bioRxiv preprint doi: https://doi.org/10.1101/298844; this version posted April 30, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

Opposing pupil responses to offered and anticipated reward values

Tyler Cash-Padgett[1], Habiba Azab[2], Seng Bum Michael Yoo[2], Benjamin Y. Hayden[1]

[1]Department of Neuroscience and
Center for Magnetic Resonance Research,
University of Minnesota, Minneapolis, Minnesota

[2]Department of Brain and Cognitive Sciences and
Center for Visual Sciences,
Center for the Origins of Cognition,
University of Rochester, Rochester, New York

*Corresponding author:
Tyler Cash-Padgett
Department of Neuroscience
University of Minnesota
Minneapolis, MN 55455
Email address: tcashpadgett@gmail.com

Acknowledgments

This work is supported by a CAREER award from NSF (BCS1253576) and a R01 from NIH (DA038615) to BYH. We thank Meghan Castagno, Marc Mancarella and Caleb Strait for assistance with data collection, and the rest of the Hayden lab for valuable discussions.

bioRxiv preprint doi: https://doi.org/10.1101/298844; this version posted April 30, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

ABSTRACT

Previous studies have shown that the pupils dilate more in anticipation of larger rewards. This finding raises the possibility of a more general association between reward amount and pupil size. We tested this idea by characterizing macaque pupil responses to offered rewards during evaluation and comparison in a binary choice task. To control attention, we made use of a design in which offers occurred in sequence. By looking at pupil responses after choice but before reward, we confirmed the previously observed positive association between pupil size and anticipated reward values. Surprisingly, however, we find that pupil size is negatively correlated with the value of offered gambles before choice, during both evaluation and comparison stages of the task. These results demonstrate a functional distinction between offered and anticipated rewards, and present evidence against a narrow version of the *simulation hypothesis*, the idea that we represent offers by reactivating states associated with anticipating them. They also suggest that pupil size is correlated with relative, not absolute, values of offers, suggestive of an accept-reject model of comparison.

KEYWORDS

Monkey, Decision-Making, Pupil, Value

bioRxiv preprint doi: https://doi.org/10.1101/298844; this version posted April 30, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

INTRODUCTION

The pupils systematically dilate and constrict in response to ongoing changes in mental state. Pupil diameter therefore provides a window into many important mental functions, ranging from attention (Hoeks & Levelt, 1993; van den Brink et al., 2016) and working memory (Kahneman & Beatty, 1966) to mental effort (Just et al., 2003; Varazzani et al., 2015) and surprise (Lavín et al., 2013; Preuschoff et al., 2011). Researchers have even used pupil size to gain insight into the mechanisms of subjective time perception (Suzuki et al., 2016), rate of learning (Nassar et al., 2012), and multi-sensory integration (Rigato et al., 2016), as well as decision-making (de Gee et al., 2014; Einhauser et al., 2010; Einhauser et al., 2008).

Previous research supports the idea that there is a positive relationship between reward magnitude and pupil size. Specifically, pupil size increases in anticipation of rewards and increases more in anticipation of larger primary rewards (Rudebeck et al., 2014). The positive relationship between pupil size and anticipated rewards is also observed in anticipation of conditioned reinforcers (Rudebeck et al., 2014; Varazzani et al., 2015). These results suggest that there may be a positive relationship between pupil size and reward amount that is observed for types of rewards other than anticipated ones.

We are particularly interested in the relationship between the encoding of anticipated (having been chosen) and offered (not yet chosen) rewards in the brain. Both types of reward are imagined, not experienced, and both can be used

bioRxiv preprint doi: https://doi.org/10.1101/298844; this version posted April 30, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

to influence upcoming actions. Despite these similarities, they are also somewhat conceptually distinct: offered rewards are not certain (they are contingent on choice) while anticipated rewards are generally certain. Offered rewards provide information that is used to directly drive choice, while anticipated rewards generally drive other processes, including preparation for reward receipt, savoring, and learning.

One hypothesis about the relationship between these reward types, the *simulation hypothesis*, holds that when we choose, we represent offered values and we do so by reactivating a domain-general representation of the experience of receiving the reward (Wang & Hayden, 2017; Kahnt 2010 et al., Howard et al., 2015). There is some evidence in favor of this hypothesis (Howard et al., 2015; Xie et al., 2016; Kahnt et al., 2010; Schoenbaum et al., 2003; Stalnaker et al., 2006). However, at least some data suggests that there are key qualitative differences in the way that offered and experienced rewards are represented (McNamee et al., 2015; Farovik et al., 2015; Tsujimoto et al., 2012; Wang & Hayden, 2017). These data then would predict that responses to reward in key reward regions differ depending on the context in which the reward was presented. We hypothesized that these contextual differences would show up in other domains, such as pupil size.

In order to examine the relationship between pupillary encoding of offered and anticipated values, we took advantage of an existing dataset based on two macaques performing a sequential choice task with risky options (Azab and Hayden, 2017; Azab and Hayden, 2018). We found that pupil size decreased in

bioRxiv preprint doi: https://doi.org/10.1101/298844; this version posted April 30, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

response to higher value offers – the opposite pattern observed for anticipated values. Consistent with this observation, pupil size following the second offer decreased less when the first was high value – a finding that is parsimoniously explained by the idea that pupils encode relative value, the key decision variable for accept-reject choices (Strait et al., 2014, Azab & Hayden 2017). Following choice, but before reward, the relationship between reward and pupil size reversed, replicating the findings of previous studies: it increased on trials in which a large reward was anticipated, and on trials in which a large reward was more likely. These findings indicate that anticipated and offered rewards are disambiguated at the level of the pupillary reward response, and suggest they are processed in at least partially distinct ways in the brain.

bioRxiv preprint doi: https://doi.org/10.1101/298844; this version posted April 30, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

METHODS

Some of the data for dorsal anterior cingulate cortex recordings were previously published (Azab & Hayden, 2017; Strait et al., 2016; Azab & Hayden, 2018; Farashahi et al., 2018; Blanchard et al, 2018). All data and analyses presented here are new.

Surgical procedures

All procedures were approved by the University Committee on Animal Resources at the University of Rochester and were designed and conducted in compliance with the Public Health Service's Guide for the Care and Use of Animals. Two male rhesus macaques (*Macaca mulatta*: subject B age 6; subject J age 7) served as subjects. A small prosthesis for holding the head was used. Animals were habituated to laboratory conditions and then trained to perform oculomotor tasks for liquid reward. Surgery was performed to implant a Cilux recording chamber (Crist Instruments) over the dorsal anterior cingulate cortex and subgenual anterior cingulate cortex. Position was verified by magnetic resonance imaging with the aid of the Brainsight software (Rogue Research Inc.). Animals received appropriate analgesics and antibiotics after all procedures. Throughout both behavioral and physiological recording sessions, the chamber was kept sterile with regular antibiotic washes and sealed with sterile caps. All recordings were performed during the animals' light cycle between 8 am and 5 pm.

bioRxiv preprint doi: https://doi.org/10.1101/298844; this version posted April 30, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

146

147 **Behavioral Task**

148 Monkeys performed a two-option gambling task (Azab & Hayden, 2017;
149 Azab and Hayden, 2018). The task was similar to one we have used previously
150 (Strait et al., 2014; Strait et al., 2015), with two major differences. First, monkeys
151 gambled for virtual tokens—rather than liquid—rewards. And, second, outcomes
152 could be losses as well as wins. Our previous research confirms that subjects'
153 behavior is consistent with understanding of the link between colors and rewards
154 and size and probability in this task and in ones with similar structures, including
155 more complex foraging-like tasks – indicating that task understanding is not likely
156 to be a limiting factor here (Azab & Hayden, 2017; Blanchard & Hayden, 2015;
157 Blanchard et al, 2015; Sleezer et al., 2016; Ebitz and Hayden, 2016).

158 Two offers were presented on each trial. Each offer was represented by a
159 rectangle 300 pixels tall and 80 pixels wide (11.35° of visual angle tall and 4.08°
160 of visual angle wide). 20% of options were safe (100% probability of either 0 or 1
161 token), while the remaining 80% were gambles. Safe offers were entirely red (0
162 tokens) or blue (1 token). The size of each portion indicated the probability of the
163 respective reward. Each gamble rectangle was divided horizontally into a top and
164 bottom portion, each colored according to the token reward offered. The size of
165 each portion indicated the probability of the respective reward. Gamble offers
166 were thus defined by three parameters: two possible token outcomes, and
167 probability of the top outcome (the probability of the bottom was strictly
168 determined by the probability of the top). The top outcome was 10%, 30%, 50%,

bioRxiv preprint doi: https://doi.org/10.1101/298844; this version posted April 30, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

70% or 90% likely. The possible combinations of outcomes were: +3/0, +3/-1, +3/-2, +2/+1, +2/0, +2/-1, +2/-2, +1/+1, +1/0, +1/-1, +1/-2, 0/0. Each non-safe combination was equally likely to occur.

Six initially unfilled circles arranged horizontally at the bottom of the screen indicated the number of tokens to be collected before the subject obtained a liquid reward. These circles were filled appropriately at the end of each trial, according to the outcome of that trial. When 6 or more tokens were collected, the tokens were covered with a solid rectangle while a liquid reward was delivered. Tokens beyond 6 did not carry over, nor could number of tokens fall below zero.

On each trial, one offer appeared on the left side of the screen and the other appeared on the right. Offers were separated from the fixation point by 550 pixels (27.53° of visual angle). The side of the first offer (left and right) was randomized by trial. Each offer appeared for 600 ms and was followed by a 150 ms blank period. Monkeys were free to fixate upon the offers when they appeared (and in our observations almost always did so). After the offers were presented separately, a central fixation spot appeared and the monkey fixated on it for 100 ms. Following this, both offers appeared simultaneously and the animal indicated its choice by shifting gaze to its preferred offer and maintaining fixation on it for 200 ms. Failure to maintain gaze for 200 ms did not lead to the end of the trial, but instead returned the monkey to a choice state; thus, monkeys were free to change their mind if they did so within 200 ms (although in our observations, they seldom did so). A successful 200 ms fixation was followed by a 750 ms delay, after which the gamble was resolved and a small reward (100 μL) was

bioRxiv preprint doi: https://doi.org/10.1101/298844; this version posted April 30, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

192 delivered—regardless of the outcome of the gamble—to sustain motivation. This
193 small reward was delivered within a 300 ms window. If 6 tokens were collected, a
194 delay of 500 ms was followed by a large liquid "jackpot" reward (300 μL) within
195 a 300 ms window, followed by a random inter-trial interval (ITI) between 0.5 and
196 1.5 s. If 6 tokens were not collected, subjects proceeded immediately to the ITI.
197 Each gamble included at least one positive or zero-outcome, ensuring that
198 every gamble carried the possibility of a win. This decreased the number of trivial
199 choices presented to subjects, and maintained motivation.
200 Eye position was sampled at 1,000 Hz by an infrared eye-monitoring
201 camera system (SR Research). Stimuli were controlled by a computer running
202 Matlab (Mathworks) with Psychtoolbox (Brainard, 1997) and Eyelink Toolbox
203 (Cornelissen et al., 2002). Visual stimuli were colored rectangles on a computer
204 monitor placed 57 cm from the animal and centered on its eyes (Figure 1A). A
205 standard solenoid valve controlled the duration of juice delivery. The relationship
206 between solenoid open time and juice volume was established and confirmed
207 before, during, and after recording.
208
209 **Statistical Methods for Behavior**
210 Subjective values for each gamble were estimated based on subjects'
211 choices in each test session according to the formula:
212
213 (1) $$SV = p * win^{\alpha} + (1 - p) * loss^{ß}$$
214

bioRxiv preprint doi: https://doi.org/10.1101/298844; this version posted April 30, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

This formula comes from Yamada et al., (2013), although since our task includes both wins and losses, we fit a parameter α for wins and another parameter ß for losses. A value for α greater than 1 and a value for ß less than 1 both indicate risk-seeking. Both subjects were risk-seeking on average (values of $\alpha > 1$ or $ß < 1$ both indicate risk-seeking; subject B: average $\alpha = 1.21$, average $ß = 0.076$; subject J: average $\alpha = 1.60$, average $ß = 0.022$). For the remainder of this study, "value" refers to subjective value.

We fit logistic regression models of behavior to predict choice of the first vs. second offer. To ensure that subjects do, in fact, pay attention to both offers, we fit a model where the value of the first and second offers were the predictors of interest, while also including the number of tokens already accumulated, the side the first offer appears on, and the choice eventually made to explain any variance these variables might contribute to:

(2) $$F(x) = \frac{1}{1+e^{-(ß_0+ß_1(offer1EV)+ ß_2(offer2EV)+ ß_3x_3+ ß_4x_4+ ß_5x_5)}}$$

Where F(x) is the probability of choosing offer 1, x_3 is the number of tokens, x_4 is the side of the first offer, and x_5 is the choice that was made. To determine whether subjects pay attention to all features of an offer, we use an extended model with the three variables characterizing each offer (the two possible outcomes, and the probability of the larger outcome) included as predictors, controlling for the same variables mentioned above.

bioRxiv preprint doi: https://doi.org/10.1101/298844; this version posted April 30, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

238 (3) $$F(y) = \frac{1}{1+e^{-(ß_0+ß_1y_1+ ß_2y_2+ ß_3y_3+ ß_4y_4+ ß_5y_5+ ß_6y_6+ ß_7y_7+ ß_8y_8+ ß_9y_9)}}$$

239

240 Where F(y) is again the probability of choosing offer 1, y_1, y_2, and y_3
241 respectively are the top and bottom outcomes and probability of the top outcome
242 for offer 1, y_4, y_5, and y_6 respectively are the top and bottom outcomes and
243 probability of the top outcome for offer 2, and then y_7, y_8, and y_9 are the
244 additional factors of token number, first offer side, and eventual choice. We fit
245 such a model for each behavioral session, and obtain the regression weights
246 associated with each of the variables of interest. We then test the vector of these
247 variables across all sessions using a one-sample t-test, to determine whether they
248 differ significantly from zero.

249 Trials lasting longer than the statistical 'upper fence'—that is, the third
250 quartile plus 1.5x the interquartile range—of trial durations were regarded as
251 lapses and discarded. This cutoff time was calculated as the third quartile of trial
252 length plus 1.5x the interquartile range.

253

254 **Statistical Methods for Pupil Size Analyses**

255 We sampled subjects' pupil diameter every 10 ms for analysis. Raw pupil
256 data were first processed in order to remove aberrations due to blinks or
257 measurement artifacts—outlier data points were excluded on the basis of raw size
258 (> 99.9th percentile), velocity of change (> 99th percentile), and acceleration of
259 change (> 99th percentile).

bioRxiv preprint doi: https://doi.org/10.1101/298844; this version posted April 30, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

Pupil sizes were then converted into z-scores on a trial-by-trial basis using the mean and standard deviation during a 500 ms normalization period, immediately preceding the start of the trial except in the instances indicated below. This length of time was chosen because it was the shortest length of the ITI, and therefore the longest normalization window that could be applied to the beginning of all trials. This normalization method was based on previously published approaches (Geng et al., 2015; Rudebeck et al., 2014), and also served the purpose of controlling for the luminance of the tokens present on the screen (we also controlled for this possibility through checking and showing no relationship, see below). During the ITI, tokens were the only object on the screen, and they remained visible on the screen throughout each trial. To analyze the effect of offer 1 value during offer 2 (figure 3), we normalized to the 500 ms preceding offer 2 onset to isolate offer-1-related pupil fluctuations and control for differing baselines. To analyze pupil effects following choice (figure 5A and 5B), we normalized pupil size to the 500 ms preceding the choice epoch, and to analyze changes in pupil size immediately following feedback (figure 5C and 5D), we normalized pupil size to the 400 ms preceding feedback appearance (the second half of the post-choice delay).

We assessed the effect of offer luminance on our results in three ways. First, we measured the screen luminance in cd/m^2 of the color of each offer, using a Tektronix J6523-2 luminance probe, under lighting conditions identical to those of the task. The screens emitted minimal baseline luminance and there were no other sources of light during the task (figure S1). Second, we estimated the

bioRxiv preprint doi: https://doi.org/10.1101/298844; this version posted April 30, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

relative luminance of each offer presented to the monkey by multiplying each of the two halves' proportion of the offer area with their respective luminance measures. We then calculated a multiple regression of the luminance and value of each offer against the mean pupil response from 150 to 350 ms following both offer 1 and offer 2 presentation on a trial by trial basis. Third, using the same time window, we performed a Pearson correlation of offer luminance and pupil response across all trials.

Offers came in several possible in a range of sizes. In our Results, 'large' and 'small' offers refer to those with subjective values greater than or less than the median offer, respectively. The onset time of offer value-related effects on pupil size was calculated by comparing the differences between the means of each trial type to shuffled data (10,000 permutations, without replacement) (Efron & Tibshirani, 1993). Similar approaches have previously been used to determine the significance of pupil size changes (de Gee et al., 2014; Nassar et al., 2012). The pupil response based on a given variable was defined as the first time bin in which the mean pupil sizes were significantly different at the threshold of $\alpha = 0.005$ (two-sided permutation test). Effects with a latency of less than 250 ms were not considered, as this is approximately the shortest amount of time in which visual stimuli can induce pupil responses (Gamlin et al., 1998). Mean pupil size for large vs. small values of the first and second offer was calculated as the mean ± SEM over the 150 ms following the initial pupil response. The significance of the difference between pupil size distributions was calculated using a two-sided student's t-test ($\alpha = 0.05$).

bioRxiv preprint doi: https://doi.org/10.1101/298844; this version posted April 30, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

To calculate the time course of the pupil response, we calculated the mean time of maximum pupil size difference between the two given conditions. Mean and SEM values of the maximum difference time were derived from bootstrapped data (10,000 permutations). The time window for bootstrapped data was, at a minimum, the second half of the offer epoch. In the case that significant pupil response (two-sided permutation test, $p < 0.005$) was observed into the delay following the offer epoch, the upper bound of the time window was either the final time bin at which a significant pupil response was observed or the onset of the next trial epoch, whichever occurred first. For the analysis of the impact of offer 1 value on pupil size following offer 2, we used a one-sided permutation test to determine the bootstrapping window in order to isolate the positive modulatory effect.

Multiple linear regression against pupil size was performed with the following regressors: offer 1 subjective value, offer 2 subjective value, number of tokens possessed, and chosen offer side. Correlations Trial-by-trial correlations with pupil size consisted were performed using the of the Pearson correlation coefficient. Correlation analyses involving offer value and pupil size were performed on a trial-by-trial basis, with pupil size calculated as the mean value during the indicated time bin. An additional regression was performed to assess the impact of pupil size during the pre-offer 2 normalization window on observed changes in pupil size following offer 2. The regressors for this analysis were offer 1 subjective value, offer 2 subjective value, and the mean pupil size during the

bioRxiv preprint doi: https://doi.org/10.1101/298844; this version posted April 30, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

500 ms leading up to offer 2 onset as calculated from pupil size data that were normalized to the ITI.

To analyze the relationship between pupil size and number of tokens possessed, we excluded trials following jackpot rewards.

We performed choice probability analysis on mean pupil size during the 200 ms following offer 2 offset (the start of the pre-choice delay) from each trial. We divided trials according to whether offer 1 or offer 2 was chosen and calculated d-prime using ROC analysis (Britten et al., 1996; Britten et al., 1992). Choice probability was calculated as the area under the ROC curve. We then generated confidence intervals ($\alpha = 0.005$, two-tailed) by performing similar analysis on 10,000 samples of bootstrapped data.

bioRxiv preprint doi: https://doi.org/10.1101/298844; this version posted April 30, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

RESULTS

Choice behavior

We recorded data from two rhesus macaques in a gambling task with asynchronously presented offers (Figure 1A). Some data from this task were previously published but the data presented here are all new (Azab & Hayden, 2017; Azab and Hayden, 2018). Both subjects were familiar with the task and appeared to understand it (Figure 1B). Specifically, both subjects chose the higher value offer more than chance (subject B: 79.5% over n = 6,906 trials; subject J: 75.3% over n = 12,617 trials, $p < 0.0001$ in all individual sessions). Choices reflected the values of both offers according to a logistic regression model that used offer values to predict choices (see Methods, equation 2). Both subjects showed positive regression coefficients for the first offer (one-sample t-test of coefficients for offer 1 value per session: subject B: $t = 16.7$; subject J: $t = 27.3$, both $p < 0.0001$) and the second offer (subject B: $t = 19.7$; subject J: $t = 24.0$, both $p < 0.0001$). Moreover, the values of the two possible outcomes within each offer as well as the probabilities of those outcomes all predict choices (one-sample T-test for coefficients of all 6 offer parameters: all $p < 0.0001$; see Methods, equation 3).

bioRxiv preprint doi: https://doi.org/10.1101/298844; this version posted April 30, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

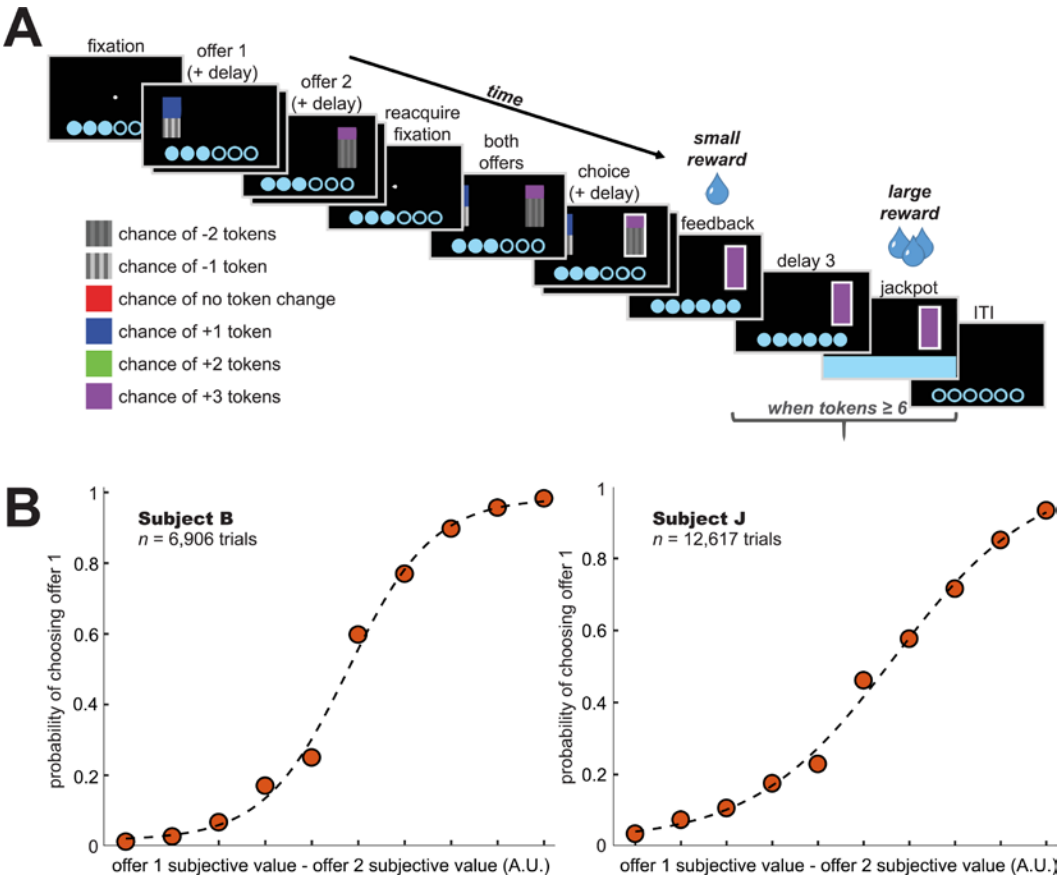


Figure 1

Task and Choice Behavior. (A) Token gambling task. Subjects viewed two probabilistic offers in sequence, chose between them, and then gained or lost tokens based on the result. Each offer contained two possible outcomes, represented by the color of the bars, with the probabilities of those outcomes represented the areas of those colors. (B) Choice behavior. Both subjects displayed an understanding of the task and the relative values of offers.

Increased offer value decreases pupil response

Figures 2A and 2B show the average pupil size following large and small first offers (large and small were defined relative to median offer size). During the

bioRxiv preprint doi: https://doi.org/10.1101/298844; this version posted April 30, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

epoch of interest (the 150 ms following onset of the response), responses were negatively correlated with the value of the first offer in both subjects (subject B: $r = -0.098$, $R^2 = 0.010$, $p < 0.0001$; subject J: $r = -0.022$, $R^2 = 0.0005$, $p = 0.017$). Immediately following onset of the offer (from 0 to 200 ms after it appeared on the screen) pupil size did not differ (this is not surprising because of the well-known slowness of pupil responses; $t = -0.076$, $p = 0.939$ for both subjects). However, following the presentation of the first offer, pupil response to large vs. small offers began to diverge rapidly. Using a sliding time window and a two-sided permutation test ($\alpha = 0.005$) we found that the pupil response to offer 1 value emerged at 340 ms (subject B) and 310 ms (subject J). The peak difference occurred at times 652.3 ± 0.2 ms (subject B) and 398.1 ± 0.3 ms (subject J) after offer 1 onset.

At the time of peak difference, the average pupil size following large offers was significantly smaller than that following small offers (subject B: -2.006 ± 0.090 for large offers vs. -0.905 ± 0.081 for small offers, two-sided Student's t-test, $t = -8.633$, $p < 0.0001$; subject J: -3.269 ± 0.076 for large offers vs. -2.830 ± 0.065, two-sided Student's t-test, $t = -4.334$, $p < 0.0001$). A regression of offer 1 SV (unbinned) against average pupil size at the time of peak difference in each subject confirms this result (subject B: ß = -0.262 ± 0.033, $t = -7.872$, $p < 0.0001$; subject J: ß = -0.059 ± 0.026, $t = -2.293$, $p = 0.022$).

The same pattern was observed in the second offer epoch (Figure 2C and D). During the focal epoch, responses were negatively correlated with the value of the second offer in both subjects (subject B: $r = -0.028$, $R^2 = 0.001$, $p = 0.029$;

bioRxiv preprint doi: https://doi.org/10.1101/298844; this version posted April 30, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

subject J: r = -0.045, R^2 = 0.002, p < 0.0001). The difference in pupil response on the basis of offer 2 value emerged at 430 ms following the appearance of the offer for subject B and 310 ms for subject J. The peak of the difference occurred at 630.1 ± 1.2 ms (subject B) and 520.3 ± 0.6 ms (subject J). At this time, for subject B, the average size of the pupil following large offers was -2.234 ± 0.101 while the size following small offers was -1.711 ± 0.102 (these values are different, two-sided Student's t-test; t = -3.413, p = 0.0006). For subject J, the average pupil size following large offers was -4.102 ± 0.091 while the size following small offers was -3.534 ± 0.084 (these values are different, two-sided Student's t-test; t = -4.501, p < 0.0001). A regression of offer 2 SV (unbinned) against average pupil size at the time of peak difference in each subject confirms this result (subject B: ß = -0.087 ± 0.039, t = -2.211, p = 0.027; subject J: ß = -0.164 ± 0.031, t = -5.212, p < 0.0001).

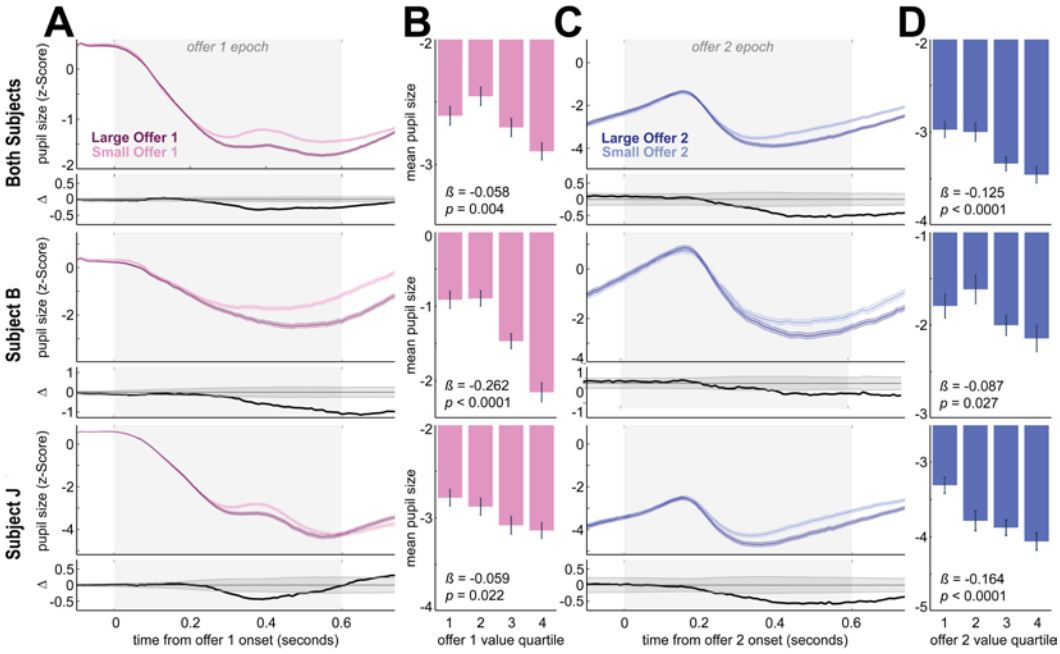


Figure 2

bioRxiv preprint doi: https://doi.org/10.1101/298844; this version posted April 30, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

Pupil responses to offer values. (A and C) Pupil response to offer 1 (2) value during the offer 1 (2) epoch. 'Large' and 'small' refer to offers above and below the median offer value, respectively. Pupil size is normalized to the 500 ms period preceding offer 1 onset. The top panel shows the z-score (± SEM) pupil size at 10 ms increments. The bottom panel shows the difference between mean pupil size on large and small offer trials; shaded gray area shows the α = 0.05 significance threshold (two-sided permutation test). (B and D) Binned offer 1 (2) value response. Mean (± SEM) pupil size during the 150 ms following the first detected offer-related difference in pupil size. ß and p values for the regression of pupil size with offer 1 (2) value, from a multiple regression against pupil size of offer 1 and 2 value, token number, and chosen offer side, at the time of maximum difference between large and small offer responses.

Pupil responses were not driven by variations in luminance in our task

Our offers were indicated by color, and thus varied, albeit quite modestly, in luminance. Our statistical methods were designed to eliminate confounds associated with variations in luminance (see Methods). Nonetheless, even without this control, we found no main effect of luminance in our dataset. While the average effect of offer value was strong and significant in both subjects (see above), luminance did not have significant effects (Figure S1A and B). Specifically, the luminance of offer 1 did not drive responses in either subject B (linear regression, ß = -0.002 ± 0.002, t = -0.888, p = 0.375) or in subject J (ß = -0.002 ± 0.001, t = -1.399, p = 0.162). The luminance of offer 2 also did not drive

bioRxiv preprint doi: https://doi.org/10.1101/298844; this version posted April 30, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

responses in either subject B (ß = -0.001 ± 0.002, t = 0.490, p = 0.625) or in subject J (ß = 0.002 ± 0.001, t = 1.252, p = 0.211). A Pearson correlation of offer luminance and pupil response across all trials confirms this result for both offer 1 (subject B: r = -0.007, p = 0.551; subject J: r = 0.007, p = 0.406) and offer 2 (subject B: r = 0.008, p = 0.523; subject J: r = -0.015, p = 0.105).

The lack of correlation between luminance and pupil size likely reflects the relatively weak luminary effects of the small area covered by the offers (300 x 80 px on a 1024 x 768 computer monitor). It is also likely attributable in part to the stimulus colors we chose, which did not have a systematic relationship between indicated value and luminance brightness (Figure S1C).

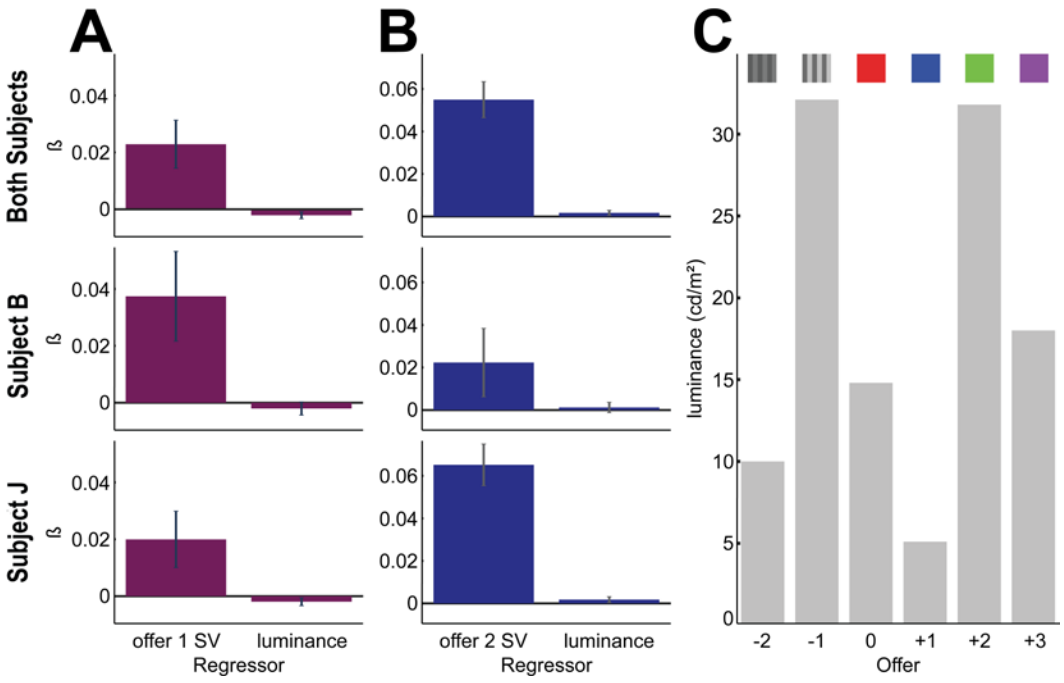


Figure S1

Pupil response to offer luminance. (A and B) ß values of offer 1 (2) value and luminance against pupil size during offer 1 (2). Pupil size was calculated as the mean value from the 150 ms following the onset of the first offer-related pupil size

bioRxiv preprint doi: https://doi.org/10.1101/298844; this version posted April 30, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

difference, the same window used for the correlations reported in this study. (C) Offer luminance. There was no systematic relationship between offer value and luminance.

Effect of offer 1 value on the pupil response to offer 2

We next asked how offer 1 value related to the pupil response to offer 2 (Figure 3). Pupil size during the offer 2 epoch increased significantly with larger values of offer 1 (subject B: offer 1: ß = 0.228 ± 0.033, t = 7.013, $p < 0.0001$; subject J: offer 1: ß = 0.035 ± 0.017, t = 2.069, p = 0.039). Thus, values stored in working memory have the opposite effect of values on the screen.

Specifically: for subject B, the peak offer 1-dependent difference in offer 2 response occurred at 594.9 ± 0.9 ms after offer 2 onset. At this time the average sizes of the pupil following large and small first offers were 0.164 ± 0.072 and -0.631 ± 0.096, respectively (these values are different, two-sided Student's t-test; t = 6.247, $p < 0.0001$). For subject J, the peak difference occurred at 641.1 ± 0.5 ms after offer 2 onset. At this time the average sizes of the pupil following large and small first offers were 0.511 ± 0.048 and 0.286 ± 0.046, respectively (these values are different, two-sided Student's t-test; t = 3.316, p = 0.0009).

Since pupil size during the normalization window for this analysis (the 500 ms leading up to offer 2) includes the differential response to offer 1, it was important to account for the potential effect of this variation in the response to offer 2. To do so, we performed a regression of pupil size at the time of peak difference (measured above) against offer 1 value, offer 2 value, and the mean

bioRxiv preprint doi: https://doi.org/10.1101/298844; this version posted April 30, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

pupil size during the normalization window. We found that, while increased pupil size during the pre-offer2 normalization window negatively correlated with pupil size observed following offer2 (subject B: ß = -0.107 ± 0.010 t = -10.356, p < 0.0001; subject J: ß = -0.071 ± 0.005, t = -14.987, p < 0.0001), the increase in pupil size with offer 1 value and decrease with offer 2 value both remained significant (subject B: offer 1: ß = 0.200 ± 0.023, t = 8.900, p < 0.0001; offer2: ß = -0.053 ± 0.022, t = -2.392, p = 0.017; subject J: offer 1: ß = 0.037 ± 0.014, t = 2.552, p = 0.011; offer2: ß = -0.1529 ± 0.014, t = -10.684, p < 0.0001).

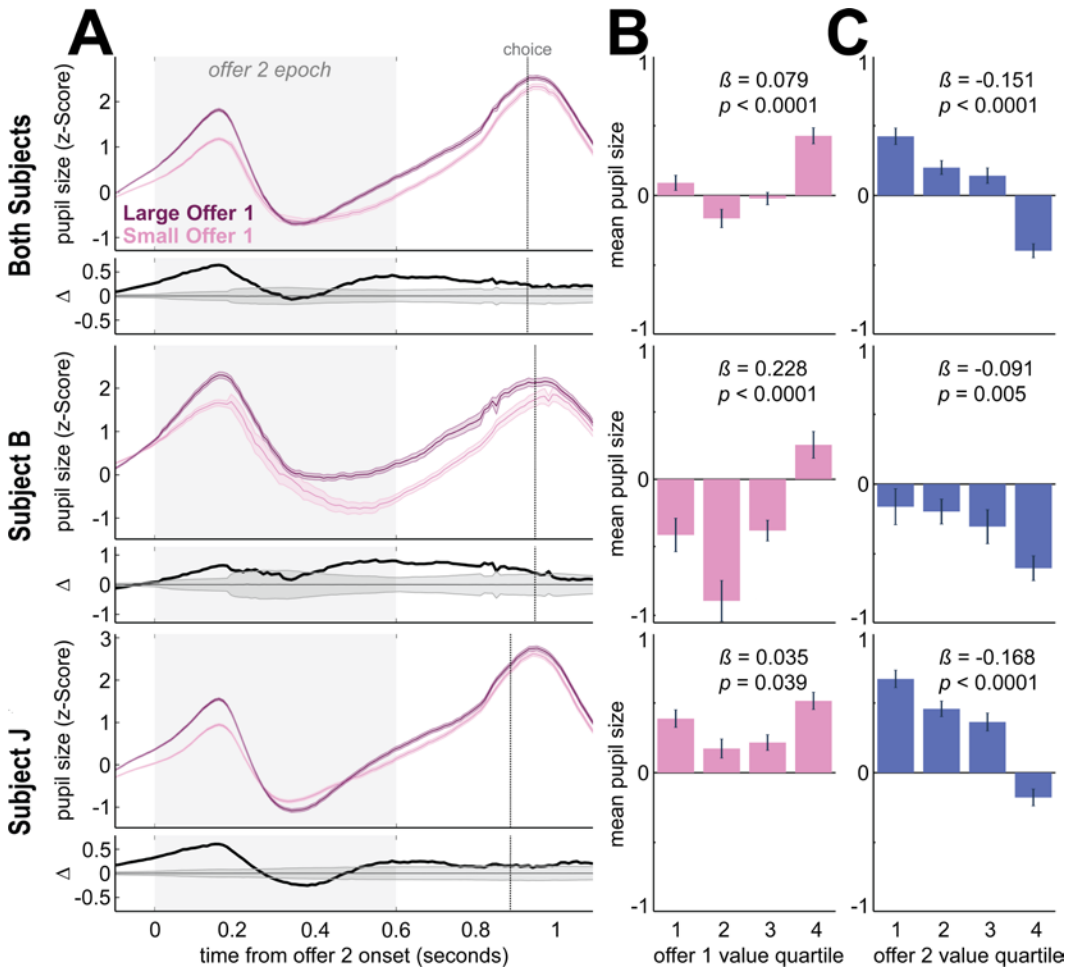


Figure 3

bioRxiv preprint doi: https://doi.org/10.1101/298844; this version posted April 30, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

Pupil response to relative value of offer 2. (A) Pupil response to offer 1 value during and after the offer 2 epoch. 'Large' and 'small' refer to offers above and below the median offer value, respectively. Pupil size is normalized to the 500 ms period preceding offer 2 onset. The top panel shows the z-score (± SEM) pupil size at 10 ms increments. The bottom panel shows the difference between mean pupil size on large and small offer trials; shaded gray area shows the $\alpha = 0.05$ significance threshold (two-sided permutation test). Dotted line represents the mean time of the beginning of the choice epoch for each subject, which depended on fixation time following the post-offer-2 delay. (B and C) Binned offer 1 (2) value response. Mean (± SEM) pupil size during the 150 ms following the first detected offer-2-related difference in pupil size; note that the initial 250 ms latency cutoff for stimulus-related pupil size effects (see methods). ß and p values for the regression of pupil size with offer 1 (2) value, from a multiple regression against pupil size of offer 1 and 2 value, token number, and chosen offer side, at the time of maximum difference between large and small offer 1 responses.

Pupil size predicts choice and reflects the value of the chosen offer more strongly than the value of the unchosen offer

Following the presentation of the second offer, pupil size steadily increased leading up to the choice epoch (Figure 4). During the pre-choice delay, when no offer stimuli were on the screen (0 ms to 200 ms following offer 2), pupil size was correlated with the value of the chosen offer in the two subjects together ($r = -0.019$, $p = 0.010$), and was significant in one subject and close, but

bioRxiv preprint doi: https://doi.org/10.1101/298844; this version posted April 30, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

not statistically significant, in the other (subject B: r = -0.024, p = 0.051; subject J: r = -0.023, p = 0.009). It was not correlated, however, with the unchosen offer in either subject (subject B: r = -0.008, p = 0.540; subject J: r = -0.010, p = 0.260), or in the two subjects averaged together (r = -0.008, p = 0.294). These findings are consistent with the idea that following presumed covert choice subjects attend the value of the chosen offer more than the value of the unchosen offer (Hayden & Moreno-Bote, 2017).

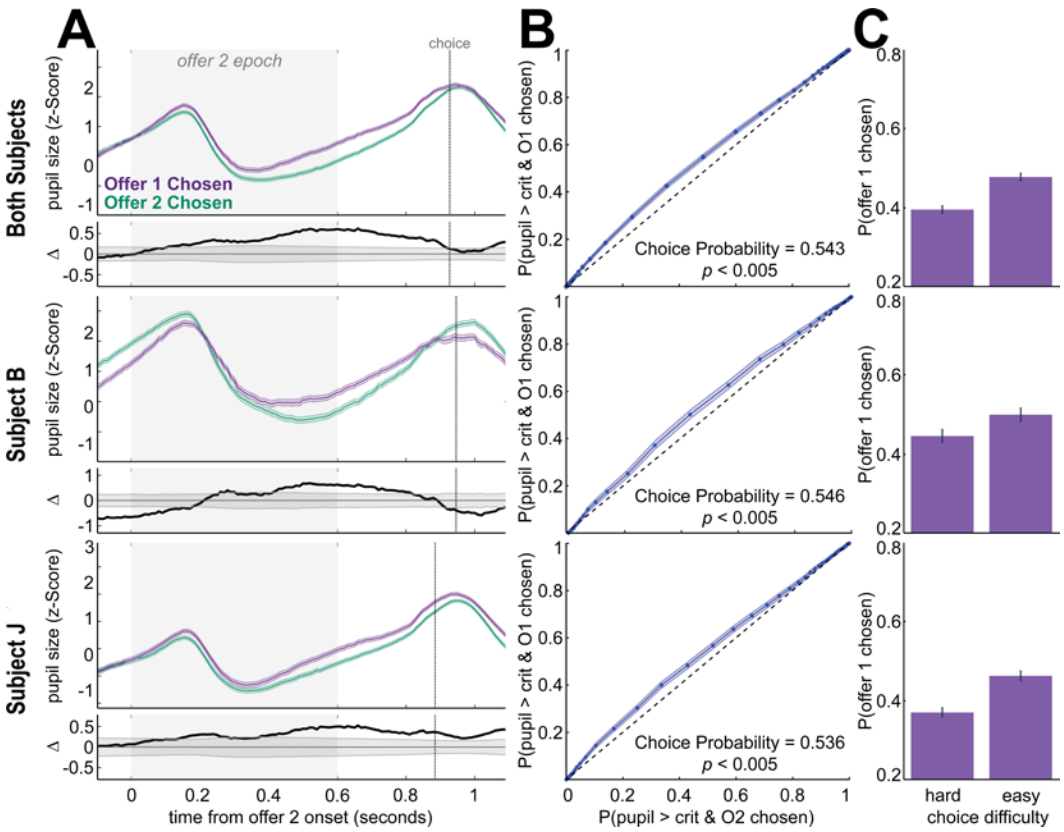


Figure 4

Pupil size by chosen offer and choice heuristic. (A) Pupil size by chosen offer during and after the offer 2 epoch. Pupil size differed on the basis of which offer was ultimately chosen. Pupil size is normalized to the 500 ms period preceding offer 1 onset. Dotted line represents the mean time of the beginning of the choice

bioRxiv preprint doi: https://doi.org/10.1101/298844; this version posted April 30, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

epoch for each subject, which depended on fixation time following the post-offer-2 delay. (B) Pupil size predicts choice. Analysis window was the 200 ms following the offer 2 epoch. Choice probability is the area under the ROC curve, indicating the probability that an ideal observer could predict the chosen offer from only the mean pupil size during the analysis window. (C) Choice heuristic. 'Hard' and 'easy' trials refer to trials in which the two offers were below or above the median difference in offer values, respectively. Both subjects chose offer 1 significantly more often on 'easy' trials than on 'hard' trials ($p < 0.05$).

Following choice, pupil size increases with anticipated value

In the delay following choice, while subjects awaited feedback on their gamble, pupil size was higher when the jackpot reward was within reach. Specifically, we compared pupil size on trials when subjects possessed 3 or more tokens to trials when they possessed fewer (two-sided Student's t-test; Subject B: $t = -4.602$, $p < 0.0001$; subject J: $t = -13.834$, $p < 0.0001$). This effect is not dependent on binning: regressing pupil size by number of tokens demonstrated a significant positive relationship (Figure 5B; subject B: $r = 0.954$, $p = 0.003$; subject J: $r = 0.866$, $p = 0.026$).

In our task, there was a delay following feedback and before the reward itself. A transient pupillary dilation coincided with the delivery of feedback on jackpot trials, demonstrating that subjects anticipated the large primary reward itself (Figure 5C). Pupil size was larger during the period immediately following feedback on jackpot trials (Figure 5D; subject B: 0.712 ± 0.020; subject J: $0.289 \pm$

bioRxiv preprint doi: https://doi.org/10.1101/298844; this version posted April 30, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

0.006) than on non-jackpot trials (subject B: 0.513 ± 0.033; subject J: 0.085 ± 0.021). These effects were significant in both subjects (2-sided Student's t-test; subject B: t = 2.599, p = 0.009; subject J: t = 4.060, p < 0.0001). Note that the appearance of feedback itself on jackpot trials (a blue bar across the bottom of the screen; see figure 1A) resulted in pupillary constriction, but the anticipatory dilation occurred during the ~200 ms immediately following feedback, before any seen information could be expected to be expressed in pupil size.

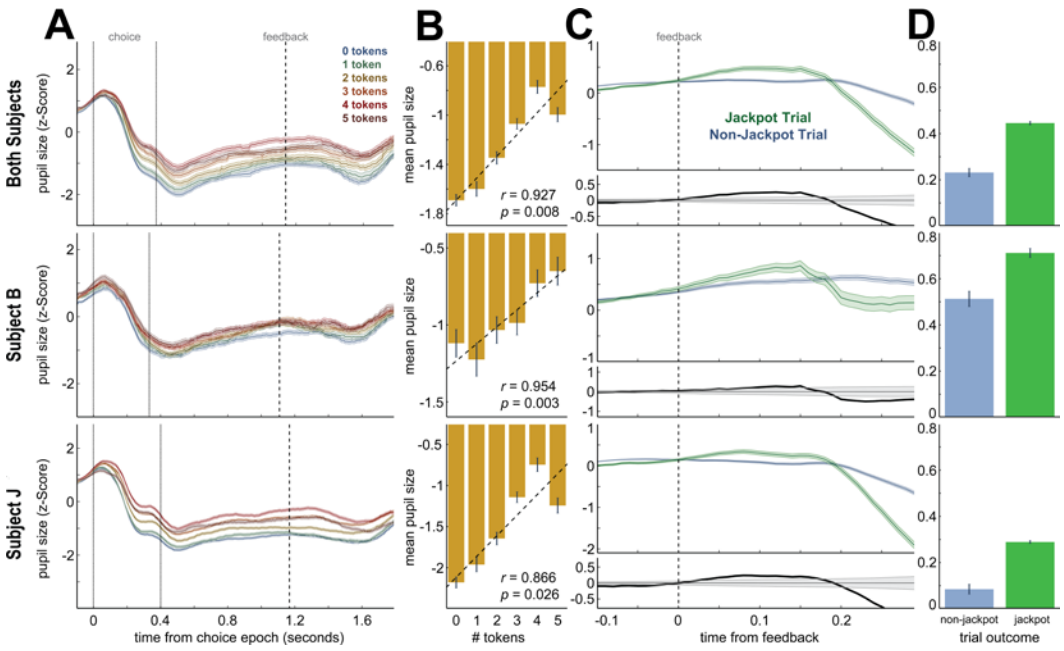


Figure 5

Pupil response to anticipated value. (A) Pupil size by number of tokens possessed during the trial. Pupil size tended to increase on trials in which the subject possessed more tokens, and thus the jackpot reward was more likely. Pupil size in 5A and 5B is normalized to the 500 ms period preceding choice epoch onset, and for figures 5C and 5D to the 400 ms period preceding feedback delivery. The lines indicate the z-score (± SEM) pupil size at 10 ms increments. The dotted lines

bioRxiv preprint doi: https://doi.org/10.1101/298844; this version posted April 30, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

represent beginning and mean end time of the choice epoch, and the dashed line represents the mean time of feedback presentation. (B) Mean pupil size from 400 to 500 ms following choice epoch onset, binned by number of tokens possessed. Pupil size increased with number of tokens. Dashed line indicates a linear regression of the mean bin values; r indicates the Pearson correlation coefficient and p the significance level. (C) Pupil size following feedback on jackpot vs. non-jackpot trials. Pupil size transiently dilated on trials in which subjects expected to receive the jackpot primary reward. (D) Mean (± SEM) pupil size following feedback on jackpot vs. non-jackpot trials. Pupil size was averaged over the 200 ms following feedback, a time period before the actual feedback information could be integrated into pupil size.

A heuristic bias in choice

We observed a novel heuristic choice bias in this dataset. The effect builds on a recency bias previously observed in macaques and extended here (Blanchard, Wilke et al., 2014; Blanchard, Wolfe, et al., 2014). Specifically, subjects chose offer 2 slightly more often than offer 1 (subject B: 52.8% ± 1.19%, subject J: 58.3% ± 0.86%, binomial proportion 95% confidence intervals, binomial test, $p < 0.0001$ for both subjects). The novel finding is that subjects were more accurate (i.e. more likely to choose the EV-maximizing option) when they chose offer 1 (subject B: 80.96% ± 1.37% vs. 74.83% ± 1.43%; subject J: 77.93% ± 1.13% vs. 70.22% ± 1.05%, binomial proportion 95% confidence intervals, Fisher's exact test, $p < 0.0001$ for both subjects). This bias can be explained by a sequential,

bioRxiv preprint doi: https://doi.org/10.1101/298844; this version posted April 30, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

accept-reject choice process: if subjects attend to and decide on one offer at a time, then at the time of choice offer 2 will tend to be the attended offer and therefore accepted more often by default. Supporting this interpretation, the bias towards offer 2 was more pronounced when decisions were difficult--that is, when options were more similar in SV (Figure 4C, Fisher's exact test, $p < 0.0001$ for both subjects).

Further supporting this idea, the strength of the bias decreased with increasing number of tokens. In our task, all trials were followed by the same amount of primary reward, except for trials on which monkeys successfully accumulated six tokens and subsequently received a large, 'jackpot' primary reward. For this reason, token number, which was displayed throughout the trial (including during the intertrial interval), provided a running measure of proximity to this large reward. When subjects had 5 tokens, 1 token away from the large primary reward, they chose offer 1 49.63% ± 3.45% of the time; when subjects had fewer than 5 tokens, they chose offer 1 only 43.10% ± 1.27% of the time (Fisher's exact test, subject B: $p = 0.038$; subject J: $p < 0.0001$). Response times also decreased when subjects possessed 5 tokens (384.2 ± 2.6 ms) vs. when they possessed fewer than 5 tokens (420.9 ± 1.4 ms; $t = -8.901$, $p < 0.0001$ for both subjects). These data suggest that offer 2, as the putative attended offer during the choice epoch, is processed more easily than offer 1 except under highly motivated conditions.

bioRxiv preprint doi: https://doi.org/10.1101/298844; this version posted April 30, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

DISCUSSION

We examined the relationship between offered and anticipated values on pupil size in rhesus macaques performing a sequential choice task with asynchronous offer presentation. Larger offered values for both the first and second offers led to stronger pupillary constrictions. The value of the second offer was encoded relative to the value of the first and not absolutely. Pupil size thus negatively tracks the relative value of the presumed attended offer. Immediately before choice, when neither offer was visible, pupil size correlated with the value of the chosen, but not unchosen offer. Following choice, pupil size was larger on trials with greater token count, which is correlated with higher base trial value. Furthermore, pupil dilation coincided with feedback on jackpot trials, when a large reward was expected. Our results confirm previous findings on anticipated value and pupil size and extend them to new contexts. We also show a relationship between offered value and pupil size, one that is the opposite of the previously published relationship between anticipated value and pupil size.

Our results indicate a clear dissociation in the effect that offered and anticipated rewards have on pupil size, and thus suggest they are not processed in the same way. These results therefore argue against the strongest versions of the *simulation hypothesis* – the idea that the way we represent offered rewards is to reactivate states associated with anticipating (and in some cases, receiving) the reward (Kahnt et al., 2010; Schoenbaum et al., 2003; Stalnaker et al., 2006; Wang & Hayden, 2017; Xie et al., 2016). Instead, they are consistent with the idea that

bioRxiv preprint doi: https://doi.org/10.1101/298844; this version posted April 30, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

623 the representation of offered rewards has elements that are qualitatively different
624 from those of anticipated rewards, leading to the difference in the way they are
625 reflected in pupil size. This distinction is also reflected in the way offered and
626 anticipated rewards are encoded in neural responses (Farovik et al., 2015;
627 McNamee et al., 2015; Tsujimoto et al., 2012; Wang & Hayden, 2017). Note that
628 our results do not argue against a weaker version of the simulation hypothesis, in
629 which offers involve partial reactivation of response patterns associated with
630 receipt but also activate other orthogonal response patterns. Other results from our
631 lab provide neuronal evidence in favor of that hypothesis (Wang & Hayden,
632 2017).

633 We have previously argued that it can be helpful to take a foraging
634 perspective to understand economic choice (Cisek, 2012; Hayden, 2018; Pearson
635 et al., 2014). From this perspective, decision-makers consider one option at a
636 time, evaluate the value of accepting it relative to the value of rejecting it, and
637 then accept it if the value is above some threshold (Freidin et al., 2009; Kacelnik
638 et al., 2011). This finding is echoed in neural responses (Krajbich et al., 2010;
639 Rich & Wallis, 2016) and, here, in pupil responses. Across the two offers, the size
640 of the pupil is correlated with the size of the attended value. Indeed, the decrease
641 in pupil size with increasing offered value may indicate attention to the presented
642 offer. The converse would then be true for the case of offer 2 on trials in which
643 offer 1 was highly valuable. That is, if the subject "accepts" a highly valuable first
644 offer, he may then pay less attention to the second and be less focused in the pre-
645 choice delay, leading to the larger pupil size that we observed during those

bioRxiv preprint doi: https://doi.org/10.1101/298844; this version posted April 30, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

646 epochs. This idea has an echo in classic idea of memory-guided decision-making,
647 in which attention to a memorandum alters the responsiveness of high-level
648 association neurons to subsequent probes, allowing for fast feed-forward decision-
649 making (Miller and Desimone, 1993; Miller et al., 1991; Mirabella et al., 2007;
650 Hayden and Gallant, 2013; Lui and Pasternak, 2011; Machens et al., 2005).

651 The observation of a heuristic bias in our subjects toward choosing offer 2
652 is consistent with this hypothesis. The second offer, being presented right before
653 the choice epoch, would naturally tend to be the attended offer at the time of
654 choice. The subject would thus be predisposed to accept it. This may have
655 resulted in the generally quicker choices and preference on difficult trials that we
656 observed toward offer 2 in both subjects. On the other hand, when offer 2 does
657 not meet the threshold for acceptance, a subject must engage in the more
658 cognitively demanding process of shifting attention to and evaluating offer 1. For
659 marginal decisions, this may have only been 'worth it' to the subjects when they
660 had 5 tokens and were thus close to receiving a large primary reward—the only
661 condition under which the bias toward offer 2 disappeared. Along these same
662 lines, but assuming less of a link between the value-based decision making system
663 and pupil-linked arousal, is the possibility that the higher pupil size in response to
664 low-value offers indicate that the subject is resisting the natural inclination to
665 accept what is currently available.

666 An advantage of viewing decision making through the lens of foraging is
667 that it provides a new perspective on the fundamental meaning of value, one of
668 the important philosophical problems of neuroeconomics (Hunt & Hayden, 2017;

bioRxiv preprint doi: https://doi.org/10.1101/298844; this version posted April 30, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

669 Levy & Glimcher, 2012; O'Doherty, 2011; Schultz, 2008; Wallis & Rich, 2011).
670 Specifically, it suggests that value is not a single entity, but a convenient name for
671 a variety of constituent cognitive processes. These processes are not necessarily
672 highly correlated; indeed, they can, as in the case of offered and anticipated
673 values, have opposing effects. They are also likely to be broadly distributed
674 throughout the brain, rather than bound to a particular population or area. It is
675 therefore no surprise that their distinct traces show up in such a global indicator of
676 brain state as pupil size.
677

678 **Disclosure of Potential Conflicts of Interest**

679 The authors declare that they have no conflict of interest.
680

681 **Statement on the Welfare of Animals**

682 All procedures performed in this study involving animals were in accordance with
683 the ethical standards of the University of Rochester.
684
685

bioRxiv preprint doi: https://doi.org/10.1101/298844; this version posted April 30, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

686 **References**

687

688 Azab, H., & Hayden, B. Y. (2017). Correlates of decisional dynamics in the
689 dorsal anterior cingulate cortex. *PLoS Biology, 15*(11), e2003091. doi:
690 10.1371/journal.pbio.2003091
691 Azab H and Hayden BY (2018) Correlates of economic decisions in the dorsal
692 and subgenual anterior cingulate cortices. *European Journal of*
693 *Neuroscience*. DOI: 10.1111/ejn.13865.
694 Blanchard, T. C., & Hayden, B. Y. (2015). Monkeys are more patient in a
695 foraging task than in a standard intertemporal choice task. *PLoS One,*
696 *10*(2), e0117057. doi: 10.1371/journal.pone.0117057
697 Blanchard, T. C., Wilke, A., & Hayden, B. Y. (2014). Hot-hand bias in rhesus
698 monkeys. *J Exp Psychol Anim Learn Cogn, 40*(3), 280-286. doi:
699 10.1037/xan0000033
700 Blanchard, T. C., Wolfe, L. S., Vlaev, I., Winston, J. S., & Hayden, B. Y. (2014).
701 Biases in preferences for sequences of outcomes in monkeys. *Cognition,*
702 *130*(3), 289-299. doi: 10.1016/j.cognition.2013.11.012
703 Blanchard, T.C., Strait, C.E., & Hayden, B.Y. (2015b). Ramping ensemble
704 activity in dorsal anterior cingulate neurons during persistent commitment
705 to a decision. *Journal of Neurophysiology* 114, 2439–2449.
706 Blanchard, T. C. & Hayden, B. Y. (2018). Robust mixture modeling reveals
707 category free selectivity in reward region neuronal ensembles. *Journal of*
708 *Neurophysiology*. doi.org/10.1152/jn.00808.2017

bioRxiv preprint doi: https://doi.org/10.1101/298844; this version posted April 30, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

709 Brainard, D. H. (1997). The Psychophysics Toolbox. *Spat Vis, 10*(4), 433-436.

710 Britten, K. H., Newsome, W. T., Shadlen, M. N., Celebrini, S., & Movshon, J. A.

711 (1996). A relationship between behavioral choice and the visual responses

712 of neurons in macaque MT. *Vis Neurosci, 13*(1), 87-100.

713 Britten, K. H., Shadlen, M. N., Newsome, W. T., & Movshon, J. A. (1992). The

714 analysis of visual motion: a comparison of neuronal and psychophysical

715 performance. *J Neurosci, 12*(12), 4745-4765.

716 Cisek, P. (2012). Making decisions through a distributed consensus. *Curr Opin*

717 *Neurobiol, 22*(6), 927-936. doi: 10.1016/j.conb.2012.05.007

718 Cornelissen, F. W., Peters, E. M., & Palmer, J. (2002). The Eyelink Toolbox: eye

719 tracking with MATLAB and the Psychophysics Toolbox. *Behav Res*

720 *Methods Instrum Comput, 34*(4), 613-617.

721 de Gee, J. W., Knapen, T., & Donner, T. H. (2014). Decision-related pupil

722 dilation reflects upcoming choice and individual bias. *Proceedings of the*

723 *National Academy of Sciences, 111*(5), E618-E625.

724 Ebitz, R. B., and Hayden, B. Y. (2016). Dorsal anterior cingulate: a Rorschach

725 test for cognitive neuroscience. *Nature Neuroscience, 19. P 1278-1279.*

726 Efron, B., & Tibshirani, R. J. (1993). Permutation tests *An introduction to the*

727 *bootstrap* (pp. 202-219): Springer.

728 Einhauser, W., Koch, C., & Carter, O. L. (2010). Pupil dilation betrays the timing

729 of decisions. *Front Hum Neurosci, 4*, 18. doi: 10.3389/fnhum.2010.00018

730 Einhauser, W., Stout, J., Koch, C., & Carter, O. (2008). Pupil dilation reflects

731 perceptual selection and predicts subsequent stability in perceptual rivalry.

bioRxiv preprint doi: https://doi.org/10.1101/298844; this version posted April 30, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

Proc Natl Acad Sci U S A, 105(5), 1704-1709. doi: 10.1073/pnas.0707727105

Farashahi, S.; Azab, H., Hayden, B. Y., & Soltani, A. (2018). On the flexibility of basic risk attitudes in monkeys. *Journal of Neuroscience. 2260-17.* 10.1523/JNEUROSCI.2260-17.2018

Farovik, A., Place, R. J., McKenzie, S., & Porter, B. (2015). Orbitofrontal cortex encodes memories within value-based schemas and represents contexts that guide memory retrieval. *Journal of Neuroscience 35*(21), 8333-8344. doi: 10.1523/jneurosci.0134-15.2015

Freidin, E., Aw, J., & Kacelnik, A. (2009). Sequential and simultaneous choices: Testing the diet selection and sequential choice models. *Behavioural processes, 80*(3), 218-223.

Gamlin, P. D., Zhang, H., Harlow, A., & Barbur, J. L. (1998). Pupil responses to stimulus color, structure and light flux increments in the rhesus monkey. *Vision Res, 38*(21), 3353-3358.

Geng, J. J., Blumenfeld, Z., Tyson, T. L., & Minzenberg, M. J. (2015). Pupil diameter reflects uncertainty in attentional selection during visual search. *Front Hum Neurosci, 9*, 435. doi: 10.3389/fnhum.2015.00435

Hayden, B. Y. (2018). Economic choice: the foraging perspective. Current Opinion in Behavioral Sciences. DOI:10.1016/j.cobeha.2017.12.002

Hayden, B., & Moreno-Bote, R. (2018). A neuronal theory of sequential economic choice. *Brain and Neuroscience Advances* 2: 1-15

bioRxiv preprint doi: https://doi.org/10.1101/298844; this version posted April 30, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

754 Hayden, B. Y. (2016). Time discounting and time preference in animals: A
755 critical review. *Psychon Bull Rev, 23*(1), 39-53. doi: 10.3758/s13423-015-
756 0879-3
757 Hayden BY and Gallant JL (2013) Working memory and decision pro- cesses in
758 visual area v4. *Frontiers in Neuroscience* 7: 18.
759 Hoeks, B., & Levelt, W. J. (1993). Pupillary dilation as a measure of attention: A
760 quantitative system analysis. *Behavior Research Methods, 25*(1), 16-26.
761 Howard, J. D., Gottfried, J. A., Tobler, P. N., & Kahnt, T. (2015). Identity-
762 specific coding of future rewards in the human orbitofrontal cortex.
763 112(16), 5195-5200. doi: 10.1073/pnas.1503550112
764 Hunt, L. T., & Hayden, B. Y. (2017). A distributed, hierarchical and recurrent
765 framework for reward-based choice. *Nat Rev Neurosci, 18*(3), 172-182.
766 doi: 10.1038/nrn.2017.7
767 Just, M. A., Carpenter, P. A., & Miyake, A. (2003). Neuroindices of cognitive
768 workload: Neuroimaging, pupillometric and event-related potential studies
769 of brain work. *Theoretical Issues in Ergonomics Science, 4*(1-2), 56-88.
770 Kacelnik, A., Vasconcelos, M., Monteiro, T., & Aw, J. (2011). Darwin's "tug-of-
771 war" vs. starlings'"horse-racing": how adaptations for sequential
772 encounters drive simultaneous choice. *Behavioral Ecology and*
773 *Sociobiology, 65*(3), 547-558.
774 Kahneman, D., & Beatty, J. (1966). Pupil diameter and load on memory. *Science,*
775 *154*(3756), 1583-1585.

bioRxiv preprint doi: https://doi.org/10.1101/298844; this version posted April 30, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

776 Kahnt, T., Heinzle, J., Park, S. Q., & Haynes, J.-D. (2010). The neural code of
777 reward anticipation in human orbitofrontal cortex. *Proceedings of the*
778 *National Academy of Sciences, 107*(13), 6010-6015.
779 Krajbich, I., Armel, C., & Rangel, A. (2010). Visual fixations and the
780 computation and comparison of value in simple choice. *Nat Neurosci*,
781 *13*(10), 1292-1298. doi:
782 http://www.nature.com/neuro/journal/v13/n10/abs/nn.2635.html#supplem
783 entary-information
784 Lavín, C., San Martín, R., & Jubal, E. R. (2013). Pupil dilation signals uncertainty
785 and surprise in a learning gambling task. *Frontiers in Behavioral*
786 *Neuroscience, 7*.
787 Levy, D. J., & Glimcher, P. W. (2012). The root of all value: a neural common
788 currency for choice. *Curr Opin Neurobiol, 22*(6), 1027-1038. doi:
789 10.1016/j.conb.2012.06.001
790 Lui LL and Pasternak T (2011) Representation of comparison signals in cortical
791 area MT during a delayed direction discrimination task. *Journal of*
792 *Neurophysiology* 106(3): 1260–1273.
793 Machens CK, Romo R and Brody CD (2005) Flexible control of mutual
794 inhibition: A neural model of two-interval discrimination. *Science*
795 307(5712): 1121–1124.
796 McNamee, D., Liljeholm, M., Zika, O., & O'Doherty, J. P. (2015). Characterizing
797 the associative content of brain structures involved in habitual and goal-

bioRxiv preprint doi: https://doi.org/10.1101/298844; this version posted April 30, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

directed actions in humans: a multivariate FMRI study. *J Neurosci, 35*(9), 3764-3771. doi: 10.1523/jneurosci.4677-14.2015

Miller EK and Desimone R (1994) Parallel neuronal mechanisms for short-term memory. *Science* 263(5146): 520–522.

Miller EK, Li L and Desimone R (1991) A neural mechanism for work- ing and recognition memory in inferior temporal cortex. *Science* 29(5036): 1377–1379.

Mirabella G, Bertini G, Samengo I, et al. (2007) Neurons in area V4 of the macaque translate attended visual features into behaviorally relevant categories. *Neuron* 54(2): 303–318.

Nassar, M. R., Rumsey, K. M., Wilson, R. C., Parikh, K., Heasly, B., & Gold, J. I. (2012). Rational regulation of learning dynamics by pupil-linked arousal systems. *Nature neuroscience*, *15*(7), 1040-1046.

O'Doherty, J. P. (2011). Contributions of the ventromedial prefrontal cortex to goal-directed action selection. *Ann N Y Acad Sci, 1239*, 118-129. doi: 10.1111/j.1749-6632.2011.06290.x

Pearson, J. M., Watson, K. K., & Platt, M. L. (2014). Decision making: the neuroethological turn. *Neuron, 82*(5), 950-965. doi: 10.1016/j.neuron.2014.04.037

Preuschoff, K., Marius't Hart, B., & Einhäuser, W. (2011). Pupil dilation signals surprise: Evidence for noradrenaline's role in decision making. *Frontiers in neuroscience*, *5*.

bioRxiv preprint doi: https://doi.org/10.1101/298844; this version posted April 30, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

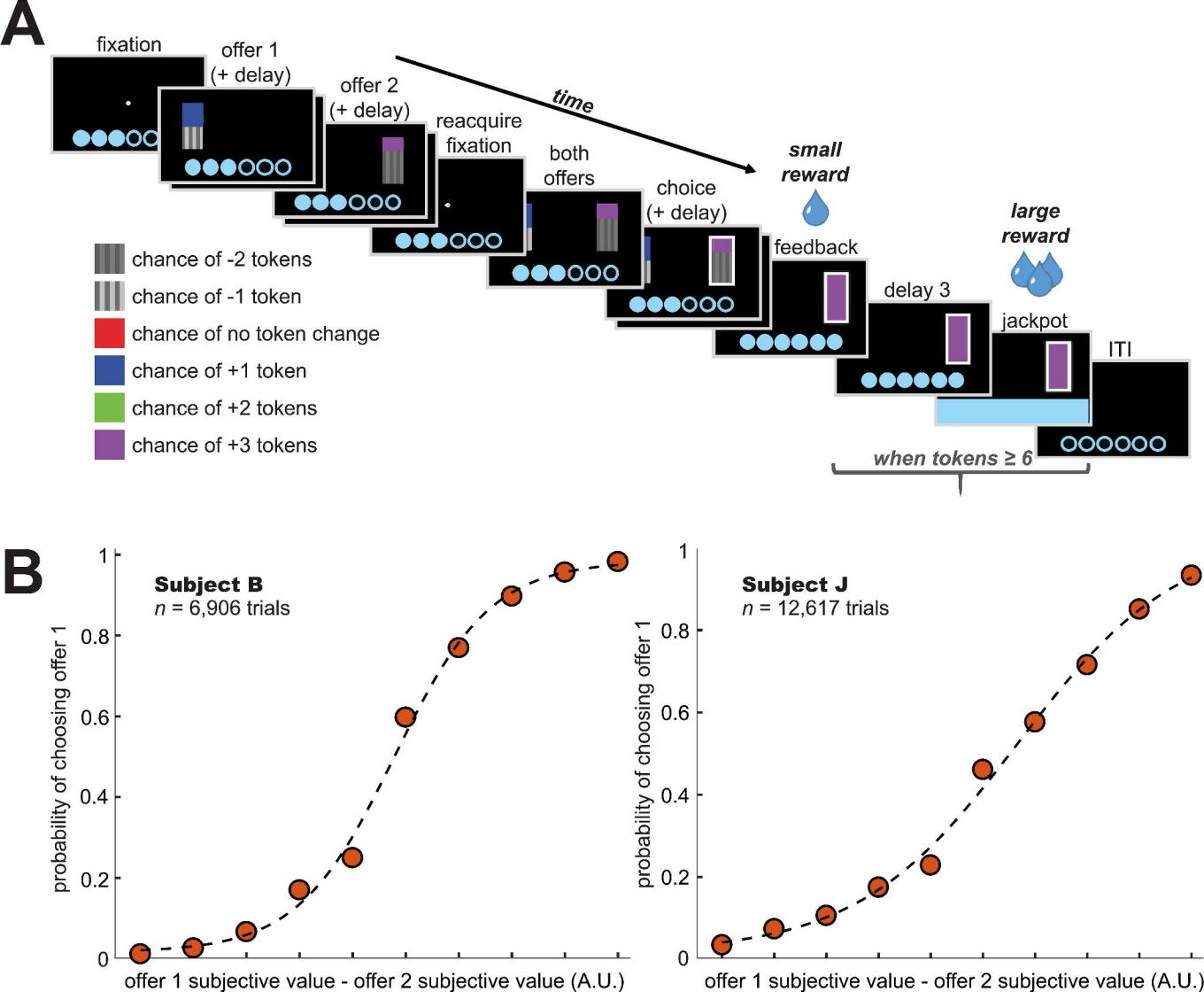
820 Rich, E. L., & Wallis, J. D. (2016). Decoding subjective decisions from
821 orbitofrontal cortex. *Nat Neurosci, 19*(7), 973-980. doi: 10.1038/nn.4320
822 Rigato, S., Rieger, G., & Romei, V. (2016). Multisensory signalling enhances
823 pupil dilation. *Scientific Reports, 6*.
824 Rudebeck, P. H., Putnam, P. T., Daniels, T. E., Yang, T., Mitz, A. R., Rhodes, S.
825 E., & Murray, E. A. (2014). A role for primate subgenual cingulate cortex
826 in sustaining autonomic arousal. *Proceedings of the National Academy of*
827 *Sciences, 111*(14), 5391-5396.
828 Schoenbaum, G., Setlow, B., Saddoris, M. P., & Gallagher, M. (2003). Encoding
829 predicted outcome and acquired value in orbitofrontal cortex during cue
830 sampling depends upon input from basolateral amygdala. *Neuron, 39*(5),
831 855-867.
832 Schultz, W. (2008). Introduction. Neuroeconomics: the promise and the profit.
833 *Philos Trans R Soc Lond B Biol Sci, 363*(1511), 3767-3769. doi:
834 10.1098/rstb.2008.0153
835 Stalnaker, T. A., Roesch, M. R., Franz, T. M., Burke, K. A., & Schoenbaum, G.
836 (2006). Abnormal associative encoding in orbitofrontal neurons in
837 cocaine-experienced rats during decision-making. *Eur J Neurosci, 24*(9),
838 2643-2653. doi: 10.1111/j.1460-9568.2006.05128.x
839 Strait, C. E., Blanchard, T. C., & Hayden, B. Y. (2014). Reward value comparison
840 via mutual inhibition in ventromedial prefrontal cortex. *Neuron, 82*(6),
841 1357-1366. doi: 10.1016/j.neuron.2014.04.032

bioRxiv preprint doi: https://doi.org/10.1101/298844; this version posted April 30, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

842 Strait, C. E., Sleezer, B. J., Blanchard, T. C., Azab, H., Castagno, M. D., &
843 Hayden, B. Y. (2016). Neuronal selectivity for spatial positions of offers
844 and choices in five reward regions. *J Neurophysiol, 115*(3), 1098-1111.
845 doi: 10.1152/jn.00325.2015
846 Strait, C. E., Sleezer, B. J., & Hayden, B. Y. (2015). Signatures of Value
847 Comparison in Ventral Striatum Neurons. *PLoS Biology, 13*(6), e1002173.
848 doi: 10.1371/journal.pbio.1002173
849 Suzuki, T. W., Kunimatsu, J., & Tanaka, M. (2016). Correlation between Pupil
850 Size and Subjective Passage of Time in Non-Human Primates. *Journal of*
851 *Neuroscience, 36*(44), 11331-11337.
852 Tsujimoto, S., Genovesio, A., & Wise, S. P. (2012). Neuronal activity during a
853 cued strategy task: comparison of dorsolateral, orbital, and polar prefrontal
854 cortex. *J Neurosci, 32*(32), 11017-11031. doi: 10.1523/jneurosci.1230-
855 12.2012
856 van den Brink, R. L., Murphy, P. R., & Nieuwenhuis, S. (2016). Pupil Diameter
857 Tracks Lapses of Attention. *PLoS One, 11*(10), e0165274. doi:
858 10.1371/journal.pone.0165274
859 Varazzani, C., San-Galli, A., Gilardeau, S., & Bouret, S. (2015). Noradrenaline
860 and dopamine neurons in the reward/effort trade-off: a direct
861 electrophysiological comparison in behaving monkeys. *Journal of*
862 *Neuroscience, 35*(20), 7866-7877.

bioRxiv preprint doi: https://doi.org/10.1101/298844; this version posted April 30, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

863 Wallis, J. D., & Rich, E. L. (2011). Challenges of Interpreting Frontal Neurons
864 during Value-Based Decision-Making. *Front Neurosci, 5*, 124. doi:
865 10.3389/fnins.2011.00124
866 Wang, M. Z., & Hayden, B. Y. (2017). Reactivation of associative structure
867 specific outcome responses during prospective evaluation in reward-based
868 choices. *Nat Commun, 8*, 15821. doi: 10.1038/ncomms15821
869 Xie, J., Frazier, P. I., & Chick, S. E. (2016). Bayesian Optimization via
870 Simulation with Pairwise Sampling and Correlated Prior Beliefs.
871 *Operations Research*, *64*(2), 542-559. doi: 10.1287/opre.2016.1480
872 Yamada, H., Tymula, A., Louie, K., & Glimcher, P. W. (2013). Thirst-dependent
873 risk preferences in monkeys identify a primitive form of wealth. *Proc Natl*
874 *Acad Sci U S A, 110*(39), 15788-15793. doi: 10.1073/pnas.1308718110


A
fixation
offer 1
(+ delay)
offer 2
(+ delay)
reacquire
fixation
both
offers
choice
(+ delay)
feedback
delay 3
jackpot
ITI
time
small
reward
large
reward
when tokens ≥ 6
chance of -2 tokens
chance of -1 token
chance of no token change
chance of +1 token
chance of +2 tokens
chance of +3 tokens
B
Subject B
n = 6,906 trials
Subject J
n = 12,617 trials
probability of choosing offer 1
offer 1 subjective value - offer 2 subjective value (A.U.)
0
0.2
0.4
0.6
0.8
1

bioRxiv preprint doi: https://doi.org/10.1101/298844; this version posted April 30, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

A

B

C

D

Both Subjects

Subject B

Subject J

offer 1 epoch

offer 2 epoch

pupil size (z-Score)

Large Offer 1

Small Offer 1

Large Offer 2

Small Offer 2

Δ

mean pupil size

ß = -0.058
p = 0.004

ß = -0.125
p < 0.0001

ß = -0.262
p < 0.0001

ß = -0.087
p = 0.027

ß = -0.059
p = 0.022

ß = -0.164
p < 0.0001

time from offer 1 onset (seconds)

offer 1 value quartile

time from offer 2 onset (seconds)

offer 2 value quartile

bioRxiv preprint doi: https://doi.org/10.1101/298844; this version posted April 30, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

A

B

C

Both Subjects

Subject B

Subject J

choice

offer 2 epoch

pupil size (z-Score)

Large Offer 1

Small Offer 1

Δ

mean pupil size

ß = 0.079
p < 0.0001

ß = -0.151
p < 0.0001

ß = 0.228
p < 0.0001

ß = -0.091
p = 0.005

ß = 0.035
p = 0.039

ß = -0.168
p < 0.0001

time from offer 2 onset (seconds)

offer 1 value quartile

offer 2 value quartile

bioRxiv preprint doi: https://doi.org/10.1101/298844; this version posted April 20, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

A

B

C

Both Subjects

Subject B

Subject J

offer 2 epoch

choice

pupil size (z-Score)

Offer 1 Chosen

Offer 2 Chosen

Δ

P(pupil > crit & O1 chosen)

P(pupil > crit & O2 chosen)

Choice Probability = 0.543

$p < 0.005$

Choice Probability = 0.546

$p < 0.005$

Choice Probability = 0.536

$p < 0.005$

P(offer 1 chosen)

hard

easy

choice difficulty

time from offer 2 onset (seconds)

bioRxiv preprint doi: https://doi.org/10.1101/298844; this version posted April 30, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

A

B

C

D

Both Subjects

Subject B

Subject J

choice

feedback

0 tokens
1 token
2 tokens
3 tokens
4 tokens
5 tokens

pupil size (z-Score)

mean pupil size

r = 0.927
p = 0.008

r = 0.954
p = 0.003

r = 0.866
p = 0.026

Jackpot Trial
Non-Jackpot Trial

time from choice epoch (seconds)

tokens

time from feedback

non-jackpot
jackpot

trial outcome

bioRxiv preprint doi: https://doi.org/10.1101/298844; this version posted April 30, 2018. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

A

B

C

Both Subjects

Subject B

Subject J

ß

0.04
0.02
0
0.06

offer 1 SV
offer 2 SV
luminance
Regressor

luminance (cd/m²)
30
25
20
15
10
5
0

-2
-1
0
+1
+2
+3
Offer