Title:

Pupil size predicts the onset of exploration in brain and behavior.

Authors:

Akram Shourkeshti[1], Gabriel Marrocco[1], Katarzyna Jurewicz[1,2], Tirin Moore[3,4], R. Becket Ebitz*[1]

Affiliations:

[1]Department of Neurosciences, Université de Montréal, Montréal, QC, Canada

[2]Department of Physiology, McGill University, Montréal, QC, Canada

[3]Department of Neurobiology, Stanford University School of Medicine, Stanford, CA, USA

[4]Howard Hughes Medical Institute, Chevy Chase, MD, USA

*Corresponding author and lead contact:

R. Becket Ebitz

Department of Neurosciences

Université de Montréal

Montréal, QC CANADA H3T 1J4

Email: becket@ebitzlab.com

Abstract

In uncertain environments, intelligent decision-makers exploit actions that have been rewarding in the past, but also explore actions that could be even better. Several neuromodulatory systems are implicated in exploration, based, in part, on work linking exploration to pupil size–a peripheral correlate of neuromodulatory tone and index of arousal. However, pupil size could instead track variables that make exploration more likely, like volatility or reward, without directly predicting either exploration or its neural bases. Here, we simultaneously measured pupil size, exploration, and neural population activity in the prefrontal cortex while two rhesus macaques explored and exploited in a dynamic environment. We found that pupil size under constant luminance specifically predicted the onset of exploration, beyond what could be explained by reward history. Pupil size also predicted disorganized patterns of prefrontal neural activity at both the single neuron and population levels, even within periods of exploitation. Ultimately, our results support a model in which pupil-linked mechanisms promote the onset of exploration via driving the prefrontal cortex through a critical tipping point where prefrontal control dynamics become disorganized and exploratory decisions are possible.

Introduction

Many decisions maximize immediate rewards. However, in uncertain or changing environments, it is important to occasionally sacrifice some immediate rewards in the service of long-term goals. This gives us an opportunity to learn about the value of alternative options and discover new, more valuable strategies for interacting with the world. In short, in complex environments, intelligent decision-makers exploit rewarding strategies, but also explore alternative strategies that could be even better.

Because exploitation maximizes immediate reward, it can rely on the same value-based decision-making processes that have been the subject of neurobiological studies for decades (Ding and Hikosaka, 2006; Jurewicz et al., 2022; Platt and Glimcher, 1999; Roesch and Olson, 2007; Schultz et al., 2008). However, we are only just beginning to understand the neural bases of exploration (Costa and Averbeck, 2020; Daw et al., 2006; Pearson et al., 2009; Wilson et al., 2021, 2014). One clue is that many organisms seem to explore via random sampling (Gershman, 2019; Wilson et al., 2021, 2014). Randomness is a critical component of exploratory discovery in bird song and motor learning (Fiete et al., 2007; Wu et al., 2014), can perform about as well as more sophisticated exploratory strategies in many environments (Dayan and Daw, 2008), and humans and other primates tend to explore randomly even when more sophisticated strategies are available (Ebitz et al., 2018; Wilson et al., 2014). There is some evidence linking random exploration to disorganized patterns of activity in the prefrontal cortex (Ebitz et al., 2019, 2018; Muller et al., 2019; Wilson et al., 2021), but more work is needed to understand how these disorganized patterns of activity emerge and what neurobiological processes drive their emergence.

One promising hypothesis is that random exploration and its neural correlates could be under the control of some process(es) linked to pupil size. Pupil size under constant luminance is a

peripheral index of autonomic arousal (Bradley et al., 2008; Ebitz and Moore, 2019; Loewenfeld, 1999) that also predicts widespread changes in neural population activity (McGinley et al., 2015; Reimer et al., 2014)–including in regions implicated in noisy decision-making (Ebitz and Platt, 2015; Tervo et al., 2014). Among other neuromodulators (Gilzenrat et al., 2010; Koss, 1986; Reimer et al., 2016), pupil size is correlated with central norepinephrine (Costa and Rudebeck, 2016; Joshi et al., 2016): a catecholamine that flattens neuronal tuning functions (Martins and Froemke, 2015) and predicts abrupt "resets" in cortical networks (Aston-Jones and Cohen, 2005; Bouret and Sara, 2005). Behaviorally, pupil size predicts noisy decision-making (Aston-Jones and Cohen, 2005; Ebitz et al., 2014; Eldar et al., 2013; Gilzenrat et al., 2010; O'Reilly et al., 2013; Wilson et al., 2021), including errors of reward-maximization (Jepma and Nieuwenhuis, 2011) and task performance (Ebitz et al., 2014; Ebitz and Platt, 2015), at least some of which are likely to be caused by exploratory processes (Ebitz et al., 2019; Jepma and Nieuwenhuis, 2011; Pisupati et al., 2021).

While a growing body of circumstantial evidence implicates pupil-linked mechanisms in exploration, there is also a plausible alternative interpretation of these results: perhaps pupil size simply tracks the variables that make exploration more likely without actually predicting exploration. Pupil size under constant luminance increases with some variables that should make exploration more likely, including the volatility of the environment, the surprise of reward outcomes, novelty, uncertainty, and context changes (Clewett et al., 2020; Filipowicz et al., 2020; Graves et al., 2021; Preuschoff et al., 2011; Slooten et al., 2018; Yokoi and Weiler, 2022). Critically, in circumstances where these variables change behavior (i.e. increasing learning, increasing decision noise, inducing exploration), it is not clear whether the pupil is signaling these variables or instead directly predicting behavioral change (Nassar et al., 2012; O'Reilly et al., 2013; Urai et al., 2017). Fortunately, recent results suggest that at least some exploration appears to occur tonically, regardless of these variables (Ebitz et al., 2019; Pisupati et al., 2021; Wilson et al., 2021). In parallel, a new computational approach now allows us to determine when exploration is occurring independently of the reward-based computations thought to drive it (Chen et al., 2021; Ebitz et al., 2020, 2019, 2018). These advances mean that it is now possible to determine whether pupil size predicts exploration itself or instead simply tracks the variables that make exploration more likely.

Here, we measured pupil size and recorded from populations of prefrontal neurons while two rhesus macaques performed a task that encouraged both exploration and exploitation. To infer whether the subjects were exploring or exploiting, we modeled exploration and exploitation as the latent goal states underlying decision-making (Chen et al., 2021; Ebitz et al., 2020, 2019, 2018). Pupil size under constant luminance was larger during explore choices than exploit choices, consistent with both the idea that pupil-linked processes are the proximate cause of exploration and the idea that pupil size tracks variables that make exploration more likely. However, the temporal relationship between pupil size and exploration was both precise and complex, with pupil size explaining variability in brain and behavior that could not be explained by rewards or time. Together, these results support the hypothesis that pupil-linked processes drive the prefrontal cortex through a critical tipping point that permits exploratory decisions.

Results

Two male rhesus macaques performed a total of 28 sessions of a classic explore/exploit task: a restless three-armed bandit (subject B: 10 sessions, subject O: 18 sessions; a total of 21,793 trials). We have previously analyzed parts of this dataset (Ebitz et al., 2018), but not the pupil size data, and all analyses presented here are new. In this task, the reward probability (value) of three targets walks randomly and independently over time (**Figure 1A**). This means that the subjects have to take advantage of valuable options when they are available (exploit), but also occasionally sample alternative options to determine if they have become more valuable (explore).

Rather than instructing subjects to explore and exploit, this task takes advantage of the subjects' natural tendency to alternate between exploration and exploitation in a changing environment. We have previously shown that both monkeys and mice exhibit 2 behavioral modes in this task: one exploitative mode in which they repeatedly choose the same option—learning little but maximizing reward—and one exploratory mode in which they alternate rapidly between the options—choosing randomly with respect to rewards and learning rapidly (Chen et al., 2021; Ebitz et al., 2018). We infer which of these modes is driving behavior with a hidden Markov model (HMM; **Figure 1B**). This approach models the exploratory and exploitative modes as latent goal states and the maximum *a posteriori* goal is taken as the state label for each choice. We have previously shown that this method identifies explore/exploit state labels that match normative definitions (Chen et al., 2021; Ebitz et al., 2018) and explain variance in prefrontal neural activity that cannot be explained by reward value, reward history, and switch/stay decisions (Ebitz et al., 2018).

Some previous studies used a different method to identify exploratory choices (Daw et al., 2006; Jepma and Nieuwenhuis, 2011; Pearson et al., 2009). This method fits a reinforcement learning (RL) model to the behavior and identifies the choices that are not consistent with the model's subjective values as exploratory. However, this approach (1) equates exploration with errors of reward maximization, not a goal that is orthogonal to reward maximization, and (2) its accuracy depends on precise knowledge of the computations involved in the choice, which are highly variable, both across individuals and over time (Chen et al., 2021, 2021; Kaske et al., 2022). The HMM approach, conversely, makes no assumptions about the computations involved in the choice and identifies choices that are orthogonal to reward value, not anti-correlated with it (Chen et al., 2021; Ebitz et al., 2018). Here, we found that state labels from the HMM method explained more variance in behavior and neural activity than choice labels from the previous, RL method (**Figure 1C;** response time: both subjects, paired t-test: $p < 0.005$, $t(27) = 3.41$, the mean difference of beta weights = 0.004, 95% CI = 0.002 to 0.007; scatter index [(Ebitz et al., 2018)]: both subjects, paired t-test: $p < 0.001$, $t(27) = 3.84$, the mean difference of beta weights = 0.15, 95% CI = 0.07 to 0.24: see **Methods**). In short, we find that the HMM approach is a more robust and accurate method, with better face validity, than the RL-based method for identifying explore choices.

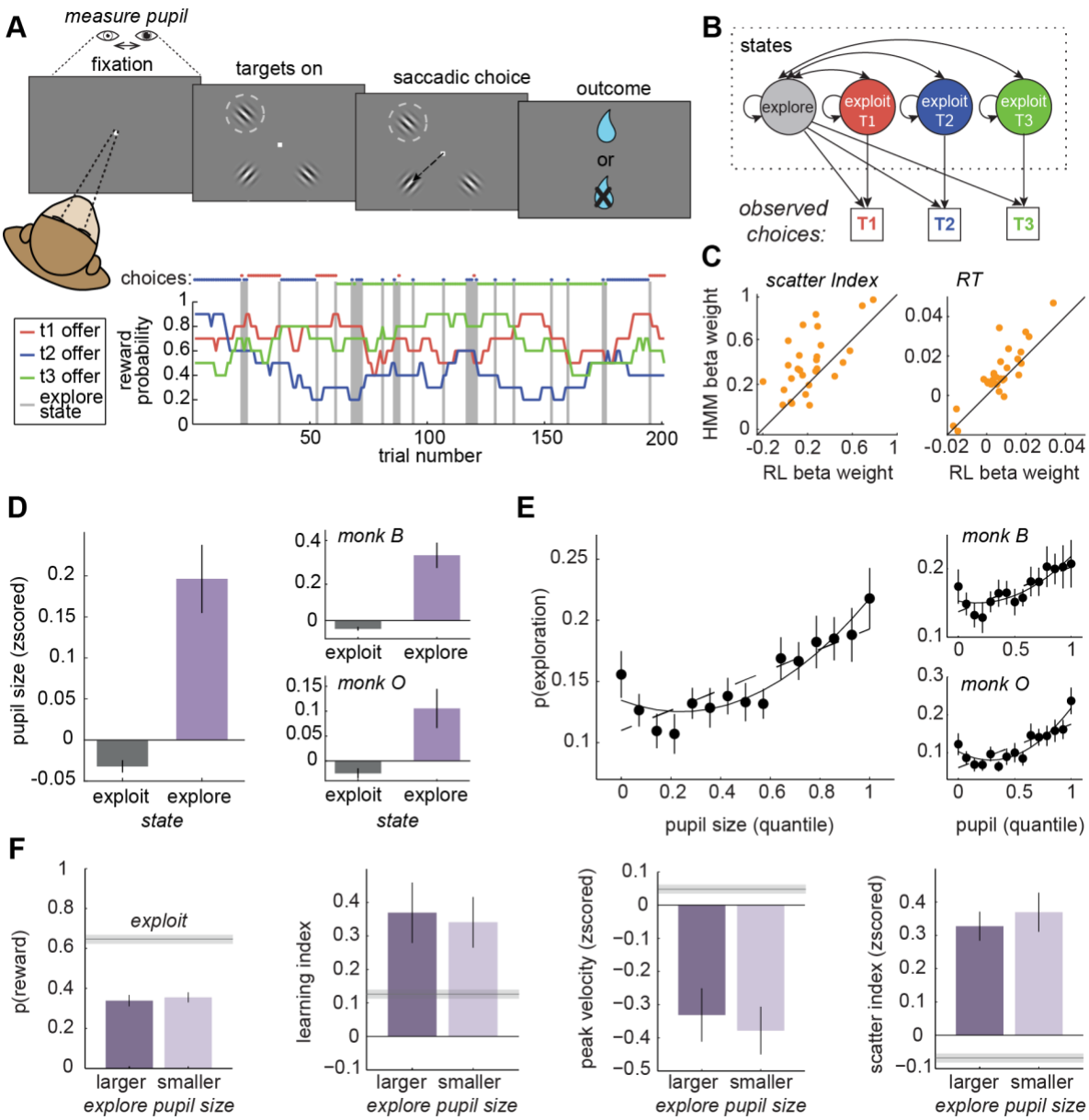

Figure 1. Task design and pupil. *A) Top: Subjects made saccadic choices between three identical options. One of the options was in the receptive field of an FEF neuron (dotted circle). Bottom: Reward probabilities for the 3 options (lines), with choices overlaid (dots) for 200 example trials. Gray bars = explore-labels. B) The HMM models exploration and exploitation as latent goal states underlying choice sequences. C) Comparing the regression coefficients HMM-inferred and RL-inferred explore choices for a measure of the disorganization of neural population responses ("scatter index"; see Methods; (Ebitz et al., 2018)) and response time. D) Average pupil size on explore and exploit choices. Right: Same for individual subjects. E) The probability of explore choices as a function of pupil size quantile. Dotted line: linear GLM fit. Solid line: quadratic fit. Right: Same for individual subjects. F) Several behavior measures compared across median-split large- and small-pupil-size explore choices. Left to right: reward probability, a one-trial-back learning index (see Methods), saccadic peak velocity of saccades, and the scatter index. No significant differences between pupil bins. The blue line is the mean ± SEM for exploit choices. Error bars depict ± SEM throughout.*

Using the previous method, Jepma & Nieuwenhuis (2011) reported that pupil size under constant luminance is larger during explore choices compared to exploit ones. Therefore, we first asked if this is also true using the HMM method. Indeed, we found that pupil size at fixation (see **Methods**) was larger on explore-labeled trials than exploit-labeled trials in both subjects (**Figure 1D**; both subjects, paired t-test: $p < 0.0001$, $t(27) = 4.95$, mean offset = 0.23, 95% CI = 0.13 to 0.32; subject B: $p < 0.001$, $t(9) = 5.50$, mean offset = 0.4, 95% CI = 0.24 to 0.57; subject O: $p < 0.02$, $t(17) = 2.85$, mean offset = 0.13, 95% CI = 0.03 to 0.23). However, the probability of exploration did not increase linearly as a function of pupil size (**Figure 1E**). Although larger pupil size generally predicted more explore choices (both subjects, 1st order GLM: beta = 0.2, $p < 0.0001$, n = 28 sessions; subject B: 1st order GLM, beta = 0.34, $p < 0.0001$, n = 10; subject O: 1st order GLM, beta = 0.13, $p < 0.0001$, n = 18), the relationship was obviously nonlinear in both subjects (2nd order, quadratic model was a better fit in both animals, 2nd order GLM, beta 1 = 0.16, $p < 0.0001$, beta 2 = 0.04, $p < 0.005$, n = 28 sessions; subject B: 2nd order GLM, beta 1 = 0.27, $p < 0.0001$, beta 2 = 0.05, $p < 0.05$, n = 10; subject O: 2nd order GLM, beta 1 = 0.11, $p < 0.0001$, beta 2 = 0.02, $p > 0.1$, n = 18; linear model AIC = 17319.5, quadratic model AIC = 17311.7, AIC weight [relative likelihood] of linear model = 0.02; see **Methods**). This was not an artifact of some systematic error in the HMM fits: there was also a U-shaped relationship between pupil size and the probability of switching (both subjects, 1st order GLM: beta = 0.2 $p < 0.0001$, n = 28 sessions; subject B: 1st order GLM, beta = 0.31, $p < 0.0001$; subject O: 1st order GLM, beta = 0.18, $p < 0.0001$, 2nd order, quadratic model was a better fit in both animals, 2nd order GLM, beta 1 = 0.16 $p < 0.0001$, beta 2 = 0.05, $p < 0.0001$; subject B: 2nd order GLM, beta 1 = 0.18, $p < 0.0005$, beta 2 = 0.09, $p < 0.0005$; subject O: 2nd order GLM, beta 1 = 0.15, $p < 0.0001$, beta 2 = 0.03, $p < 0.01$; linear model AIC = 16407.9, quadratic model AIC = 16390.6, AIC weight of linear model = 0.0001). Thus, although pupil size was generally larger during exploration, compared to exploitation, the relationship between pupil size and exploration was U-shaped.

A U-shaped relationship would be expected if some “explore” choices (or switch choices) were not real explore choices, but instead the result of disengagement at low levels of arousal. However, if this were the case, then the valid, large-pupil explore choices would systematically differ from the false, small-pupil “explore” choices. They did not. Small- and large-pupil explore choices (median split) were indistinguishable along several of the key dimensions that differentiate explore choices from exploit choices (**Figure 1F**). For example, both were equally likely to be rewarded (mean difference = 0.03 ± 0.24 STD) between large- and small pupil-explore choices ($p > 0.4$, $t(1,27) = 0.75$, paired t-test; AUC for discriminating explore and exploit = 0.65 ± 0.05 STD across sessions). Both had similar peak saccadic velocities (mean difference = -0.05 ± 0.23 STD, $p > 0.2$, $t(27) = -1.08$; explore/exploit AUC = 0.61 ± 0.10 STD) and both had more variability in neural population choice information (“scatter index”, mean difference = 0.03 ± 0.33 STD, $p > 0.6$, $t(27) = 0.45$; explore/exploit AUC = 0.60 ± 0.07 STD). Both had similar levels of reward learning (see **Methods**; the mean difference = -0.03 ± 0.57 STD, $p > 0.7$, $t(27) = 0.27$): in both cases, learning was substantially enhanced relative to the exploit choices (small-pupil, the mean difference from exploit = 0.24 ± 0.48 STD, $p < 0.02$, $t(27) = 2.69$; large-pupil, the mean difference from exploit = 0.21 ± 0.39 STD, $p < 0.01$, $t(27) = 2.91$). These results are incompatible with the idea that either type of explore choice reflects disengagement in the

task or that small- and large-pupil explore choices have different causes. Instead, we will see that the U-shape was due to the complex temporal relationship between pupil size and exploration.

Pupil size ramped up across trials before explore choices in both subjects and shrank down to below-baseline levels when exploitation began (**Figure 2A**). This ramping meant that pupil size was larger not just during exploration, but also during the exploit choices immediately before exploration (both subjects, GLM slope = 0.01, $p < 0.005$, n = 28; subject B: beta = 0.02, $p < 0.02$, n = 10; subject O: beta = 0.01, $p < 0.05$, n = 18; average pupil size compared to the exploit choices, post-hoc paired t-tests, 1 trial before exploration mean = 0.12, $p < 0.005$, $t(27) = 3.42$; 2 trials mean = 0.09, $p < 0.03$, $t(27) = 2.41$; 3 trials mean = 0.03, $p > 0.1$, $t(27) = 1.42$; 4 trials mean = 0.05, $p < 0.05$, $t(27) = 2.07$). By the first exploit choice after exploration, pupil size had already begun shrinking to below-baseline levels (post-hoc paired t-tests, 1 trial after exploration mean = 0.03, $p = 0.09$, $t(27) = 1.73$; 2 trials after mean = -0.11, $p < 0.02$, $t(27) = -2.67$; 3 trials after mean = -0.16, $p < 0.02$, $t(27) = -2.72$; 4 trials after mean = -0.08, $p > 0.2$, $t(27) = -1.27$; 5 trials after mean = -0.16, $p < 0.001$, $t(27) = -3.94$; p-values are significant with a Holm-Bonferroni correction). The shrinking to below-baseline levels could suggest a refractory mechanism that would prevent exploration from re-occurring immediately after it happened.

Neither the ramping in pupil size before exploration nor the shrinking after were artifacts of some misalignment in the model's labels. We saw no evidence of ramping in peak saccadic velocity, another behavioral measure that differentiated explore trials and exploit trials (**Figure 2B**; no significant decrease from baseline 1 trial before, paired t-test: $p > 0.7$, $t(27) = 0.42$; a GLM was nonsignificant with the trend pointing in the opposite direction: 10 trials preceding exploration, beta = 0.008, $p > 0.1$) and no significant change from baseline afterward (not greater than the baseline during the 5 trials after exploration, when pupil shrinking was maximal, mean = -0.47 ± 0.15 STD, $p > 0.9$, one-sided $t(27) = -1.67$). We previously reported similar results for certain neural measures (Ebitz et al., 2018). Thus, while pupil size ramped before the onset of exploration and shrank afterward, the same was not true of other behavioral and neural variables, suggesting that these dynamics were not some artifact of misalignment.

Next, we examined the extent to which these across-trial pupil dynamics were affected by exploration (see **Methods**). When the subjects did not explore the pupil size increased steadily across trials (**Figure 2C**; both subjects, GLM: beta = 0.004, $p < 0.0001$; subject B: beta = 0.003, $p < 0.0001$; subject O: beta = 0.005, $p < 0.0001$, n = 25 lags over 28 sessions). This implies that the ramping in pupil size before explore choices may be a general dynamic of how pupil size evolves in the absence of exploration. However, a different pattern emerged when we looked at how the pupil changed between exploit trials that were separated by exploration. When 2 exploit trials were separated by at least 1 explore choice, pupil size was smaller on the second exploit trial (both subjects, GLM: beta = -0.09, $p < 0.0001$; subject B: beta = -0.14, $p < 0.0001$; subject O: beta = -0.07, $p < 0.0001$). Critically, passing through exploration only produced a baseline decrease in pupil size but did not alter the rate at which pupil size grew over trials (no significant interaction between slope and condition in both subjects, GLM: beta < -0.0001, $p > 0.9$; subject B: beta = 0.003, $p < 0.05$; subject O: beta = -0.002, $p > 0.1$; also nonsignificant on trials 5-25:

both subjects: beta < 0.0005, p > 0.5). Therefore, pupil size tended to ramp across trials but exploit choices temporarily decreased pupil size without disrupting this ramping in the long term.

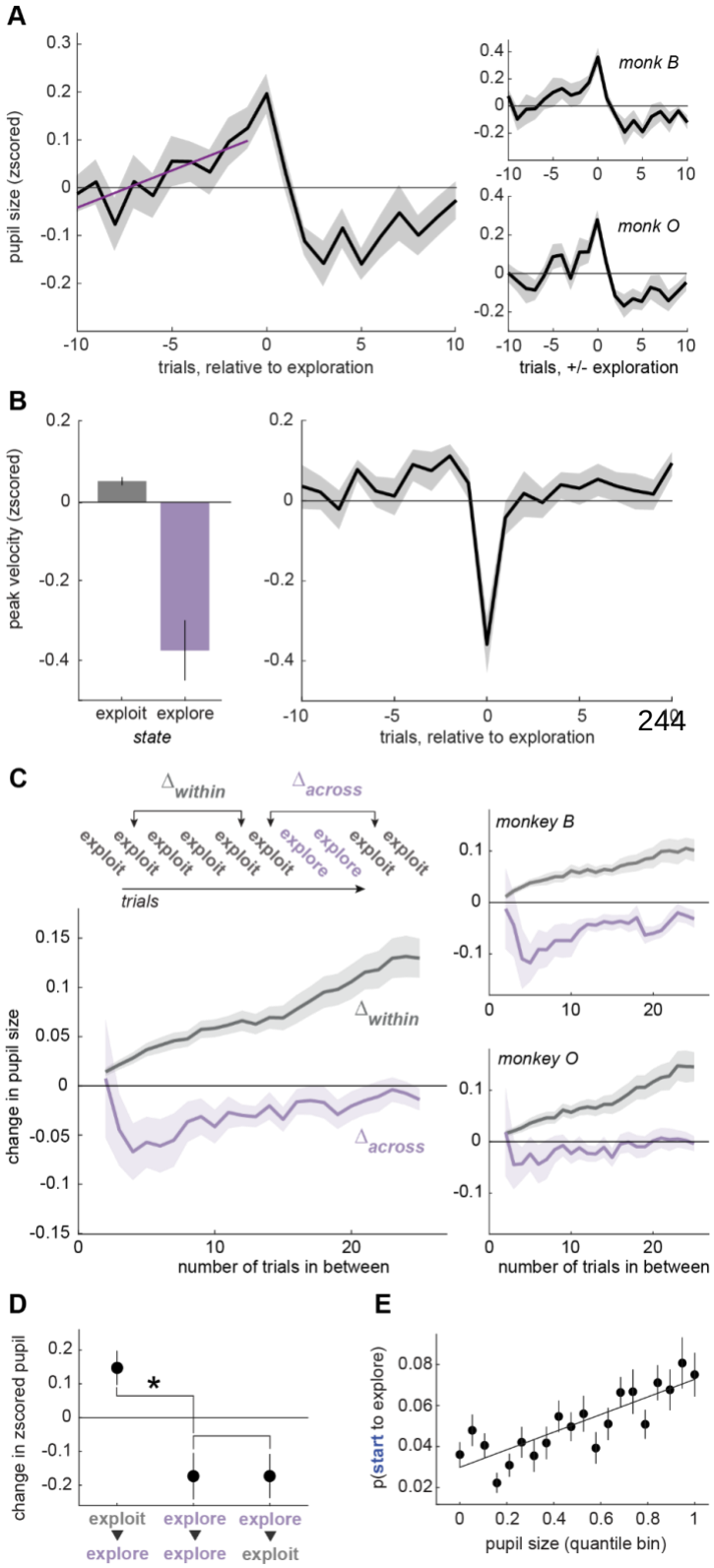

Figure 2. Pupil size ramps up before exploration and shrinks down after. *A) Average pupil size for 10 trials before and 10 trials after explore choices. Purple line: GLM fit. Right: Same for each subject separately. B) Same as Figures 1D and 2A but for peak velocity rather than pupil size. C) Change in pupil size between exploit trials that are either in a single bout of exploitation (gray) or separated by explore trials (purple). Right: Same for each subject separately. D) Change in pupil size over certain pairs of trials: starting (exploit to explore), during (explore to explore), and leaving (explore to exploit) exploration. *p < 0.001 E) The probability of starting to explore as a function of pupil size quantile. Solid line: Linear GLM fit. Error bars and shaded regions depict mean ± SEM.*

Pupil size was generally smaller after explore choices, but was this driven by the onset of exploration or the onset of exploitation? If the pupil starts to shrink only after exploration ends, it would support models that suggest that pupil size decreases with commitment to a new option or belief state (O'Reilly et al., 2013). Conversely, if the pupil shrinks immediately after exploration begins, it might suggest that pupil-linked mechanisms are important for initiating exploration, but not sustaining it. Our results were consistent with the latter hypothesis: the pupil immediately began shrinking as soon as exploration began, not when it ended (**Figure 2D**; mean change in pupil size between neighboring explore choices = -0.17, t-test, $t(27) = -2.69$, $p < 0.02$; 95% CI = -0.30 to -0.04). This was essentially identical to the magnitude with which the pupil shrank on exploit trials that followed explore trials (mean change = -0.17, t-test, $t(27) = -2.56$, $p < 0.02$; 95% CI = -0.31 to -0.03). Validating the ramping we observed with other methods, we also found that pupil size tended to grow on explore trials that followed exploit trials here (mean change = 0.14, t-test, $t(27) = 2.96$, $p < 0.01$; 95% CI = 0.04 to 0.24). Together, these results suggest that pupil size and pupil-linked mechanisms specifically predict the onset of exploration and may not be important for sustaining exploration after the first explore choice.

The fact that pupil size increased before exploration and shrank after the first explore trial in a sequence could explain the U-shaped relationship between pupil size and exploration. Perhaps the small-pupil-size explore choices are the later explore choices in a sequence and larger pupil size only predicts the first explore choice, the "onset" of exploration. Indeed, pupil size had a purely linear relationship with the onset of exploration (**Figure 2E**; 1st order GLM: beta = 0.26, $p < 0.0001$, n = 28 sessions; 1st order, linear model AIC = 8443.1, 2nd order, quadratic model AIC = 8444.7, AIC weight of quadratic model = 0.45; see **Methods**). Conversely, there was no special relationship between pupil size and probability of starting to exploit (1st order GLM: beta = 0.05, $p > 0.05$). Thus, pupil size specifically predicted the onset of exploration, rather than explore choices or state switches more generally.

It remained possible that the relationship between pupil size and the onset of exploration was a by-product of the effect of reward history on both variables. Exploration (Daw et al., 2006; Ebitz et al., 2018; Wilson et al., 2014) and pupil size (Bijleveld et al., 2009; Jepma and Nieuwenhuis, 2011) both tend to increase when rewards are omitted. To determine if there was a direct effect of pupil-related processes on exploration, we compared pupil size across exploit trials before exploration with pupil size from matched trial sequences where exploration did not happen (see **Methods**). There was a significant increase in pupil size during the trials before exploration compared to "matched rewards" control trials (**Figure 3A**; GLM, beta = 0.025, $p < 0.01$, n = 28), suggesting that pupil size predicted the onset of exploration beyond what could be explained by reward. Again, pupil size ramped up over time (GLM, beta = 0.119, $p < 0.02$, n = 28), but this ramping did not differ between the traces (GLM, beta = 0.007, $p > 0.5$, n = 28). This implies that either reward history or time (i.e. the number of trials) may explain the pupil ramping before exploration, although there is still an offset in pupil size that predicts the onset of exploration above and beyond the effect of reward history.

Critically, the trials where pupil size best predicted the onset of exploration were not those immediately before exploration (trial t-1, t-2, etc.). Instead, they were earlier trials (**Figure 3B**;

trial t-4, mean difference = 0.117, $p < 0.05$, $t(27) = 2.09$; trial t-5 = 0.170, $p < 0.01$, $t(27) = 2.84$). Visual inspection suggested that this could be due to pupil size being out of phase in the trials before exploration compared to matched-reward controls. To test this hypothesis, we asked if the onset of exploration was phase-locked to the pupil size (see **Methods**). Median trial length in this task was ~3 seconds (range = [2.2, 3.2]), meaning that the ~5 trial period we observed in **Figure 3B** would correspond to an oscillation in the 0.06-0.09 Hz range. This is close to the reported frequency of the Mayer wave (0.05-1 Hz; (Borjon et al., 2016; Julien, 2006)): a well-known oscillation of the autonomic system that appears in heart rate, blood pressure, and sympathetic efferents (Borjon et al., 2016; Japundzic et al., 1990; Julien, 2020, 2006; Kamiya et al., 2005). We found that pupil phase at the onset of exploration was concentrated at the rising phase (**Figure 3C**; mean phase = 47.18°, Hodges-Ajne test for non-uniformity, $p < 0.01$, vector length = 0.075, same for bootstrapped null distribution = 0.026, 95% CI = 0.004 to 0.057, $p < 0.0001$). In contrast, the distribution of phases in reward-matched trials pointed in the opposite direction (mean phase = 207.58°; significantly different from onsets: $p < 0.02$, Watsons $U^2 = 0.25$, n = 2170 phases including 1135 onsets). Thus, the onset of exploration was phase-locked to a slow oscillation in pupil size across trials, suggesting a model in which reward information interacts with oscillations in arousal to trigger exploration (**Figure 3D**).

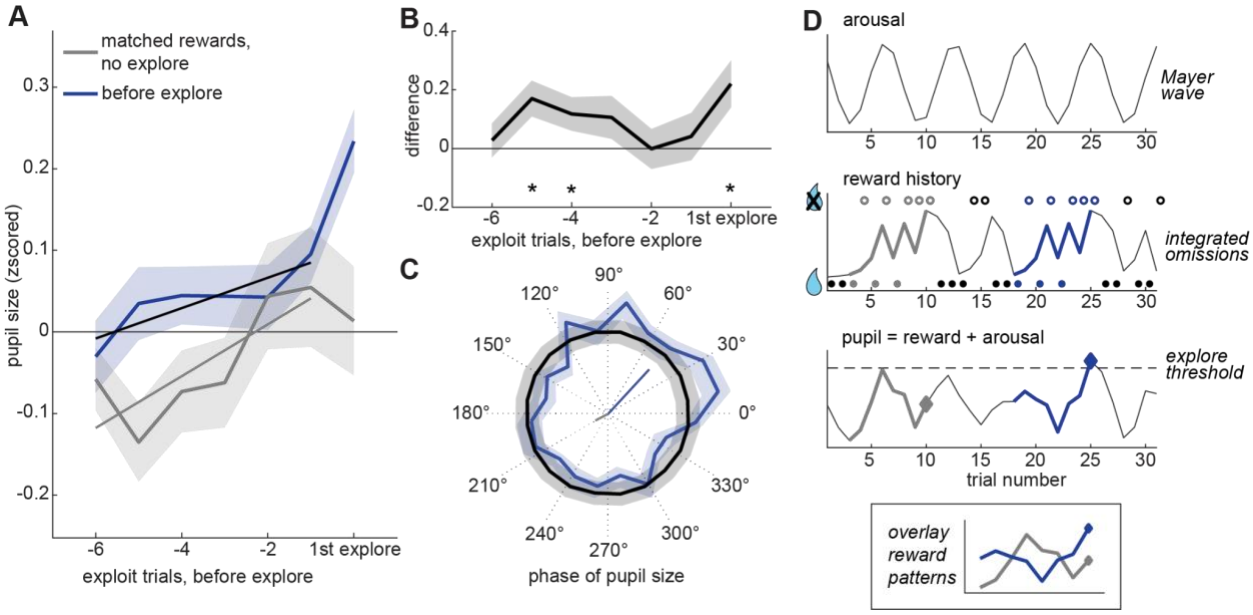

Figure 3. The onset of exploration is phase-locked to pupil size. *A) Average pupil size over sequences of exploit trials before the onset of exploration (black line) and sequences with matched rewards, but no exploration at the end (gray line). Lines: GLM fit. B) Difference in pupil size between the traces in A. C) Phase distribution of pupil size at the onset of exploration (blue) and bootstrapped null distribution (black). The vectors at the center indicate the mean vector direction and length for the trials before exploration (blue) and the matched reward trials (gray). Shaded areas ± SEM throughout. D) Cartoon illustrating how oscillations in arousal (top) could interact with reward history (middle), to regulate exploration. The bottom panel illustrates a hypothetical pupil trace that has an additive effect of reward omissions and by oscillating arousal. Exploration (diamond shapes) begins when pupil size reaches a threshold (dotted line). Note that identical patterns of reward delivery and omission have different*

outcomes, depending on how they align with the phase of arousal (gray = no exploration, blue = exploration).

To understand the pupil-linked neural mechanisms that might contribute to the onset of exploration, we next looked at the relationship between pupil size and certain neural signatures of exploration in the frontal eye fields (FEF), a part of the prefrontal cortex implicated in directing gaze and attention (Bruce and Goldberg, 1985; Moore and Armstrong, 2003; Moore and Fallah, 2001; Schall and Hanes, 1993) (**Figure 4A**). We previously reported that exploration is associated with flattened neuronal turning curves in FEF (Ebitz et al., 2018). While FEF neurons tend to predict the choice the subject will make during exploration, many neurons do not differentiate between choices to different options during exploration. Here, we found that pupil size also predicted flattened tuning in FEF neurons. A total of 88 out of 155 single neurons were tuned for choice (**Figure 4B**; 57%, one sample proportion test: $p < 0.001$). Of those neurons, 21 were also modulated by pupil size (24%; $p < 0.05$), and 16 had a significant interaction between choices and pupil size (18%; $p < 0.5$). On average, we found that neuronal tuning curves tended to flatten as pupil size increased (**Figure 4C-D**).

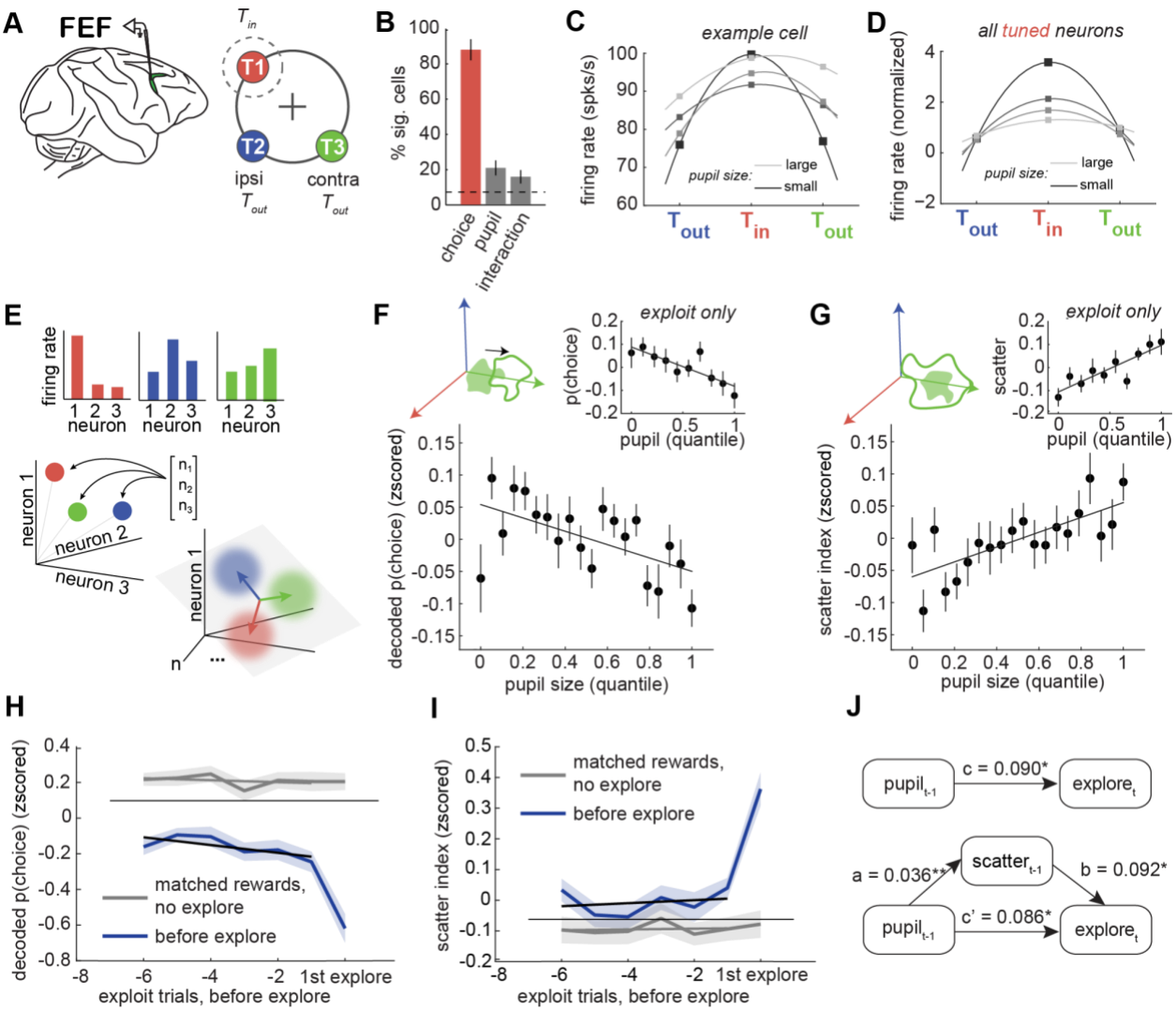

Figure 4. Pupil size predicts choice tuning curves and population disorganization. *A) Recordings were made in the FEF. Right: The cartoon illustrates the relative positions of the receptive field target (T_{in}, red) and the ipsilateral and contralateral targets (T_{out}, blue and green). B) Percent of neurons with significant tuning for choice target, pupil size, and the interaction. C) Tuning curve for an example neuron across target locations, separated by pupil size. Lighter = larger pupil. D) Same for all tuned neurons. E) Cartoon illustrating how neural population measures consider patterns of firing rates across neurons as vectors in neural state space. Targeted dimensionality reduction is used to find the hyperplane where the distribution of neural activity across trials best predicts choice. Vectors here are the coding dimensions that separate the choices. F) The decoded choice probability (projection onto the correct coding dimension) plotted as a function of pupil size quantile. Inset: Same for exploit trials alone. G) The scatter index, a measure of the variance in choice-predictive population activity, plotted as a function of pupil size quantile. Inset: Same for exploit trials. H) Mediation analysis between pupil size, scatter index, and the onset of exploration. Top: Direct model. Bottom: Indirect, mediated model. Asterisks marked significant paths (*p < 0.01 **p < 0.001). I) Decoded choice probability for trials before the onset of exploration (in blue) and trials with matched rewards (in gray). J) Scatter index for trials before the onset of exploration (in blue) and trials with matched rewards (in gray). Error bars and shaded regions ± SEM.*

Neuronal tuning functions are too noisy to partial out the contributions of exploration and pupil size, but changes in single-neuron tuning functions also imply changes in the organization of the neural population (Ebitz and Hayden, 2021; **Figure 4E**). Indeed, we found that pupil size also predicted changes in how accurately we could decode choice information from populations of simultaneously-recorded FEF neurons. Consistent with the results of our previous study (Ebitz et al., 2018), there was a decrease in decoded choice probability during explore choices compared to exploit choices (paired t-test: both subjects, $p < 0.0001$, $t(27) = 8.65$; subject B, $p < 0.005$, $t(9) = -4.72$; subject O, $p < 0.0001$, $t(17) = -7.97$). Critically, larger pupil size predicted less choice information both across all trials (**Figure 4F**; GLM: beta = -0.032, $p < 0.0001$), and within exploit trials alone (GLM: beta = -0.037, $p < 0.005$). Therefore, changes in pupil size predicted variations in the amount of choice-predictive information in FEF neurons, even within periods of exploitation.

Our previous study reported that the decrease in choice-predictive activity in FEF was related to an increase in what we called the “scatter index” of FEF populations (Ebitz et al., 2018): the spread within clusters of same-choice population activity (see **Methods**). A high scatter index indicates that neural activity on a given trial was dissimilar to other trials where the same choice was made, whereas a low scatter index indicates that neural activity was tightly clustered. In the present study, we observed that increasing pupil size predicted an increase in the scatter index in both subjects (**Figure 4G**; GLM: beta = 0.04, $p < 0.0001$). Again, this was true and of a similar magnitude even within exploit trials (beta = 0.03, $p < 0.0005$). Thus, pupil size predicted disorganization of choice-predictive signals in the FEF, at both the level of single neurons and in the population.

To determine if neural population measures also predicted transition into exploration, we looked at how they evolved across trials before exploration, compared to matched-reward control trials. While sudden changes in the decoded choice probability and scatter index were largely aligned with the onset of exploration (as reported previously), these neural measures were at a different average level on the trials preceding exploration, compared to reward-matched controls (**Figure 4H-I**; choice probability, offset = -0.611, $p < 0.001$, $n = 28$; scatter index = 0.258, $p < 0.001$). Reward information did not cause a change in either variable (choice probability, slope = -0.004, $p > 0.5$; scatter index = 0.002, $p > 0.5$), while small, but significant interaction terms suggested that both variables anticipated the onset of exploration (choice probability interaction = -0.058, $p < 0.01$; scatter index interaction: beta = 0.040, $p < 0.001$). To determine if these neural measures might explain or mediate some of the relationship between pupil size and exploration, we turned to structural equation modeling (Preacher et al., 2007; Sobel, 1986). We found that the scatter index was a significant mediator of the relationship between pupil size and the onset of exploration (**Figure 4J**; effect of mediation, ab = 0.003, $p < 0.005$; full report in Table S1). Together, these results suggest that pupil size predicts disruptions in the organization of prefrontal neural activity that mediate its relationship with the onset of exploration.

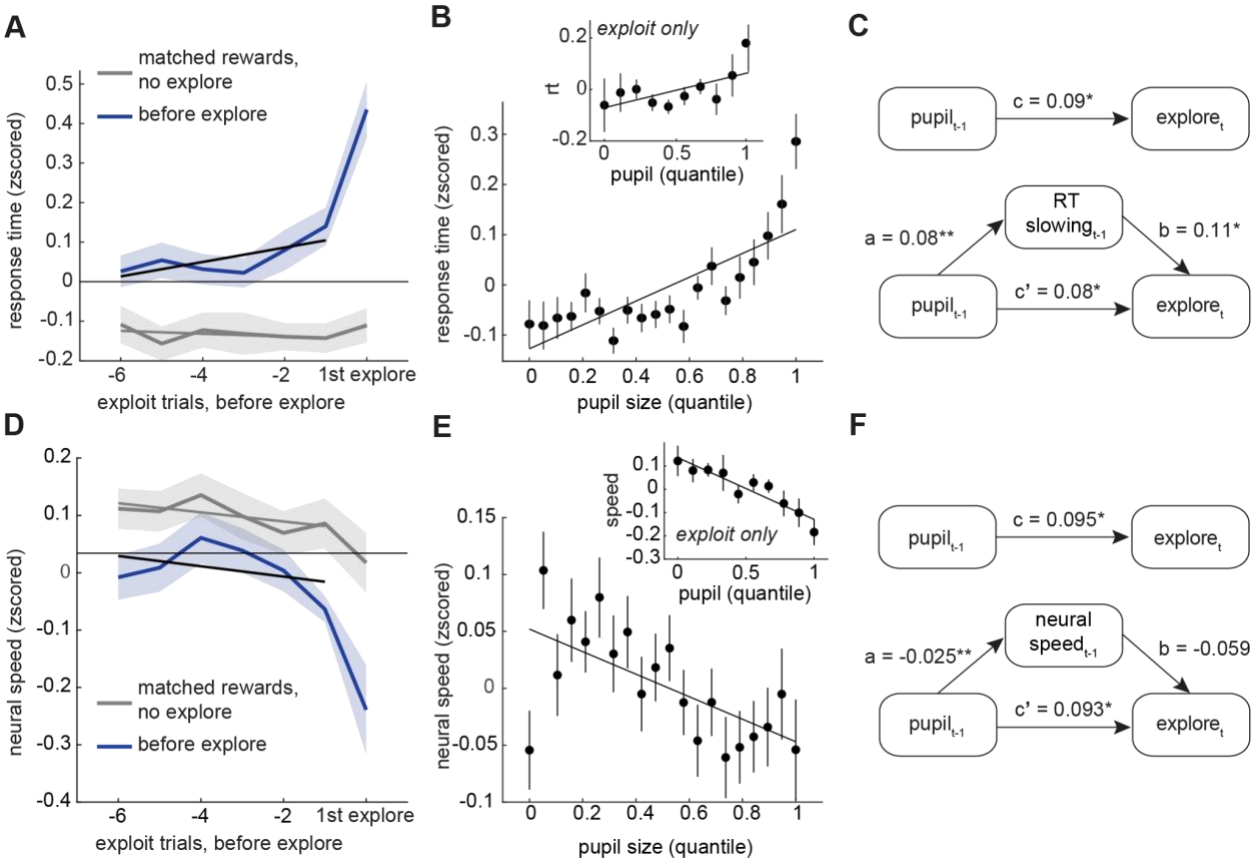

Figure 5. Pupil size predicts behavioral and neural slowing. *A) Response time on exploit trials before the onset of exploration (blue) and trials with matched rewards but no exploration (gray). B) Response time plotted as a function of pupil size quantile. Inset: Same for exploit trials alone. C) Mediation analysis between pupil size, response time, and the onset of exploration. Top: Direct model. Asterisks marked significant paths (*p < 0.01). Bottom: Indirect, mediated model. D) Neural speed on exploit trials before the onset of exploration (in blue) and trials with matched rewards (in gray). E-F) Same as B-C for neural speed. Shaded areas and error bars ± SEM.*

Complex systems like neural networks can experience tipping points: irreversible “critical transitions” that mark the passage from one operating regime into another (O’Byrne and Jerbi, 2022; Scheffer, 2020; Scheffer et al., 2009; Wang et al., 2012). Because exploration occurs as the brain passes from exploiting one target to exploiting another, it is worth considering the possibility that exploration may represent a critical transition in brain states. Indeed, during exploration, we previously reported (Ebitz et al., 2018) several phenomena in the FEF and in behavior that are hallmarks of critical transitions, including a rapid flickering back and forth between choices (Wang et al., 2012), an increase in the variance in neural activity (Scheffer et al., 2009), and a disruption of long-term neuronal autocorrelations that suggests that passing through exploration causes time-irreversible changes in the FEF network (Scheffer, 2020). However, there is another classic feature of critical transitions that we did not consider: an early warning signal known as “critical slowing”. As the system nears the tipping point, the dynamics within the system begin to flatten out in preparation for the change. As a result, the systems’ processes slow down and take longer to trace the same paths (Scheffer et al., 2009). Therefore,

we next asked if there was any evidence that decision-making slowed down in advance exploration in this dataset.

We considered two measures of the speed of decision-making: one behavioral and one neural. First, we looked at response time, a measure of how long it takes the brain to generate saccadic decisions. Response time was not only slower in the trials before exploration, compared to matched-reward control trials (Figure 5A-C; GLM offset = 0.39, $p < 0.0001$, n = 28), but it slowed down over trials before the onset of exploration (interaction = 0.05, $p < 0.001$). Second, we looked at the mean rate of change in neural population choice signals during the decision process ("neural speed", see **Methods**). Neural speed was only weakly correlated with response time across sessions (mean = -0.07, min = -0.36, max = 0.09, Pearson's correlation), suggesting that the measures were complementary, rather than redundant. Like response time, neural speed was also significantly slowed in the trials before exploration, compared to matched-reward controls (**Figure 5D-F**; GLM offset = -0.17, $p < 0.0001$, n = 28; interaction = -0.01, $p = 0.08$). Although the notion that the brain may be subject to critical tipping points is controversial (O'Byrne and Jerbi, 2022), these results are consistent with the idea that exploration could reflect a critical transition between exploiting one option and exploiting another.

In the last analysis, we found that typical explore-triggered reward histories did not, by themselves, have a significant effect on neural or behavioral slowing (response time: slope of matched-reward trials = 0.0002, $p > 0.5$; neural speed: slope = -0.018, $p > 0.1$). This suggests that some internal variable, like arousal, could be driving slowing and, perhaps, also the systems' proximity to a tipping point. Indeed, increasing pupil size predicted slower response times (**Figure 5B**; GLM beta = 0.08, $p < 0.0001$, n = 28 sessions), even within periods of exploitation (beta = 0.05, $p < 0.0001$). The same was true of neural slowing (**Figure 5E**; all trials: beta = -0.03, $p < 0.0005$; exploit only: beta = -0.09, $p < 0.0001$). Further, structural equation modeling revealed that both measures of slowing mediated the relationship between pupil size and the onset of exploration (**Figure 5C and F**; Table S2-3). In sum, the pupil-linked mechanisms that anticipated the onset of exploration included an increase in the disorganization and trial-to-trial variability of neural activity, and a slowing of decision-making computations in brain and behavior.

Discussion

Random decision-making is a powerful strategy for exploration (Dayan and Daw, 2008; Ebitz et al., 2018; Gershman, 2019; Wilson et al., 2021, 2014) that is linked to disorganized patterns of neural activity in the prefrontal cortex (Ebitz et al., 2018; Muller et al., 2019; Wilson et al., 2021). Here, we sought to identify some of the neurobiological mechanisms that drive random exploration and its neural signatures. We found that pupil size, a peripheral correlate of autonomic arousal, predicted exploration and certain measures of neural population activity previously linked to exploration. Consistent with previous studies (Jepma and Nieuwenhuis, 2011), pupil size was generally larger during exploration, compared to exploitation. However, there was also a complex temporal relationship, where pupil size ramped up between periods of

exploration and decreased during exploration. As a result, pupil size was largest at the beginning or “onset” of exploration and explained variance in the onset of exploration that could not be explained by other variables. Together, these results suggest that pupil-linked mechanisms may play a role in driving the brain into an exploratory state.

Our behavioral results largely replicate previous findings linking exploration to increased pupil size (Jepma and Nieuwenhuis, 2011). However, where we found gradual ramping before exploration and sudden constriction after, Jepma and Nieuwenhuis (2011) reported an abrupt (if modest) increase of pupil size at the onset of exploration and then a gradual decrease at the return to exploitation. The discrepancy may be due to differences in the operational definition of exploration. Jepma and Nieuwenhuis (2011) fit an RL model to behavior and defined “explore choices” as the choices that were not reward-maximizing according to the model. This definition conflates exploration with errors of reward maximization. A strategy that is non-reward-maximizing would produce choices that are orthogonal to value, not consistently bad. Here, we used an HMM to identify latent explore and explore states on the basis of the temporal profiles of choices alone, with no assumptions on the underlying value computations. This allowed us to dissociate the effects of reward history from the explore/exploit choice labels. We reported here (**Figure 1C**), and in previous studies (Chen et al., 2021; Ebitz et al., 2018), that HMM labels outperform RL labels in explaining behavioral and neural measures, suggesting that the HMM may more accurately separate distinct neural and behavioral states. If the HMM allows for more precise identification of exploratory and exploitative choices, it would follow that it also allows for more precise reconstruction of the temporal relationship between the pupil and exploration.

The precision of our explore/exploit labels revealed that the U-shaped relationship between pupil size and exploration was caused by a refractory constriction in the pupil. When exploration was plotted as a function of pupil size, the relationship appeared non-linear: both small- and large-pupil choices were more likely to be exploratory. This superficially resonated with the idea of a U-shaped relationship between arousal and task performance (i.e. the “Yerkes-Dodson curve”; (Aston-Jones and Cohen, 2005; Yerkes and Dodson, 1908)): perhaps reliable exploitation is only possible at intermediate levels of arousal. However, when we examined the temporal relationship between exploration and pupil size, we found that pupil size only predicted the onset of exploration, the first explore choice in a sequence. Small-pupil explore choices happened because starting to explore seemed to “reset” the level of pupil-linked arousal, causing it to quickly fall below baseline. If increased pupil size promotes a transition to exploration, then it is possible that post-exploration constriction represents a refractory period for exploration. Given that uncertainty grows with time in this task (and in all dynamic environments), it may not be smart to start to explore again immediately after you have just explored. A refractory period could ensure that non-reward-maximizing explore choices are deployed only when needed. Future work is needed to test this hypothesis and to determine the cognitive and/or neurobiological mechanisms at play.

Before exploration, we observed an oscillatory dynamic that was about twice as fast as the 10 trials it took the pupil to recover after exploration. This 5 trial, 0.06-0.09 Hz oscillation entrained the onset of exploration: onsets tended to occur during the rising phase of pupil size, whereas

identical trial sequences that did not result in exploration were on the opposite phase. This implies that it is the confluence of pupil size, pupil phase, and trial history that best predicts the onset of exploration. This result reinforces the idea that arousal or arousal-linked mechanisms help trigger random exploration (Ebitz and Moore, 2019; Gilzenrat et al., 2010; Reimer et al., 2016), rather than just tracking the reward-linked variables that make exploration more probable. It is also notable that the period of the pupil oscillation was close to the frequency of the Mayer wave: an oscillation in blood pressure that entrains other autonomic measures, including respiration and heart rate (Borjon et al., 2016; Japundzic et al., 1990; Julien, 2020, 2006; Kamiya et al., 2005). There is precedent for the idea that behavior can be entrained by the Mayer wave: in marmosets, fluctuations in arousal predict the spontaneous onset of a call (Borjon et al., 2016). This paper argued that the Mayer wave may function to organize vocal communication by bringing the system closer to the threshold for transitioning from inaction to action. It is possible that oscillations in the pupil and pupil-linked mechanisms function the same way here, organizing important state changes in time. In parallel, pupil-linked mechanisms seem to anticipate other state transitions, including belief updating (Filipowicz et al., 2020; O'Reilly et al., 2013), task disengagement (Kane et al., 2017), and other behavioral state changes (Bouret and Sara, 2005). Together, these results suggest an important role for pupil-linked mechanisms in driving successful transitions between certain neural and behavioral states.

Critically, pupil size and pupil oscillations did not predict all state transitions here, but only the transition into exploration. What kinds of state transitions might be entrained by pupil- linked arousal? It is possible that the pupil may have a special relationship with certain "critical" kinds of transitions. Critical transitions are abrupt, large-scale, and irreversible changes in the dynamics and behavior of complex systems, like the brain. As these systems go from being in one conformation (i.e. always choosing the left option) into another conformation (i.e. always choosing the right), the system dynamics that support the old state have to disappear and the new dynamics have to emerge. During this brief transitory period, when both dynamics co-exist in the system, certain signatures can be observed in the system. We previously reported that the exploration was accompanied by abrupt changes in neural population activity, certain patterns of noise in brain and behavior, and disruptions in long-term neuronal autocorrelations: all observations that could be interpreted as suggesting that exploration is a critical transition in the brain (Ebitz et al., 2018). Here, we found that pupil size predicts these features of neural activity and also an prominent "early warning sign" of critical transitions: a slowing, in brain and behavior, of the decision process. While there are certain patterns of activity in FEF that predict response speed (Hauser et al., 2018; Yao and Vanduffel, 2023), here we identified *independent* neural and behavioral measures of decision speed that both mediated the relationship between pupil size and exploration. Together these results suggest that pupil-linked arousal pushes neural and behavioral states to a critical tipping point and highlights the crucial role of pupil-linked mechanisms in changing the dynamics of the brain.

What underlying, pupil-linked mechanisms could support critical transitions? Changes in pupil diameter coincide with neuromodulator system activity, especially norepinephrine (NE) and acetylcholine (Breton-Provencher and Sur, 2019; de Gee et al., 2020; Joshi et al., 2016; Joshi and Gold, 2020; Murphy et al., 2014; Reimer et al., 2016). At the neuronal level, central NE

flattens tuning curves, at least in the auditory cortex (Martins and Froemke, 2015), though it may have different effects in non-cortical structures (Manella et al., 2017). Here, we made a parallel observation: as pupil size increases, neuronal turning curves flattened and choice-predictive neural population activity became disorganized. These results resonate with a particularly influential theory of NE function: the idea that NE release may facilitate “resets” in cortical networks in order to effect long-lasting changes in brain and behavior (Aston-Jones and Cohen, 2005; Bouret and Sara, 2005). More recent studies seem to consistently report that elevated levels of NE predict an increase in behavioral variability, while pharmacological blockade of NE receptors reduces variability (Chen et al., 2023; Kane et al., 2017; Sadacca et al., 2017; Tervo et al., 2014). In combination with the present study, these results could suggest that phasic NE signaling functions to push the brain towards a critical tipping point where it is better able to transition from one regime to another. In this view, behavioral variability would be linked to NE not because NE increases variability directly, but because the brain is more likely to transition into a high variability regime after it is released. Of course, pupil size is also associated with other neuromodulatory systems, cognitive factors, and other measures of arousal. Thus, future work is needed to identify the neurobiological mechanisms that underpin the relationship between pupil size and critical transitions that we report here.

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Author Contributions

R.B.E. collected the data. K.J., T.M., and R.B.E., secured funding. R.B.E., G.M., and A.S. formulated the hypotheses. A.S., G.M., K.J., and R.B.E. analyzed the data. A.S., G.M., and R.B.E. drafted the manuscript. A.S., G.M., K.J., T.M., and R.B.E. reviewed and edited the manuscript.

Declaration of Interests

The authors declare no competing interests.

Resource Availability

Lead Contact

Further information and requests for resources should be directed to and will be fulfilled by the Lead Contact, Becket Ebitz (becket@ebitzlab.com).

Materials Availability

This study did not involve generating new material.

Data and Code Availability

Data and software are available upon request to the Lead Contact (Becket Ebitz, becket@ebitzlab.com)

Methods

Surgical and electrophysiological procedures. All procedures were approved by the Stanford University Institutional Animal Care and Use Committee. Subjects were two male rhesus macaques, surgically-prepared with head restraint prostheses, craniotomies, and recording chambers under isoflurane anesthesia via techniques described previously (Ebitz et al., 2018). Following surgery, analgesics were used to minimize discomfort, and antibiotics were delivered prophylactically. After recovery, subjects were acclimated to the laboratory and head restraint, then placed on controlled access to fluids and trained to perform the task.

Recording sites were located within the FEF, which was identified via a combination of anatomical and functional criteria. The location of recording sites in the anterior bank of the arcuate sulcus was verified histologically in one subject and via microstimulation in both subjects (Ebitz et al., 2018). Recordings were conducted with 16-channel U-probes (Plexon), located such that each contact was within gray matter at an FEF site. An average of 20 units were recorded in each session (131 single units, 443 multi units; 576 total units across 28 sessions).

General behavioral procedures. Eye position and pupil size were monitored at 1000 Hz via an infrared eye tracking system (SR Research; Eyelink). The manufacturer's standard methods for calculating pupil area were used. MATLAB (Psychtoolbox-3; (Kleiner et al., 2007)) was used to display stimuli and record behavioral responses and pupil size measurements. Task stimuli were presented against a dark gray background (7 cd/m2) on a 47.5 cm wide LCD monitor (Samsung; 120 Hz refresh rate, 1680 x 1050 resolution), located 34 cm in front of the subject.

Three-armed bandit task. The subjects performed a sequential decision-making task in which they chose between 3 targets whose values changed over time. The subject first fixated a central fixation square (0.5° stimulus, +/- 1.5-2° of error) for a variable interval (450-750ms). At any point within 2s after the onset of the targets, subjects indicated their choice by making a

saccade to one of the targets and fixating it (+/- 3°) for 150 ms. Reward magnitude was fixed within session (0.2-0.4 μL). Reward probability was determined by the current reward probability of the chosen target, which changed independently over trials for each of the three targets. On every correct trial, each target had a 10% chance of the reward parameter changing either up or down by a fixed step of 0.1, bounded at 0.1 and 0.9. Because rewards were variable, independent, and probabilistic, the subjects could only infer the values of the different targets by sampling them and integrating noisy experienced rewards over multiple trials.

General analysis procedures. Data were analyzed with custom software in MATLAB. Unless otherwise noted, all t-tests were paired, two-sided t-tests, and generalized linear models were run on raw data, with session number coded as a dummy variable to account for session-to-session variability. Model comparison was based on standard methods that involve calculating the likelihood of the data and Akaike information criteria (AIC) of each model, then using AIC weights to identify (1) the model that is most likely to minimize information loss, and (2) the relative likelihood of competing models to do the same (Burnham and Anderson, 2004). For analyses of any behavioral or neural variables on the trials before or after exploration, continuous runs of exploit trials were required. The values of behavioral and neural variables were *z*-scored within a session to facilitate comparisons across sessions.

Pupil size. Pupil size was measured during the first 200 ms of fixation, a time at which the eye was fixed at a known point on the screen, illumination was identical across trials, and anticipatory changes in the pupil were minimal. To remove any blinks or movement artifacts, trials where pupil size or the change in pupil size from the first time bin of this epoch to the last was +/- 6 standard deviations from average were eliminated from further analyses. A total of 178 trials (out of 21,793, approximately 0.8% of observations) were outliers.

Reinforcement learning model. To compare goal state labels derived from an RL and HMM model, we employed a Rescorla-Wagner model (Rescorla and Wagner, 1972). This was fit using maximum likelihood estimation. The value of each option is iteratively updated according to:

$$\mathrm{V_{i,t+1} = V_{i,t} + \alpha(r_t - V_{i,t})}$$

Where $V_{i,t}$ is the value of option *i* at time *t*, r_t is the reward at time *t*, and α represents the fitted learning rate, which determines how much the difference between the predicted and actual reward (the prediction error) influences value. To make a decision, the values are passed through a softmax decision rule:

$$p_{\mathrm{i,t}} = \frac{\exp(\beta \mathrm{V}_{\mathrm{i,t}})}{\Sigma_{j=1:n} \exp(\beta \mathrm{V}_{\mathrm{j,t}})}$$

Where *n* is the total number of available options, and *β* is the inverse temperature, which controls the level of random noise in decision-making. After (Daw et al., 2006; Jepma and Nieuwenhuis, 2011; Pearson et al., 2009), decisions that were not reward maximizing were labeled as exploratory (i.e. any decision where $V_{chosen,t}$ was not the maximum V at time *t*).

Learning Index. To investigate whether learning differed with pupil size within the exploratory choices, we calculated a learning index that captured the effect of rewards experienced during exploration on future choices. Because reward effects decay exponentially quickly (Lau and Glimcher, 2008), a 1-trial-ahead index should capture most of the variability in how much is learned between trial types. The equation was:

$$\text{learning index}_{\mathrm{t}} = \frac{p(\text{switch}_{\mathrm{t+1}} \mid \text{reward}_{\mathrm{t}}) - p(\text{switch}_{\mathrm{t+1}} \mid \text{no reward}_{\mathrm{t}})}{p(\text{switch}_{\mathrm{t+1}})}$$

Lagged change in pupil size. To determine whether exploration impacted pupil size, we measured the change in pupil size (Δ pupil) between pairs of trials that either were or were not separated by at least 1 explore trial. Segments of twenty-five consecutive trials were identified that either included a single bout of exploration or did not include exploration. For each pair of trials within these sequences, we then measured the change in pupil size between the first exploit trial of the sequence (t1) and the remaining exploit trials in the sequence (t2:25). This was repeated for all unique pairs of trials that met our selection criteria.

Matched reward trials. To test whether the rising trend in pupil size before exploration is best explained by reward history, we identified trial sequences with identical reward and state histories that did not end in exploration ("matched rewards"). For each onset of exploration preceded by at least 6 exploit trials, we searched for identical sequences of exploit trials, with identical reward histories, that did not end in exploration. We chose 6 previous trials because this was the longest sequence of reward history we could regularly match within the majority of sessions (we could find at least 10 matched sequences in 96% [27/28] of sessions for 6 trials sequences; that dropped to 75% [21/28] at 7 trials). Identical results were obtained with other sequence lengths, though these analyses included fewer sessions.

Mediation analysis. To determine if the predictive relationship between pupil size and exploration was mediated by other variables, we used structural equation modeling to test for mediation. Mediation analyses involve fitting three regression models. The first model measures

the total effect (c) of the independent variable (here, pupil size) on the independent variable (here, onset of exploration):

$$\mathrm{Explore}_{\mathrm{t}} = \gamma_1 + c(\mathrm{Pupil}_{\mathrm{t\text{-}1}}) + \epsilon_1$$

In these equations, γ represents the intercept for each equation, while ε represents the error of the model. Note that the estimated parameter c will include both direct effects of pupil size on exploration, but also indirect effects that may be mediated by other variables. Therefore, we also fit a second model that tests if the independent variable also predicts a potential mediator variable (here, neural network scatter):

$$\mathrm{Scatter}_{\mathrm{t\text{-}1}} = \gamma_2 + a(\mathrm{Pupil}_{\mathrm{t\text{-}1}}) + \epsilon_2$$

Model parameter a thus captures the effect of pupil size on the mediator. Finally, a third model estimates the unique contributions of both the potential mediator (scatter, b) and the independent variable (pupil size, c'), now controlling for the mediator:

$$\mathrm{Explore}_{\mathrm{t}} = \gamma_3 + b(\mathrm{Scatter}_{\mathrm{t\text{-}1}}) + c'(\mathrm{Pupil}_{\mathrm{t\text{-}1}}) + \epsilon_3$$

A drop between c and c' indicates that the effect of the independent variable (pupil) on the dependent variable (exploration) is reduced when the mediating variable is considered. The mediation effect (the indirect effect of the pupil size on the onset of exploration via the mediating factor) can also be estimated directly, via taking the product of the coefficients a and b. Sobel's test is used to determine the significance of the mediation path (Sobel, 1986).

Phase analysis. To determine if the onset of exploration happened at a specific phase of pupil size over trials, we performed a wavelet analysis. Because this method only assumes local stationarity, it is more suitable than other methods for analyzing pupil size, which tended to ramp over trials. A wavelet was constructed by multiplying a complex sine wave (frequency = 5 trials) with a Gaussian envelope (μ = 0, σ = cycles / (2π*frequency), cycles = 5; (Cohen, 2014)). The wavelet was convolved with the baseline pupil size time series and the phase of the signal was calculated on each trial (Matlab; angle). Standard circular statistics were used to measure the differences between phase distributions for explore onsets and reward-matched controls (Zar, 1999) and the phase alignment within these trial types (Berens, 2009). The latter was also verified via comparison with bootstrapped null distributions (1000 samples).

Targeted dimensionality reduction. Neural state spaces have as many dimensions as there are recorded neurons, but converging evidence suggests (1) that the neural states that are observed in practice are generally confined to a lower-dimensional "manifold", and (2) that task-relevant information is encoded by a small number of dimensions in that manifold. Because we wanted to isolate the effects of arousal on choice-related activity from well-known effects of

arousal on neural activity (Ebitz and Platt, 2015; McGinley et al., 2015; Pfeffer et al., 2022; Podvalny et al., 2021; Reimer et al., 2016, 2014; van Kempen et al., 2019; Waschke et al., 2019), we focused all our neural population analyses on activity within the choice-predictive subspace, rather than on neural activity more broadly.

To do this, we used targeted dimensionality reduction to identify the choice-predictive dimensions of the neural state space (Cohen and Maunsell, 2010; Cunningham and Yu, 2014; Ebitz et al., 2018; Peixoto et al., 2021). Specifically, we used multinomial logistic regression (Matlab; mnrfit, mnrval, (Hastie et al., 2009)) to identify the separating hyperplanes that best discriminated each choice from the alternative choices. This is equivalent to fitting a system of binary classifiers of the form:

$$p(\text{choice} = \text{k} \mid \text{X}) = \frac{1}{1 - \exp^{-\beta_k \text{X}}}$$

Where one classifier discriminates target 1 choices from targets 2 and 3 and a second discriminates target 2 choices from targets 1 and 3. The classifier that discriminates target 3 from targets 1 and 2 is then just the negative of target 1 and target 2. These axes span the subspace in which neural activity best predicts choice. Classifiers were trained on firing rates from an epoch that began when the targets appeared and ended at the time of the saccade. Mean imputation was used for the small number of occasions where a unit was not held for the whole duration of the session (~3% of trials, ~12% of units) and a small fraction of units were omitted from these analyses because their mean firing rates were less than 2 spikes/s, which makes their weights difficult to identify (~8% of units).

Choice Probability Decoding. Within the choice-predictive subspace, the distance from the separating hyperplanes (the vectors illustrated in **Figure 4E**) are the decoding vectors: the vectors along which we can project neural activity in order to decode the log odds of choice. This projection is equivalent to the decoded choice probability from the multinomial logistic regression model and this is the figure we took as the decoded choice probability in **Figures 3F** and **3H**. We evaluated decoding accuracy by measuring how often the most-likely choice predicted by the model coincided with the choice the subject made.

Scatter index. The scatter index measures how much choice-predictive population neural activity is clustered between trials with the same choice (Ebitz et al., 2018). It is calculated by measuring the average Euclidean distance of each trial from all other trials where the same choice was made and dividing it by the average Euclidean distance to all other trials where a different choice was made:

$$\text{scatter} = \frac{\text{d}_{\text{within}}}{\text{d}_{\text{between}}}$$

Each trial thus has its own scatter index value, with a value of 1 indicating no difference in clustering between same-choice and different-choice trials, and a value less than 1 indicating greater clustering with same-choice trials compared to different-choice trials.

Neural speed. To determine how the speed of the decision-making process changed before and during exploration, we calculated the rate of change in neural states within the choice-predictive subspace during the first 400 ms following target presentation. Each trial's neural activity was sampled in non-overlapping 20 ms bins and then projected into the choice-predictive subspace. The change in neural activity within the subspace was then calculated between each pair of samples. Finally, the changes were averaged together across the trial and normalized to the bin width to produce an average rate of change in choice-predictive activity for that trial.

Table S1

Regression coefficients and p values for the mediation analysis testing whether the scatter index mediates the relationship between pupil size and the onset of exploration. Related to **Figure 4J**.

		$pupil_{t-1} \rightarrow scatter_{t-1} \rightarrow explore_t$	
		est. coefficient	p value <
Total effect	c	0.090	0.005
Effect on mediator	a	0.036	0.0005
Unique mediator effect	b	0.092	0.005
Indirect effect	ab	0.003 (z = 2.70*)	0.005
Direct effect	c’	0.086	0.005

*Sobel’s test

Table S2

Regression coefficients and p values for the mediation analysis testing whether response time slowing mediates the relationship between pupil size and the onset of exploration on the next trial. Related to **Figure 5C**.

		$pupil_{t-1} \rightarrow RT\ slowing_{t-1} \rightarrow explore_t$	
		est. coefficient	p value <
Total effect	c	0.090	0.005
Effect on mediator	a	0.078	0.0001
Unique mediator effect	b	0.106	0.0005
Indirect effect	ab	0.008 (z = 3.48*)	0.0005
Direct effect	c’	0.080	0.01

*Sobel’s test

Table S3

Regression coefficients and p values for the mediation analysis testing whether neural slowing mediates the relationship between pupil size and the onset of exploration on the next trial. Related to **Figure 5F**.

		$pupil_{t-1}$ → neural $slowing_{t-1}$ → $explore_t$	
		est. coefficient	p value <
Total effect	c	0.095	0.005
Effect on mediator	a	-0.025	0.0005
Unique mediator effect	b	-0.059	0.06
Indirect effect	ab	0.001 (z = 1.69*)	0.05
Direct effect	c’	0.093	0.005

*Sobel’s test

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