Balancing Risk-Return Decisions by Manipulating the Mesofrontal Circuits in Primates

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One-Sentence Summary: The mesofrontal dopaminergic pathway to ventral Brodmann area 6 is crucial for risk-return decision balance in primates.

Decision-making is always coupled with some level of risk with more pathological forms of risk-taking decisions manifesting as gambling disorders. In macaque monkeys trained in a high risk-high return (HH) versus low risk-low return (LL) choice task, we found that the reversible pharmacological inactivation of ventral Brodmann area 6 (6V) impaired the risk-dependency of decision-making. Selective optogenetic activation of the mesofrontal pathway from the ventral tegmental area (VTA) to the ventral aspect of 6V resulted in stronger preference for HH, while activation of the pathway from VTA to the dorsal aspect of 6V led to LL preference. Lastly, computational decoding captured the modulations of behavioral preference. Our results suggest that VTA inputs to 6V determine the decision balance between HH and LL.

The real world is full of uncertainty, and our decisions are always accompanied by some level of risk. Decision making between high risk-high return (HH) and low risk-low return (LL) choices is regulated by the subject's utility function (*1, 2*), which varies significantly from person to person. Pathological risk-taking decisions are known to underlie problematic behaviors, such as gambling disorders (*3-6*). Dysregulation of the reward circuitry, including the ventral striatum and orbitofrontal and medial prefrontal cortices, is implicated in gambling disorders (*7-12*); however, their causal role is still elusive due to technical limitations of human studies.

Risky choice behavior has also been investigated in psychopharmacological studies in rats (*13, 14*). In humans and rodents, risk-dependent decisions are frequently assessed using variants of the Iowa Gambling Task (*15*). However, this task cannot uncouple HH and LL choices from the negative and positive expected values (EVs), respectively. Furthermore, although preferences for risky choices have also been reported in nonhuman primates (*16, 17*) this again could not clearly dissociate risk levels and EVs. Because decision making is usually linked to more variable combinations of risk levels and EVs, we investigated the brain regions involved in risk-dependent decision-making using macaque monkeys trained to perform HH vs LL decision task with a variable combination of reward probabilities and EVs.

Identification of frontal brain areas regulating risk-dependent decision making

Six macaque monkeys were trained to perform a cue/target choice task (Fig. 1(A)). While a monkey fixated to a central point, we presented two colored cues (selected from either 16 or 25 possible colors) in the left and right hemifields, respectively. We assigned different probabilities and EVs of water reward delivery to the different colors (Fig. 1(B)). The colors corresponded to different reward probabilities with the same EV along the horizontal axis and changed in EVs systematically along the vertical axis (4 [n = 2 monkeys] or 5 [n = 4 monkeys] levels between 100 and 250 μL). As an example, when a red cue is selected, the reward would be given in only 10% of the trials with a reward size of 1,000 μL, corresponding to HH choice, whereas the blue cue would be rewarded in 90% of the trials with a reward size of 111.1 μL, representing a LL choice. In both cases, the resulting net EV of the reward would be the same (100 μL). Thus, this task allows to clarify the decisional balance between HH- and LL-preference with fixed net EV.

In a two dimensional heatmap representing the proportion chosen, which is computed based on the frequency of choosing a given option against all other options in the matrix, all six monkeys (Y, S, M, J, C and H) showed a preference for the left-uppermost corner of the matrix, corresponding to the HH choice with the largest EV (Fig. 1(C)). The line plot above the matrices indicates the risk-dependent choices of the monkeys at consistent EVs with a linear regression, showing that the monkeys prefer HH options without any EV-dependence. The HH preference was also statistically not significantly different depending on the EV blocks (paired t-test, $t(5) = 2.021$, $p = 0.099$). We also estimated the monkey's utility and probability weighting functions from their choice using standard parameters described in the literature (*18-20*), which suggested the risk attitude in decision-making (Fig. S1). This was common in all the monkeys, which fits with the framework of utility function in monkeys (*2*) and prospect theory of decision making in humans (*21*).

To identify the frontal brain areas involved in processing risk information, we injected a $GABA_A$ receptor agonist, muscimol (0.2–0.5 μL, 5 μg/μL), into a variety of bilateral symmetric prefrontal regions, including Brodmann ventral area 6 (area 6V) and area 12 (Fig. 2(A-C)) which has previously been suggested to play a role in coding mental operation (*22*). Neurons in this area have also been associated with probability of reward in decision-making (*23*) (described as vlPFC), suggesting that area 6V might be a potential candidate for the

representation of complex risk-return computation. Muscimol injection into ventral aspect of area 6V (6VV; see Fig. 3(C)) eliminated the risk-dependency of decision making, which recovered on the following day (Fig. 2(E), compare the difference of slope (post - pre) to HH-LL between muscimol and saline injection in six experiments in two animals; monkey S, Wilcoxon rank-sum test, $P = 0.026$; monkey M, Wilcoxon rank-sum test, $P = 0.016$). Area 6VV is known for its roles in representing motor actions in many studies. Additionally, a few studies (*22, 24, 25*) have suggested its role in coding for human decision making. The EV-dependency of decision making was not affected by area 6VV inactivation (Fig. 2(F), Wilcoxon rank-sum test, $P > 0.05$). We observed no effect from other candidate areas, muscimol injections into the orbitofrontal cortex (OFC (area 14); four sessions) and dorsal anterior cingulate cortex (dACC; four sessions) had no effect (Fig. 2 (E,F), Wilcoxon rank-sum test, $P > 0.05$). These results suggest that the area 6VV plays an important role for regulating HH-LL decisions, while the OFC and dACC play no critical role in such complex computation.

Optogenetic activation of the mesofrontal pathway in risk-return decision making

As reward information is critical for risk-dependent decision making, we next investigated the role of input from the VTA, a core area of the midbrain dopaminergic system (*26*), which projects to the superficial and deeper layers of area 6VV (see Fig. 3(E) right panel) (*27*). We expressed a red light-activatable opsin, ChrimsonR (*28*), in the bilateral VTA using an adeno-associated viral vector (AAV2.1-Syn-ChrimsonR-tdTomato) (Fig. S2) and selectively stimulated the combination of LED channels belonging either to VTA-6VV/dorsal aspect of area 6V (6VD)/ventrolateral prefrontal cortex (vlPFC) pathway coupled with electrocorticogram (ECoG) electrodes (*29*) which were chronically implanted on the surface of the bilateral target areas (see Fig. 3(C,D), Fig. S3) in monkeys J, C, Y and H. We used a non-selective promotor (Syn) to express ChrimsonR, because we could not see with immunohistochemistry staining the axon terminals in the frontal cortex in a pilot experiment using a dopamine neuron-specific promotor, likely suggesting weak expression with the specific vector. Upon confirming expression at the injection site in the VTA of two monkeys (J and H), we observed that tdTomato was expressed in the majority of VTA neurons around the injection site, with 78% (776/1,000) and 66% (570/860) in monkey J and H, respectively (Fig. 3(E-H)). These neurons were tyrosine hydroxylase (TH)-positive, suggesting that a majority of the activated neurons were dopaminergic.

Next, to ask whether the neural activities in 6VV/6VD/vlPFC were modulated based on HH or LL choices, we recorded their activity with the ECoG electrodes during the HH-LL choice task. Cue-related α-band (8–13 Hz) activity in all channels at 100–500 ms after cue presentation (Fig. 3(I)), when the monkey presumably made its decision, was higher for HH choices (10% reward probability) than for LL choices (90% reward probability, Wilcoxon rank-sum test, $P < 0.05$; Fig. 3(J)). Then, we stimulated the VTA-6VV/6VD/vlPFC pathways optogenetically with red LEDs right after target onset (Fig. 3(B); three repetitions of 20-ms ON and 80-ms OFF, 625 nm wavelength, intensity: 0.782 mW at 2 mA, 1.824 mW at 4 mA). Saccades were initiated at 200–500 ms after target presentation. In these experiments, one of the cues was always fixed at 50% reward probability and 175 μL EV (Fig. 3(A), right panel), while another cue was selected from the 25 color possibilities (Fig. 3(A), left panel). During these sessions, we divided the trials randomly into 50% stimulated (LED-ON) and 50% unstimulated (LED-OFF) trials. In monkey J (Fig. 3(M) top panel), photostimulation of the VTA-6VV pathway, delivered at 2 mA during epoch II (0–220 ms after cue presentation), led to a shift in decision making to the HH-preferring mode, without affecting EV-dependency (Fig. 3(M), bottom panel). Analysis of the population data (Fig. 3(O) top), whereby the preference for HH was evaluated by a threshold for HH-preferring decision in the

psychometric function, showed that the preference for HH was higher during the LED-ON trials than during the LED-OFF trials (Wilcoxon signed-rank test, $z = -3.89$, $P = 1.01 \times 10^{-4}$), while EV-dependency was not affected (Fig. 3(O) bottom, $z = 0.26$, $P = 0.79$). Furthermore, the cue-related α-band response in channels located in area 6VV was enhanced during the LED-ON trials compared to the LED-OFF trials (Fig. 3(K), [LED-ON: 3,213 trials, LED-OFF: 3,203 trials], Wilcoxon rank-sum test, $P < 0.05$). To understand the temporal dynamics of this response, we also applied the stimulation during various time epochs (Fig. S4(A), epoch I, III and IV); the period before cue onset (epoch I: -500 – -280 ms), after cue onset (epoch III: 500–720 ms), and at reward delivery (epoch IV: 1,000–1,220 ms). We observed no change in the risk- and EV-dependency of decision making when photostimulation was applied during epochs I, III, and IV (Fig. S4(A-G), Wilcoxon signed-rank test, $P > 0.05$). Thus, optogenetic stimulation of VTA terminals in the 6VV resulted in modification of risk-dependent decision to HH-preferring, but not EV-dependent decisions, only during epoch II, when the monkeys were presumably making decisions to select a cue.

In contrast, photostimulation of area 6VD relieved the HH-preferring mode (Fig. 3(N,P), top panels). The decision changed to LL-preferring during the LED-ON trials than during the LED-OFF trials (Wilcoxon signed-rank test, $z = 4.55$, $P = 5.33 \times 10^{-6}$), while not affecting the EV-dependency (Fig. 3(P), bottom panel, $z = -0.57$, $P = 0.56$). Additionally, the cue-related α-band responses in area 6VD were inhibited during the LED-ON trials compared to the LED-OFF trials (Fig. 3(L), Wilcoxon rank-sum test, $P < 0.05$), hence having an opposite effect to photostimulation at area 6VV. It is worth emphasizing that more localized photostimulation still convincingly enhanced or relieved the HH-preferring mode (Fig. S5). Photostimulation primarily at vlPFC caused no effect in both risk-dependency (Fig. 3(Q), top panel, $z = 0.10$, $P = 0.91$) and EV-dependency (Fig. 3(Q), bottom panel, $z = 0.61$, $P = 0.61$). Behavioral threshold and brain activities in the control animal (monkey Y) who was injected with the control vector carrying no ChrimsonR sequence (AAV2.1-Syn-tdTomato) were not affected (Fig. S6). Importantly, we could largely exclude that these effects were due to side-effects of heat generated from photostimulation, as the temperature changes induced by LED stimulation were less than 0.5°C (Fig. S7).

Accumulation of Stimulus Effects on Risk-Dependent Behavioral Choices

The photostimulation-dependent effects on choice behavior accumulated over time. In monkey J, after six control sessions without stimulation, we introduced photostimulation at 6VV or 6VD, randomly interleaved (Fig. 4(A)). Thereafter, the HH preference indices for both the LED-ON and LED-OFF trials increased gradually (lower threshold of the psychometric function for HH preference). During the initial six photostimulation sessions, HH-preference was higher in the LED-ON trials than in the LED-OFF trials, but after the seventh session, HH-preference became saturated, and HH preference in the LED-ON and LED-OFF trials became nearly equal. This result implies that the HH-preferring mode might accumulate more easily as compared to LL-preferring mode. To clearly distinguish the stimulation effect between 6VV and 6VD, we stimulated each area in a block task design for the second monkey (monkey H, Fig. 4(B)). The preference for HH became higher in the LED-ON trials than in the LED-OFF trials after three sessions (sessions 23–25). The effect became saturated at session 40, and stimulation was stopped for nine sessions (sessions 41–49). Upon restarting stimulation, the HH-preference reappeared quickly (sessions 49–50) before it became saturated again (Fig. 4(B), magenta line). We subsequently began photostimulation at 6VD, whereby HH preference clearly dissipated over time (Fig. 4(B), cyan line). Similar behavioral effects of 6VD stimulation were also observed in the third monkey (C), where HH-preference was relieved over time and saturated (Fig. 4(C), cyan line).

To investigate whether brain activities are coupled to these behavioral changes, we compared the cue-related α-band ECoG responses during the early period (Fig. 4(A), 6VV: grayish magenta area; 6VD: grayish cyan area) of photostimulation when the facilitatory effects promoting HH-preference occurred, and during the late period (Fig. 4(A), 6VV: light magenta; 6VD: light cyan area) when stimulation-induced HH-preference became saturated. The cue-related α-band responses were measured from both stimulus locations, namely 6VV (inset Fig. 4, magenta circles) and 6VD (inset Fig. 4, cyan circles). Upon 6VV photostimulation, the cue-related α-band responses became markedly enhanced even in the LED-OFF trials as HH-preference was enhanced without stimulation during the late period (2757 trials) compared with the early period (952 trials) (Fig. 4(D), Wilcoxon rank-sum test, $P < 0.05$). Similar results were also observed in monkey H (643 trials in the early and 536 trials in the late period, Fig. 4(F)). Consistent with the behavioral responses, upon 6VD photostimulation, we observed a response inhibition that was opposite to the effect of 6VV stimulation (Fig. 4(E,G,H); 507-958 trials).

Since it remained unclear exactly how neural representation in these regions (activation or inhibition) was causally linked to behavioral HH/LL preference mode, we next investigated the changes in neural dynamics for this decision balancing. To directly address this question, we looked to see if neural population decoding can capture the modulation of behavioral preference caused by the optogenetic stimulation.

Linear decoding of lower band activity captures behavioral preference modulation by photostimulation

We first identified the dimension of the power signals relevant to HH-LL by demixed principal component analysis (dPCA) (*30*) (Fig. 5(A)). The time course of normalized power of ECoG activities for each axis (HH-LL or EV) were clearly separated depending on each stimulus intensity (Fig. 5(B)). Two-dimensional trajectory of α-band population activity in HH-LL and EV axes were also clearly separated under each stimulus condition (Fig. 5(C)) and the most separated dPCs (Fig. 5(D), also Fig. 5(C), dots of x-y plane) were roughly consistent with the stimulus dimension. Thus, the 1st dPC should be the most prominent decoder axis of HH-LL as a linear classifier. For this purpose, we trained the decoder separately for LED-ON and LED-OFF conditions (see Methods for details). We then performed linear decoding to classify a given target as an HH (i.e., 10% and 30%) or LL (i.e., 70% and 90%) option based on power signals of all channels in each frequency band to measure the decoder threshold as HH-LL preference. The HH-LL decoder preferred HH options when area 6VV was photostimulated, with the decoder performance curve becoming steeper with photostimulation (Fig. 5(E), compare magenta and black curves). In contrast, decoding of 6VD responses, the performance curve became shallower with photostimulation (Fig. 5(F), cyan and black curve). Both decoders revealed a pattern of results quite similar to behavior (Fig. 3(M,N), top panels). Results for the HH-LL decoder were similar to behavioral performance for both LED-ON and LED-OFF conditions. The decoder threshold for HH-LL was extremely sensitive when photostimulation was applied (Fig. 5(G), magenta symbols: t-test, monkey H; $t(58) = -5.36$, $p = 1.50 \times 10^{-6}$, monkey J; $t(58) = -5.07$, $p = 4.34 \times 10^{-6}$). In contrast, the HH-LL decoder significantly diminished HH-preference when area 6VD was photostimulated (Fig. 5(F,G), cyan symbols: t-test, monkey C; $t(58) = 4.26$, $p = 7.59 \times 10^{-4}$, monkey H; $t(58) = 3.99$, $p = 1.84 \times 10^{-4}$, monkey J; $t(58) = 8.31$, $p = 1.79 \times 10^{-11}$), while photostimulation of vlPFC had no effect. In light of these results, neural population decoding could capture the behavioral preference modulation induced by optogenetic photostimulation in area 6V, suggesting that neural dynamics of mesofrontal pathway is involved in cognitive computation for modulation of the risk-return decision balance.

Discussion

Until recently, pathway-selective optogenetic manipulation studies aiming to modulate behavior were rare in macaques (*31, 32*), although widely spread non-selective activation could promote learning of reward value (*33, 34*) and produce plastic changes in cortical BOLD responses (*35, 36*). We successfully modulated risk-dependent decision making in macaques by selective manipulation of the mesofrontal pathway from VTA to area 6V. Activation of the VTA-6VV pathway enhanced HH-preferring cue-related responses in area 6VV and facilitated HH-preferring decisions, whereas activation of the VTA-6VD pathway inhibited HH-preferring cue-related responses in area 6VD and relieved HH-preferring decisions. The effects observed by activation of the VTA-6VV pathway may be due to the short-term modulation of synaptic transmission through the activation of dopamine receptors, because the majority of vector-infected cells in the VTA were dopaminergic (Fig. 3(F-H)). The success of optogenetic manipulation might be due to application of ChrimsonR, which can be activated by red light that penetrates brain tissue better than green light to activate channel rhodopsin. Another reason might be that the rich axonal projections from the VTA to area 6V terminate in the most superficial layer of the area 6V (*27*), which enabled better access by the optogenetic stimulation from outside the brain. Though unlikely, we are unable to exclude the possibility that this cortical area may be organized in a mosaic-like fashion, whereby 'risk-seeking' hot spots are adjacent to 'risk-averse' hot spots. More detailed structural analysis will be necessary in order to discern this possibility in the future.

The dACC and OFC play important roles for the reward value computation in monkeys (*23, 37-41*). Therefore, the role of area 6V, and not dACC and OFC, in risk-dependent decision making was highly unexpected, especially as the macaque area 6V has been long considered to be a motor-related area (*42-44*). Nonetheless, as EV-dependency might be more widely prevalent in frontal cortical regions and in the midbrain (*23, 38-41*), it is likely that area 6VV is not the sole center responsible for this behavioral property. Evidence from human MRI (area 6 (*22*); the inferior frontal gyrus (IFG) (*24, 25*)) and patient studies (*7, 8, 10, 11*) support the notion of area 6 playing a role in behavioral flexibility and risky decision making in humans, thereby suggesting the evolutionary conserved function of these neural circuits between non-human primates and humans.

We also observed that activation of the VTA-area 6V pathway induced an accumulation of the modulatory effects; HH-preference in LED-OFF trials gradually enhanced and saturated after a series of sessions with area 6VV photostimulation. In contrast, HH-preference was relieved with area 6VD photostimulation. The behavioral changes were accompanied by an enhancement of the cue-related α-band responses in area 6VV and a suppression in area 6VD (Fig. 4(D-H)) in LED-OFF trials, respectively. Such changes in the neural responses are likely induced by long-term dopamine-dependent plasticity mechanisms (*45*). Moreover, the existence of sub-areas with distinct functions might open up an interesting new direction for future studies. One can speculate that the distinct dopamine subcircuits to the areas 6VV and 6VD might separately encode for different risk-return computation. Another possibility might be like the nucleus accumbens, where distinct subpopulations of D2R+ cells (*46*), separately encode the selection of risky options. Thus, the pathway from area 6VV/6VD to these distinct populations in NAc neurons may be interesting to investigate in the future studies.

We further extended our optogenetic experiment to the computational framework. We observed that neural population decoding could capture the photostimulation effect of HH-preference mode of subjects. Thus, we directly compared neural and behavioral correlates of dynamically changing HH-preferring mode, allowing for a more direct assessment of whether changes in neural activity with HH-preferring mode can explain behavior. However, only future studies will reveal whether this state in primates is comparable to patients with

gambling disorders. Because the D3 receptor agonist pramipexol administered for treatment of Parkinson disease promotes gambling disorder (*47*), our findings not only have broad implications for answering such clinically relevant questions but also provide opportunities to better understand the underlying neural mechanism of gambling disorder in humans.

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Supplementary Materials

Materials and Methods

Supplementary Text

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Figs. S1 to S7

Fig. 1. Task design and behavior. (A) The monkeys were required to choose one of two cues by saccade to receive a certain amount of water reward. **(B)** Assignment of the reward probabilities and EVs for each cue color (top) and the relationship between the reward probabilities and the reward sizes (bottom). **(C)** Proportions of choosing each combination of reward probability and EV, computed by all comparison against other options, are shown as a color contour map for the six monkeys. The scatter plot show proportion choices for reward probabilities (top) computed by the consistent EV, and proportion choices for EV (left) computed by the consistent probability. The line plot represents their linear regression.

Fig. 2. Effects of muscimol injections into frontal cortical regions on risky choice decisions. (A) Surface view of the macaque cortex showing the rostro-caudal levels of the planes in **c** and approximate location of area 6VV (yellow). **(B)** MRI of the coronal plane from monkey S including area 6VV. The arrowhead indicates the Gd^{3+} injection site. **(C)** Effective muscimol injection sites in area 6VV (red-filled circles). The results from two animals are superimposed. **(D)** Proportion chosen for single session (Monkey S) plotted against reward probability computed by the consistent EV at each time window from injection (Pre, 0–30 min, 30–60 min, 60–130 min, 130–200 min, and 24 h). **(E)** The difference of slope to reward probability (HH-LL) between before and after injection at each injection site (OFC (area 14) and dACC) in two monkeys. **(F)** The same arrangement as **E** for the difference of slope to the expected value (EV). Plots with * exhibit a statistically significant effect (Wilcoxon rank-sum test, * $P < 0.05$).

Fig. 3. Optogenetic stimulation of the mesocortical pathway. (A) Cues in the optogenetic experiments; one from 25 choices vs the grey one. **(B)** Photostimulation timing indicated by vertical color bars. **(C)** Location of the LED/ECoG probes on area 6VV, 6VD and vlPFC. **(D)** Experimental design. Inset; anti-RFP immunohistochemistry showing positive axons in 6VV. Scale bar; 500 μm. **(E)** Low magnification view of VTA with anti-RFP immunohistochemistry. Scale bar; 10 mm. **(F,G,H)** High magnification view of VTA. Anti-RFP (F), anti-TH immunostaining (g), and merged image (H). Scale bar; 100 μm. **(I)** Averaged time-frequency plots of ECoG at 6VV for HH (left) and LL choice (right). **(J)** α-band activity for the HH and LL choices in (I). **(K,L)** The time course of α-Band activity for the LED-ON (colored curve) and LED-OFF (black curve) conditions in each 6VV (K) and 6VD (L). **(M)** Psychometric function of reward probability (top) and EV (bottom) (Stimulation given at 6VV). The smooth curve shows cumulative Gaussian fitting to the data. **(N)** The same arrangement as (M) (Stimulation given at 6VD). **(O-Q)** Comparison population behavioral thresholds with LED-OFF and LED-ON for the HH-LL (top) and EVs (bottom). Stimulation given at VTA-6VV pathway (n = 33, O), VTA-6VD pathway (n = 73, P) and VTA-vlPFC pathway (n = 16, Q). Photostimulations were delivered sub-areal sets; either one or two local line(s) or sub-areal spots (see also Fig. S5).

Fig. 4. Accumulation of the stimulus effect. (A-C) Accumulation of the stimulus effect. Behavioral thresholds are plotted for each experiment session in monkey J. Magenta trace: LED-ON trials stimulated at 6VV; Cyan trace: LED-ON trials stimulated at 6VD; black trace: LED-OFF trials. Light orange vertical band indicates the six sessions before the start of photostimulation, for 6VV photostimulation, grayish magenta band indicates the five early sessions, and the light magenta band indicates the three late sessions. For 6VD photostimulation, grayish cyan band and light cyan band indicate early and late sessions, respectively. **(B,C)** The same arrangement as (A) for Monkey H and C. Light grey horizontal line for monkey H (B) indicates the sessions with 2 mA stimulation, which was ineffective. For monkey C, only 6VD stimulation was completed. **(D-H)** α-band ECoG activity in 6VV (D,F) and 6VD (E, G, H) during the LED-OFF trials are compared between the early (grayish red and blue line traces) and late (light red and blue line traces). The insert panel represents the used channels for this analysis at 6VV (magenta circles) and 6VD (cyan circles) respectively. The same arrangement as Fig.3(K,L). The inset in (H) represents the ECoG channels used for this analysis.

Fig. 5. Decoding of risk preference in low dimensional power signal. (A) Schematic diagram of dimensionality reduction by demixed principal component analysis (dPCA) which decomposes the population activity of individual channels into dimensions relevant to HH-LL, EV and condition independent axes. **(B)** The 1st demixed principal components for each variable in α-band for each reward probability (top panel) and EV (middle panel) and others (lowest panel) from monkey C. The solid and dashed vertical lines indicate the timing of target onset and mean reaction time, respectively. **(C)** Trajectory of lower band population activity (≤ 13-Hz) in HH-LL and EV axes. The line color corresponds to the condition matrix (inset). The dots in the x-y plane indicates data at time when the trajectories are most separated apart (time at 0.2 s) which is also shown in **(D)**. **(E,F)** Psychometric functions constructed by choice of decoders that use the 1st demixed principal component of HH-LL as a linear classifier. The proportion chosen was computed by aggregating over all 20 trial repetitions (assuming single session). **(G)** Summary of decoder behavioral thresholds as a comparison between LED-ON and -OFF trials. Plots and error bars represent the mean and 95% confidence interval across 20 decoding sessions, respectively.