

Single unit and local field potential activity during reward processing in the human ventral striatum - Supplemental Material

July 13, 2011

Supplemental Description of Experimental Procedures

We designed our experimental task based on previous experience with behavioral tasks in the intraoperative environment [1] raised the concern that patients would suffer a lack of motivation during a study if a complicated reward-learning paradigm was attempted. In previous DBS surgeries, we found that single unit activity recorded from the ventral striatum is minimal unless patients are prompted to contemplate pleasant thoughts, specifically pleasant images or sensations. We therefore designed a study in which the participant played a simple video game in order to receive reward stimuli. During her pre-operative consultation, the participant performed a task in which her preferences for different categories of visual stimuli were assessed. The goal was to identify the most and least preferred categories of stimuli to insure that the images used as reward stimuli during the intraoperative task were salient to the individual, and therefore more likely to elicit a response in reward-sensitive cells in the ventral striatum. Eleven categories were selected, and 120 different images from each category were compiled from the International Affective Picture System (IAPS) database and supplemented from additional internet image archives [2]. The categories were selected in an attempt to appeal to a range of aesthetic tastes. The eleven categories were: pictures of attractive men, pictures of attractive women, pictures of celebrities of both sexes, pictures of beautiful nature scenery, pictures of beautiful urban/structure scenery, pictures of savory foods, pictures of sweet foods, pictures of smoking/cigarette paraphernalia, pictures of alcoholic beverages and alcohol paraphernalia, pictures of cute animals, and pictures of desirable cars. The pre-operative preference-ranking task consisted of repeated presentation of randomly selected images from each category with no repeated presentations. The participant saw representative images from two categories at one time, and was instructed to click either the left or right response button to indicate which image she preferred to view. Preferences were ranked using the Tideman method of ranked pairs [3]. Response time was held to a maximum of 2 seconds per image pair, although in practice the participant

required around 1 second per pair. The first, third, and fifth ranked preferences were chosen for use in the final experiment. The preference ordering elicited by this method was tested on normal volunteers to insure that the ordering was consistent with stated preferences in post-session interviews. The participant ultimately made 276 judgments to achieve her preference ranking.

The experimental task consisted of a game in which the participant was asked to track the movement of a target object on the screen and then to click either the left or right response button when the object was within a target area (Figure 1). The premise of the game was that the participant played the role of a photographer assigned to capture images of different things. The “camera” was the handheld response button. The speed of the object moving toward the viewfinder was adjusted on every trial to achieve 70% accuracy. Prior to each trial, the participant was cued as to the category from which the reward image would come if the game task was successfully executed and a reward received. The cue image was a cartoon drawing representing one of the three categories of images that were used (categories 1, 3 and 5 from the preference ranking session). Successful game completion was rewarded by the full presentation of an example image from the category of images that had been cued accompanied by a reinforcing tone (positive feedback). Failed game completion trials were followed by one of three images of trash or unkempt urban streets and a buzz tone (negative feedback). The game portion also included neutral-reward trials in which the participant was cued that no positive or negative feedback was on offer for that trial. These trials required the participant to click a button when prompted after viewing a moving stimulus. Ethical constraints prevented remuneration of medical patients under the ongoing care of a physician and enrolled in a clinical trial for the efficacy of deep brain stimulation for depression. The participant was given a practice session of the experimental task (the video game portion) immediately following the preference voting session, to familiarize her with the task before the intraoperative session. She confirmed in a post-session interview that she was motivated to succeed on the game and that the reward images were pleasurable to view.

This novel experimental paradigm was developed to avoid pitfalls encountered during previous intraoperative single unit recordings performed by our group. That is, motivation to continue in a task often wanes when the task is complex, the rewards abstract, or the game boring. Examples of reward paradigms from the literature often rely on actual financial rewards, not available to us because the participant was enrolled in a national trial of DBS for depression and ethical concerns of undue coercion were present. A simple video game with immediate rewards that was adaptive in difficulty was therefore desirable. In addition, we wanted to test the receipt of rewards for which a hierarchy of preferences could be developed [4]. We therefore settled on visual images as the rewards, the content of which was drawn from previous fMRI investigations [5, 6, 7, 8].

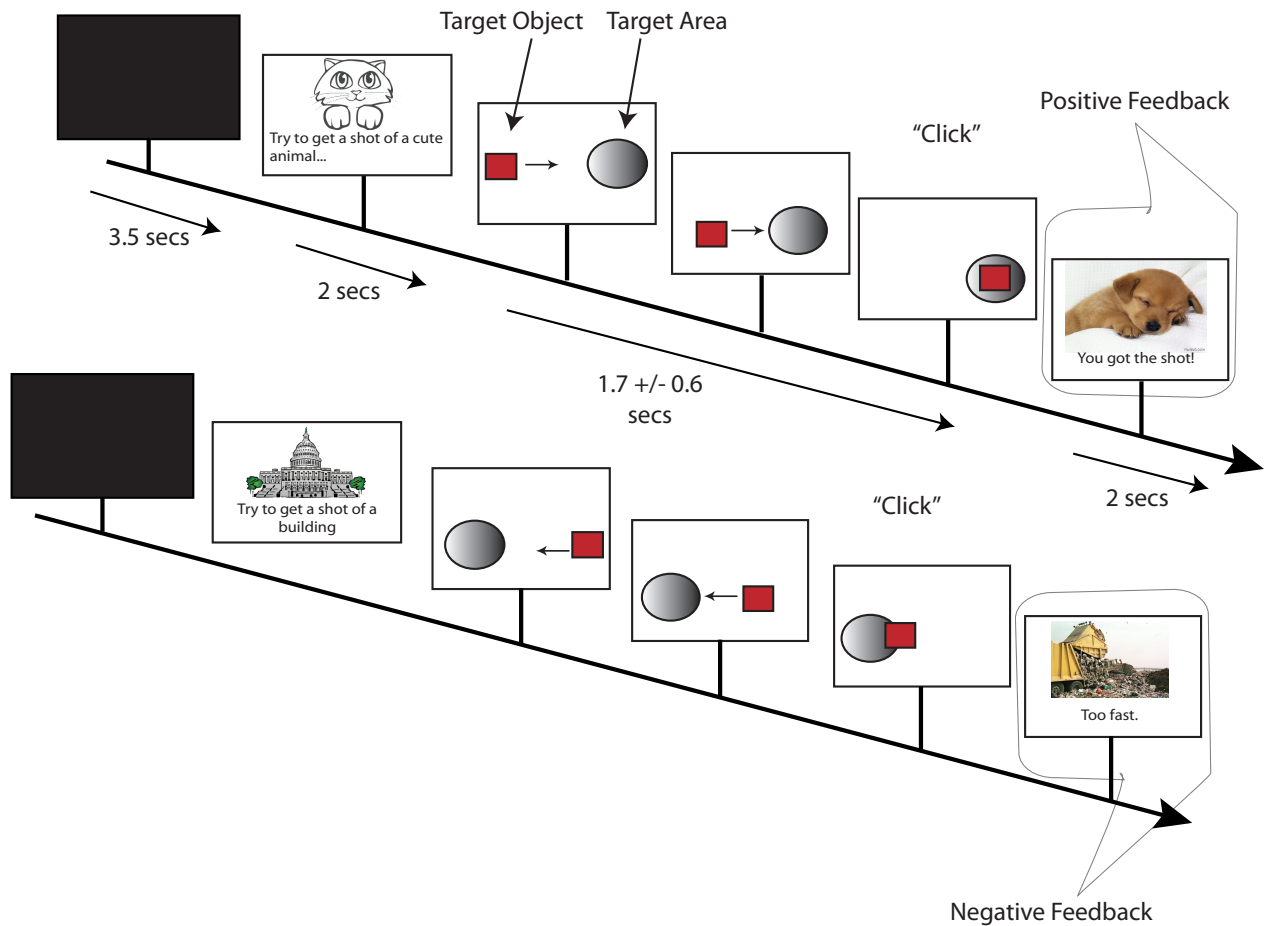


Figure 1: **Intraoperative reward feedback task.** A two second blank screen precedes the appearance of a cue stimulus, which informs the participant of the category of reward feedback that will appear upon successful completion of the game. The game consists of a moving target, the speed of which is adjusted to maintain performance near 70%. Average duration of this portion of the experiment was 1.7 seconds, dependent upon the speed of the target object (difficulty of the trail). The top panel describes a successful trial, in which the button was clicked exactly as the object landed in the target area. Positive and negative feedback is displayed for two seconds. Neutral feedback trials, in which the participant merely clicks a button to move to the feedback screen, are cued separately.

Analysis for differences in oscillatory power

We used Morlet wavelet decomposition (wave number of 6) to compute the spectral power as a function of time for analysis of local field potentials. We selectively notch filtered signals 60 Hz. We sampled frequencies logarithmically between 2 Hz and 200 Hz for analysis [9]. For significance testing, we compared power between conditions using a Wilcoxon rank sum test with a permutation procedure applied to two time windows: 0-750 msec and 750-1500 msec after stimulus onset, bisecting the period immediately following the presentation of feedback stimuli. Power values at each frequency and for each event were averaged across these time periods and compared between positive, negative, and neutral feedback conditions [10]. In this case, we permuted the labels for conditions 1000 times and calculated a rank-sum statistic from the distributions of power values of the feedback conditions at each frequency. We compared the original unshuffled rank sum statistic to the permuted distribution. The rank sum value relative to the distribution of permuted rank sum values was used to calculate a p value. Significance threshold was corrected for multiple comparisons (frequencies used) using a false discovery rate correction with a q value of 0.05 calculated from a vector of p values at all frequencies from the rank sum test applied to the non-shuffled data.

Influence of phase on spiking activity

We calculated phase preference of spiking activity by identifying time points relative to stimuli events at which spikes occurred. We extracted phase information for the theta (4-8 Hz), alpha (10-14 Hz), and beta (16-26 Hz) bands using the Hilbert transform to identify a single phase value at each time point after the stimuli corresponding to the times at which spiking events occurred. We generated a test statistic to characterize the uniformity of phase distribution using the Rayleigh test. We computed the \bar{R} value separately for spikes from positive and negative feedback events for each of these 3 phase bins. A permutation procedure was used to assess significance of the calculated \bar{R} statistic by shuffling the phase values at each timepoint in the sample and then using the spike times to select the phases for input into 1000 Rayleigh tests to create a distribution of \bar{R} values. The p value was determined by calculating the position of the \bar{R} value from the real data in the distribution of shuffled \bar{R} values.

Modulation Index

To confirm the results of our analysis of the phase modulation of gamma band oscillatory power, we attempted to use the modulation index as described by Canolty et al. to assess the significance of the modulation of gamma power by the phase of the alpha oscillation (10-14 Hz) and theta oscillation (4-8 Hz) [11]. For this we calculated the modulation index:

$$m_f = \left| \frac{1}{n} \sum_{t=1}^n a_{tf} e^{i\phi_t} \right|$$

where m is the modulation index, n is the number of time points in the series, a_{tf} is the instantaneous gamma-range power at a frequency f at time t , and ϕ_t is the alpha band or theta band oscillation phase value at time t . This was done separately for positive and negative feedback events. We extracted phase information using the Hilbert transform and power via wavelet decomposition as described above. The modulation values (m) were transformed by $\arcsin \sqrt{m}$. A permutation procedure was performed to determine the significance of the calculated modulation values in which the power values of the time series were shuffled randomly while preserving the phase. A z value for the modulation index was determined by subtracting the mean and dividing by the standard deviation of the 200 shuffled modulation values. Modulation indices for the alpha and theta bands were calculated separately.

Analysis of Phase Reset

We analyzed our data for evidence of phase reset induced by the feedback stimulus. To do this, we extracted phase information for the theta (4–8 Hz), alpha (10–14 Hz) and beta (16–24 Hz) frequency bands using the Hilbert transform as above, for a 1500 msec time window surrounding the onset of feedback. At each time sample in the period, we applied a Rayleigh test to the distribution of phases for each of the frequency bands in question. Following existing methods [12], we considered a finding significant only if the phases of an oscillation were non-uniformly distributed for 2 successive cycles of the oscillation.

We examined our data for evidence of a phase reset elicited by feedback stimuli. Following the methods of Rizzuto et al. (2006), we analyzed signal in a 1500 msec window centered on the onset of feedback (-500 to 1000 msec relative to the onset of feedback). This time window was extended to 500 msec before the onset of stimulus after an initial window (-250 to 1000 msec) suggested significant synchrony at the earliest samples in the time series. During the time period in which the alpha phase reset occurs, the participant was engaged in the video game task and had not yet pressed the response button. A reward-related effect preceding the onset of feedback is consistent with evidence of changes in spiking and oscillatory activity that precede the appearance of reward feedback stimuli in animals and humans [13, 14, 15], given that the participant was sufficiently well-trained to anticipate the appearance of the feedback stimulus. We identified a noteworthy divergence between alpha and theta oscillations: alpha oscillations exhibited phase reset \sim 400 msec before the onset of the stimulus, while theta oscillations were reset 100 msec after the stimulus ($p < 0.05$ for two successive cycles of the oscillation, Rayleigh test). This difference is visible in Figure 5. This theta effect was not significant when analyzing positive and negative feedback events separately ($p > 0.10$, Rayleigh test).

Supplemental Data

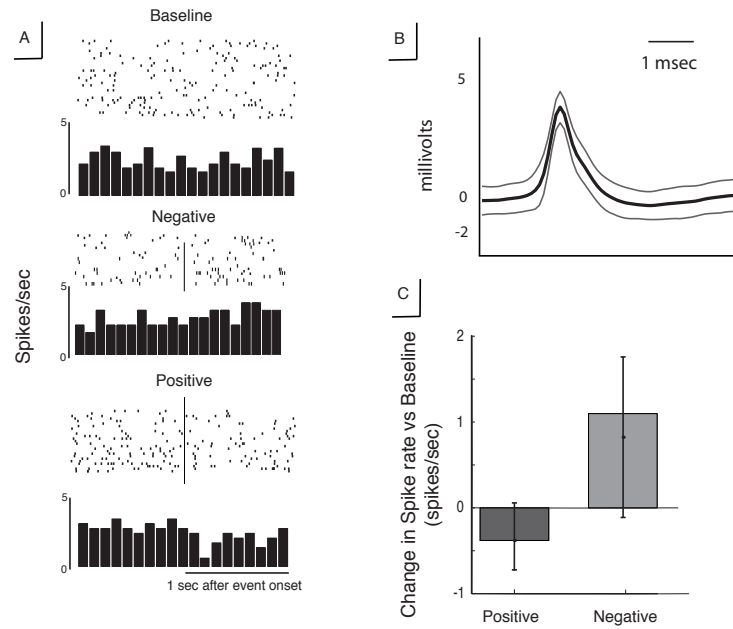


Figure 2: **Summary of spiking activity from left cell A.** Raster plots and peri-event histograms for spiking activity surrounding each category of stimuli. **B.** Average spike waveform, showing broad depolarization and long after-spike hyperpolarization. **C.** Plot showing change in spiking activity relative to baseline period. An increase in spiking activity for negative feedback is visible, though this did not reach statistical significance ($t(11) = 1.73, p = 0.11$, t-test). Phase locking of the spiking activity was not significant in any frequency band ($p > 0.20$, Rayleigh test with permutation procedure)

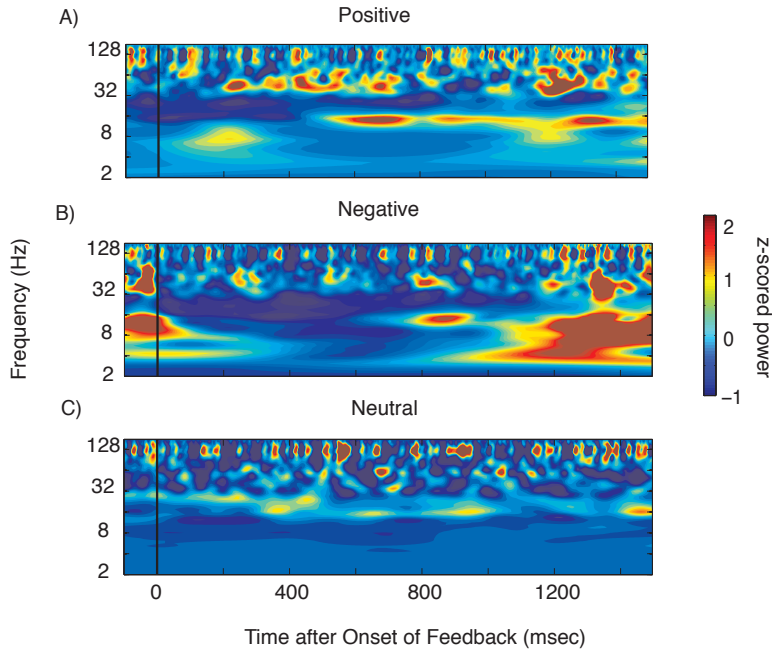


Figure 3: **Normalized power from oscillatory activity of dorsal electrode.** This electrode was located on the edge of the ventral striatum. The pattern is grossly similar to the ventral electrode. As with the more ventral electrode, no gamma band effects were identified. **A.** Positive feedback. The alpha oscillatory burst is visible, although it is not as powerful as for the ventral electrode though still higher for positive feedback events ($p = 0.03$, rank sum with permutation procedure). This p value did not meet the FDR correction threshold ($p = 0.012$). **B.** Negative feedback. The theta burst beginning at ~ 800 msec is visible and significantly higher for negative feedback ($p = 0.008$, rank sum with permutation procedure). **C.** Neutral feedback. The beta oscillation observed during neutral feedback trials is visible in this electrode, though the difference between neutral and non-neutral feedback is not significant for the dorsal electrode ($p = 0.02$, rank-sum test with permutation procedure) because it did not survive FDR correction.

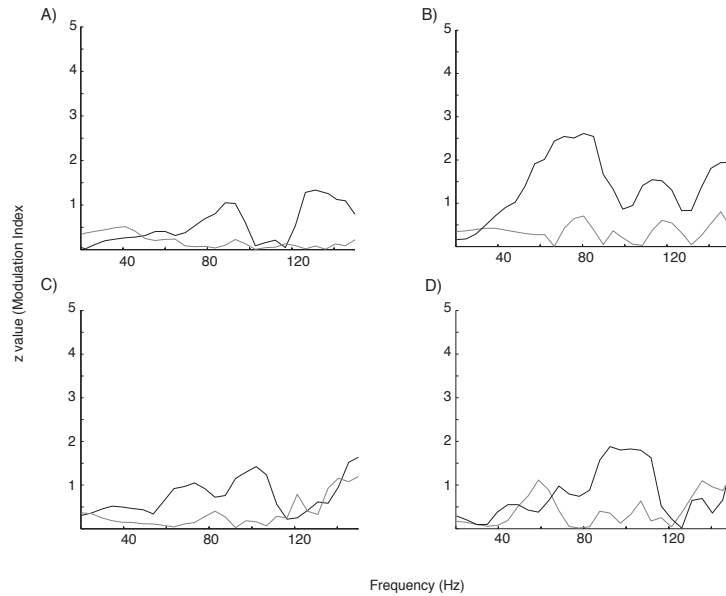


Figure 4: **Modulation index calculated for effect of alpha and theta phase on gamma oscillatory power.** The pattern of significance was similar both to our results obtained using ANOVA applied to phase bins and to the results of Cohen et al. (2009). Z values obtained via bootstrapping procedure for modulation index are plotted. Black line represents positive feedback events and gray line negative feedback events. **A.** Ventral electrode, theta band phase. **B.** Ventral electrode, alpha band phase. **C.** Dorsal electrode, theta band phase **D.** Dorsal electrode, alpha band phase.

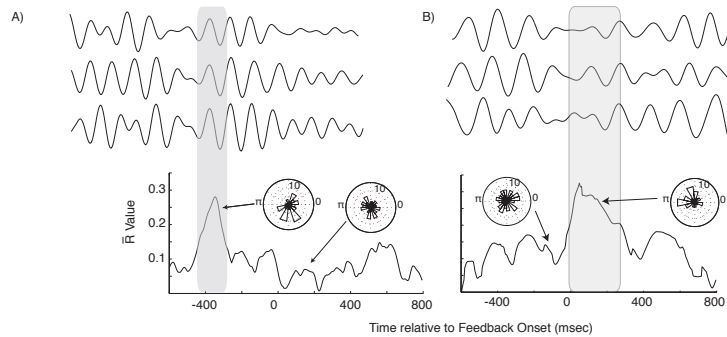


Figure 5: **Differential phase reset of theta and alpha oscillations.** **A.** Phase reset of alpha oscillations. Timepoints at which non-uniform phase distributions were found are highlighted in gray. Three bandpass filtered (10–14 Hz) tracings are shown above for a 2 second window centered on the period of phase alignment. The bottom panel shows the \bar{R} value calculated from a Rayleigh test for the 1500 msec time window surrounding the stimulus onset. Phase reset occurs 400 msec before the feedback stimulus is presented. During the time period in which the alpha phase reset occurs, the participant was engaged in the video game task and had not yet pressed the response button. A reward-related effect preceding the onset of feedback is consistent with evidence of changes in spiking and oscillatory activity that precede the appearance of reward feedback stimuli in animals and humans [13, 14, 15], given that the participant was sufficiently well-trained to anticipate the appearance of the feedback stimulus. Inset roseplots show the distribution of phases at the timepoints indicated. **B.** Phase reset of theta oscillations. Three bandpass filtered (4–8 Hz) tracings are plotted above. \bar{R} values indicate that phase reset occurs at ~ 100 msec after the feedback stimulus is presented.

Supplemental References

References

- [1] Kareem A. Zaghoul, Justin A. Blanco, Christoph T. Weidemann, Kathryn McGill, Jurg L. Jaggi, Gordon H. Baltuch, and Michael J. Kahana. Human substantia nigra neurons encode unexpected financial rewards. *Science*, 323:1496–1499, 2009.
- [2] PJ Lang, MM Bradley, and BN Cuthbert. International affective picture system (iaps): Technical manual and affective ratings. *Gainesville, FL: NIMH Center for the study of emotion and attention, University of Florida*, 1999.
- [3] T.N. Tideman and G. Tullock. A new and superior process for making social choices. *The Journal of Political Economy*, pages 1145–1159, 1976.
- [4] H.C. Cromwell, O.K. Hassani, and W. Schultz. Relative reward processing in primate striatum. *Experimental Brain Research*, 162(4):520–525, 2005.
- [5] J.D. Beaver, A.D. Lawrence, J. van Ditzhuijzen, M.H. Davis, A. Woods, and A.J. Calder. Individual differences in reward drive predict neural responses to images of food. *Journal of Neuroscience*, 26(19):5160, 2006.
- [6] M. Walter, F. Bermpohl, H. Mouras, K. Schiltz, C. Tempelmann, M. Rotte, H.J. Heinze, B. Bogerts, and G. Northoff. Distinguishing specific sexual and general emotional effects in fMRI–Subcortical and cortical arousal during erotic picture viewing. *Neuroimage*, 40(4):1482–1494, 2008.
- [7] S. Erk, M. Spitzer, A.P. Wunderlich, L. Galley, and H. Walter. Cultural objects modulate reward circuitry. *Neuroreport*, 13(18):2499, 2002.
- [8] DF Braus, J. Wrase, S. Grusser, D. Hermann, M. Ruf, H. Flor, K. Mann, and A. Heinz. Alcohol-associated stimuli activate the ventral striatum in abstinent alcoholics. *Journal of Neural transmission*, 108(7):887–894, 2001.
- [9] M. K. van Vugt, P. B. Sederberg, and M. J. Kahana. Comparison of spectral analysis methods for characterizing brain oscillations. *Journal of Neuroscience Methods*, 162(1-2):49–63, 2007.
- [10] P. B. Sederberg, M. J. Kahana, M. W. Howard, Elizabeth J. Donner, and Joseph R. Madsen. Theta and gamma oscillations during encoding predict subsequent recall. *Journal of Neuroscience*, 23(34):10809–10814, 2003.

- [11] R. T. Canolty, E. Edwards, S. S. Dalal, M. Soltani, S. S. Nagarajan, H. E. Kirsch, M. S. Berger, N. M. Barbaro, and R. T. Knight. High gamma power is phase-locked to theta oscillations in human neocortex. *Science*, 313(5793):1626–1628, 2006.
- [12] D.S. Rizzuto, J. R. Madsen, E. B. Bromfield, A. Schulze-Bonhage, and M. J. Kahana. Human neocortical oscillations exhibit theta phase differences between encoding and retrieval. *NeuroImage*, 31(3):1352–1358, 2006.
- [13] M.X. Cohen, C.E. Elger, and J. Fell. Oscillatory Activity and Phase–Amplitude Coupling in the Human Medial Frontal Cortex during Decision Making. *Journal of cognitive neuroscience*, 21(2):390–402, 2009.
- [14] B. Knutson, C.M. Adams, G.W. Fong, and D. Hommer. Anticipation of increasing monetary reward selectively recruits nucleus accumbens. *Journal of Neuroscience*, 21(16):159, 2001.
- [15] Wolfram Schultz, Peter Dayan, and P. Read Montague. A neural substrate of prediction and reward. *Science*, 275:1593–1599, 1997.