, D.L., Culhane, M., 2008. Single dose of a dopamine agonist impairs reinforcement learning in humans: behavioral evidence from a laboratory-based measure of reward responsiveness. Psychopharmacology (Berl.) 196, 221–232. http://dx.doi.org/10.1007/s00213-007-0957-y.
Rinne, J.O., Hietala, J., Ruotsalainen, U., Säkö, E., Laihinen, A., Någren, K., Lehikoinen, P., Oikonen, V., Syvälahti, E., 1993. Decrease in human striatal dopamine D2 receptor density with age: a PET study with [11C]raclopride. J. Cereb. Blood Flow Metab. 13, 310–314. http://dx.doi.org/10.1038/jcbfm.1993.39.
Slagter, H.A., Davidson, R.J., Tomer, R., 2010. Eye-blink rate predicts individual differences in pseudoneglect. Neuropsychologia 48, 1265–1268. http://dx.doi.org/10.1016/j.neuropsychologia.2009.12.027.
Slagter, H.A., Georgopoulou, K., 2013. Distractor inhibition predicts individual differences in recovery from the attentional blink. PLoS One 8, e64681. http://dx.doi.org/10.1371/journal.pone.0064681.

Smittenaar, P., Chase, H.W., Aarts, E., Nusselein, B., Bloem, B.R., Cools, R., 2012. Decomposing effects of dopaminergic medication in Parkinson's disease on probabilistic action selection–learning or performance? Eur. J. Neurosci. 35, 1144–1151. http://dx.doi.org/10.1111/j.1460-9568.2012.08043.x.

Tai, L.-H., Lee, A.M., Benavidez, N., Bonci, A., Wilbrecht, L., 2012. Transient stimulation of distinct subpopulations of striatal neurons mimics changes in action value. Nat. Neurosci. 15, 1281–1289. http://dx.doi.org/10.1038/nn.3188.

Taylor, J.R., Elsworth, J.D., Lawrence, M.S., Sladek Jr., J.R., Roth, R.H., Redmond Jr., D. E., 1999. Spontaneous blink rates correlate with dopamine levels in the caudate nucleus of MPTP-treated monkeys. Exp. Neurol. 158, 214–220. http://dx.doi.org/10.1006/exnr.1999.7093.

Van der Post, J., de Waal, P.P., de Kam, M.L., Cohen, A.F., van Gerven, J.M.A., 2004. No evidence of the usefulness of eye blinking as a marker for central dopaminergic activity. J. Psychopharmacol. (Oxf.) 18, 109–114. http://dx.doi.org/10.1177/0269881104042832.

Van der Schaaf, M.E., van Schouwenburg, M.R., Geurts, D.E.M., Schellekens, A.F.A., Buitelaar, J.K., Verkes, R.J., Cools, R., 2014. Establishing the dopamine dependency of human striatal signals during reward and punishment reversal learning. Cereb. Cortex 24, 633–642. http://dx.doi.org/10.1093/cercor/bhs344.

Wiecki, T.V., Frank, M.J., 2010. Neurocomputational models of motor and cognitive deficits in Parkinson's disease. Prog. Brain Res. 183, 275–297. http://dx.doi.org/10.1016/S0079-6123(10)83014-6.