

Behavioral strategy shapes activation of the Vip-Sst disinhibitory circuit in visual cortex

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Abstract

In complex environments, animals can adopt diverse strategies to find rewards. How distinct strategies differentially engage brain circuits is not well understood. Here we investigate this question, focusing on the cortical Vip-Sst disinhibitory circuit. We characterize the behavioral strategies used by mice during a visual change detection task. Using a dynamic logistic regression model we find individual mice use mixtures of a visual comparison strategy and a statistical timing strategy. Separately, mice also have periods of task engagement and disengagement. Two-photon calcium imaging shows large strategy dependent differences in neural activity in excitatory, Sst inhibitory, and Vip inhibitory cells in response to both image changes and image omissions. In contrast, task engagement has limited effects on neural population activity. We find the diversity of neural correlates of strategy can be understood parsimoniously as increased activation of the Vip-Sst disinhibitory circuit during the visual comparison strategy which facilitates task appropriate responses.

Introduction

Circuitry across the brain, including sensory cortex, does not operate in isolation but rather serves behavioral demands. As such, quantitative behavioral analysis is an essential step in detailed understanding of brain circuits (Carandini 2012; Gomez-Marin et al. 2014; Krakauer et al. 2017; Niv 2021). Recently a suite of computational tools has emerged for precise analysis of behavioral tasks used in neuroscience laboratories including the description of behavioral strategies (Brunton et al. 2013; Berman 2018; Roy et al. 2018; Roy et al. 2021; Ashwood et al. 2022; Jha et al. 2022; Le et al. 2022). These tools vary in their statistical structure but all parameterize a space of possible behaviors which are then constrained by behavioral data. This has led to a greater appreciation of behavioral diversity during laboratory tasks, including across subject variability, and within subject variability across individual behavioral sessions and task learning.

Behavioral strategies have been shown to alter which brain regions and pathways are active during a task. Gilad et al. 2018 found mice used either an active or passive whisking strategy which altered the location of short term memory in the cortex. Bolkan et al. 2022 found that both task difficulty as well as the subject's behavioral state determined how striatal pathways influenced behavior. Other studies have demonstrated strategy dependent changes in neural dynamics across human fMRI (Venkatraman et al. 2009; Yang et al. 2023), rodent wide-field imaging (Pinto et al. 2019), and cellular activity in the fruit fly (Calhoun et al. 2019). Prefrontal structures, including the anterior cingulate cortex and medial prefrontal cortex, have been proposed to track strategy preferences and control strategy execution (Tervo et al. 2021; Domenech et al. 2020; Schuck et al. 2015; Proskurin et al. 2022). Behaviorally relevant signals have also been shown to modify activity in sensory cortex (Tseng et al. 2022) including visual flow (Leinweber et al. 2017; Schneider 2020), amplifying task relevant signals (Kim et al. 2020), dynamically scaling the range of stimulus encoding (Waiblinger et al. 2022), and value signals (Banerjee et al. 2020).

Simultaneously, there has been growing appreciation for the role neural cell types play in

47 mediating specific computations (Pinto et al. 2015; Sylwestrak et al. 2022). Merging lines
48 of evidence suggest a disinhibitory circuit between vasoactive intestinal peptide-positive (Vip)
49 interneurons, somatostatin-positive (Sst) interneurons, and excitatory cells (Pfeffer et al. 2013;
50 Kullander et al. 2021; Campagnola et al. 2022; Karnani et al. 2016). The circuit is disinhibitory,
51 whereby Vip neurons disinhibit pyramidal activity through inhibition of Sst inhibitory neurons
52 (Kamigaki 2019). In the visual cortex, the Vip-Sst disinhibition circuit has been implicated in
53 a variety of computational mechanisms. Millman et al. 2020 found that Vip-Sst antagonism
54 controlled the dynamic range of stimulus contrast for excitatory cells. Keller et al. 2020 found
55 that the Vip-Sst disinhibitory circuit mediates the influence of visual context on excitatory cells.
56 Fu et al. 2014 found that running in mice activates the Vip-Sst disinhibition of excitatory cells.
57 Finally, anatomical (Williams et al. 2019; Kamigaki 2019; Ma et al. 2021) as well as functional
58 studies (Pi et al. 2013) demonstrate that top-down feedback is preferentially routed through Vip
59 neurons, influencing local circuits through Vip disinhibition.

60 Despite recent progress in analysis of behavior and cell type circuit dissection, it remains
61 unclear how behavioral strategies influence cortical circuits through specific cell types. Given
62 the range of circuit functions mentioned above, the Vip-Sst disinhibitory circuit is a promising
63 substrate for mediating behavioral strategies. Here we investigate how the Vip-Sst circuit in
64 visual cortex mediates strategy dependent demands. We used the recently collected Allen Insti-
65 tute Visual Behavior - 2p calcium imaging dataset to examine how the activity of Vip, Sst, and
66 excitatory cells depend on strategy preferences during a change detection task (Garrett et al.
67 2023; brain-map.org). This dataset, collected with the Allen Brain Observatory experimental
68 pipeline, contains two-photon calcium imaging in genetically defined cell types collected while
69 mice performed a visual change detection task. This large systematic survey contains behavior
70 from 376 imaging sessions from 82 mice thus permitting analysis of behavioral diversity. We
71 used a dynamic logistic regression model (Roy et al. 2018) to identify strategies used by mice on
72 this task. We find individual mice have stable strategy mixtures of a visual comparison strategy
73 and a statistical timing strategy. Vip, Sst, and excitatory cells recorded from mice predomi-
74 nantly using each of these strategies show dramatic differences in activity. Further, the effects
75 of behavioral strategy were independent from task engagement and stimulus novelty. Finally,
76 we show that strategy differences can be succinctly described by the degree of activation of the
77 Vip-Sst disinhibitory circuit.

78 Results

79 Visual change detection task

80 To examine the relationship between behavioral strategies and cortical circuits, we analyzed
81 the diversity of behaviors in the Allen Institute Visual Behavior - 2p calcium imaging dataset
82 (brain-map.org). This public dataset contains 2-photon calcium imaging from transgenic mice
83 expressing the calcium indicator GCaMP6f in excitatory neurons (Slc17a7-IRES2-Cre;Camk2a-
84 tTa;Ai93), Sst inhibitory neurons (Sst-IRES-Cre;Ai148), and Vip inhibitory neurons (Vip-IRES-
85 Cre;Ai148). The data was collected with the Allen Brain Observatory experimental pipeline
86 which uses standardized data collection and processing (Garrett et al. 2023; de Vries et al. 2020).
87 We focused our analysis on recordings from two visual areas, V1 and LM, at multiple cortical
88 depths. During imaging, mice performed a visual change detection task (Fig. 1A). In this task,
89 head fixed mice were shown a series of natural images (250ms stimulus duration) interspersed
90 with periods of a gray screen (500ms inter-stimulus duration). This task uses a roving baseline
91 paradigm whereby an individual image repeats a variable number of times before a new image
92 is presented and then itself repeats. Mice were given a water reward for licking in response to
93 image changes. Premature licking delayed the time of the next image change. Further, to serve
94 as distractors, 5% of image repeats were omitted and replaced with a continuation of the gray
95 screen for the same duration as image presentations. Image omissions therefore did not disrupt

96 the rhythmic nature of the stimulus. Image changes as well as the image immediately before the
97 change were not omitted. Mice performed the task on a running disk and were free to run or not
98 run. Running had no bearing on the task. These mice learned the task through a standardized
99 training pipeline and were selected for imaging based on a consistent criteria of minimum task
100 performance (Garrett et al. 2023; Groblewski et al. 2020).

101 Mice could potentially perform this task in multiple ways. In one possible strategy, mice
102 could hold a memory of the previous image and perform a visual comparison to the subsequent
103 image. This visual comparison strategy may be vulnerable to distraction from image omissions.
104 Alternatively, mice could learn the statistical distribution of when images change and make
105 educated guesses based on the time since the last image change (Fig. 1A). To illustrate these
106 strategies we can examine licking patterns around time points relevant to each strategy (Fig.
107 1B). For one example session we can see: (top left) licking aligned to image changes, which
108 results in a water reward, (top right) licking during image omissions, which never results in a
109 reward, (bottom left) licking on the image after an omission, which never results in a reward,
110 and (bottom right) licking on the fifth image after the last lick, which sometimes results in a
111 water reward. Supplemental Note 1 shows distributions of mouse behavior across the dataset.

112

113 Behavioral strategy model

114 In order to identify these strategy patterns across our dataset we used a dynamic logistic regres-
115 sion model (Roy et al. 2018). Our model predicts whether the mouse will start a licking bout
116 in response to each image based on the weighted influence of each strategy. Importantly, the
117 strategy weights were allowed to vary across the course of the session constrained by a smoothing
118 prior described in detail below.

119 We will now describe how we processed the data and constructed our strategy model (Fig.
120 1C). First, individual mouse licks were segmented into licking bouts based on an inter-lick interval
121 of 700ms (Supplemental Note 2A). The duration of licking bouts was largely governed by whether
122 the mouse received and then consumed a water reward (Supplemental Note 2B). Therefore, we
123 focused our analysis on the start of each licking bout. Licking bout onsets were time-locked to
124 image presentations, thus for each licking bout we identified the last image or omission presented
125 before the bout started (Supplemental Note 2C). Since our model predicts the start of licking
126 bouts, we ignore image presentations when the mouse was already engaged in a licking bout. The
127 design matrix of our strategy model is composed of vectors that describe the probability each
128 strategy would start a licking bout on each image presentation. For the licking bias strategy,
129 which is simply a bias term, the licking probability is 1 on all images representing a constant
130 drive to lick. For the visual strategy, the probability is 1 on image changes, and 0 otherwise.
131 For the omission strategy, the probability is 1 during image omissions, and 0 otherwise. The
132 post-omission strategy has a probability of 1 during the first image after an omission, and 0
133 otherwise. For the timing strategy, the licking probability is a sigmoidal function of how many
134 images have been presented since the end of the last licking bout. The licking probability is low
135 immediately after a licking bout, rises to 0.5 at 4 images after a licking bout, and then a high
136 licking probability at longer durations. The parameters of the sigmoidal function were learned
137 from a subset of the data (Supplemental Note 3). All strategies other than the licking bias were
138 mean-centered.

139 Using standard, non-dynamic, logistic regression our strategy model would predict the prob-
140 ability a mouse licked on a given image presentation, $p(\vec{x}_i)$, by using fixed weights, $\vec{\beta}$, to combine
141 the strategy vector for that image, \vec{x}_i , and passing that sum through a logistic function:

$$p(\vec{x}_i) = \frac{1}{1 + e^{-(\vec{\beta}\vec{x}_i)}}. \quad (1)$$

142 However, by using the dynamic logistic regression model, developed in Roy et al. 2018, our model
143 lets the weight for each strategy, k , vary for each image presentation subject to a smoothing

144 prior. The prior is implemented as letting the weights for each strategy undergo a random walk
145 with standard deviation σ_k :

$$\beta_{k,i+1} = \beta_{k,i} + \mathcal{N}(0, \sigma_k^2). \quad (2)$$

146 The smoothing prior σ_k is a hyper-parameter unique to each strategy during each session and
147 controls the volatility of each strategy. These hyper-parameters were fit to the behavioral data by
148 maximizing the model evidence as described in Roy et al. 2018. The smoothing prior constrains
149 the strategy weights to evolve gradually over time. This balances the ability of the model to
150 dynamically track changing behavioral patterns against over-fitting to the responses on each
151 stimulus. The dynamic model has the same form as the standard model with the weights now
152 a function of each image, β_i :

$$p(\vec{x}_i) = \frac{1}{1 + e^{-(\beta_i \vec{x}_i)}}. \quad (3)$$

153 The strategy model was fit to each one-hour behavioral session by the maximum a posteriori
154 (MAP) estimate of the weights given the data and the hyper-parameters. Figure 1D shows
155 the example output of the model for one session. For this session the licking bias and timing
156 strategies have more volatile weights than the visual, omission, and post-omission strategies.
157 The model successfully captures the time-varying probability of licking in the data as the mouse
158 goes through epochs of hits, misses, as well as high and low licking rates.

159 **Mouse behavior is largely described by the visual and timing strategies**

160 We quantified the performance of the model with the area under the receiver operating char-
161 acteristic (ROC) curve (Fig. 2A). In this analysis we use the model's cross validated licking
162 probability prediction on each image as a classifier of whether the mouse started a licking bout
163 on each image presentation. The ROC curve computes the true positive rate and false positive
164 rate of a classifier as the classification threshold is varied. The area under this curve (AUC)
165 ranges from .5 (classifier at chance), to 1 (perfect classification across all thresholds). The static,
166 or standard, logistic regression model performs poorly, often at chance. The dynamic model per-
167 forms well, with an average AUC value of 0.83. See Supplemental Note 4 for additional model
168 validation details.

170 For each behavioral session we can analyze the best fitting strategy weights (Fig. 2B) and
171 the smoothing prior for each strategy (Fig. 2C). The weights are multiplied against the strategy
172 design matrix and then passed through the logistic function. The licking bias strategy sets the
173 average licking probability on each image presentation. A licking bias weight of 0 would translate
174 to a 50% licking probability, with smaller weights leading to lower licking probabilities, and larger
175 weights leading to higher licking probabilities. The other strategies are mean-centered (the sum
176 of their strategy design vectors equals 0), which means we can interpret the strategy weights
177 relative to the licking bias term. A weight of 0 would have no influence on the licking probability,
178 a negative weight would result in less licking than the bias term, and a positive weight would
179 result in more licking than the bias term. Across our population, the omission strategy has a
180 negative value, meaning on average mice are less likely to lick during image omissions. The
181 other three strategies have, on average, positive values, meaning mice are more likely to lick on
182 the image after an omission (post omission strategy), on image changes (visual strategy), and at
183 the expected image change frequency (timing strategy). However there is significant variability
184 across the behavioral sessions. Supplemental Note 5 shows additional characterization of how
185 strategy weights are correlated with the number of hits, misses, and licking probability within
186 each session. The smoothing priors for each strategy govern how variable the strategy weights
187 can be within each session from image to image, and constrain the strategy weights to evolve
188 gradually over time. On average the strategies have smoothing priors within the same order
189 of magnitude, with the licking bias and timing strategies generally being the most variable.
190 However, there is significant variability across behavioral sessions.

191 To evaluate the importance of each strategy, we measured the reduction in model evidence
192 after removing each strategy (Fig. 2D). The model evidence, or marginal likelihood, measures
193 the probability of the data given the hyper-parameters after integrating over possible parameter
194 values. Model comparison metrics such as Bayes factor and Bayesian information criterion are
195 based on comparing the model evidence of two models. In general, if the model evidence decreases
196 after removing a strategy then the model performs worse at describing the data. We did not
197 evaluate the model evidence without the licking bias term because it sets the average licking
198 rate and removing it breaks the model in a trivial manner. Across our population, removing
199 the omission strategy does not lead to a reduction in model evidence. We therefore conclude
200 that the omission strategy is not a meaningful descriptor of mouse behavior. Removing the
201 post omission strategy leads to a small decrease in model evidence, demonstrating a minor role
202 in describing mouse behavior. Removing the visual and timing strategies leads to significant
203 decreases in model performance, albeit with large variability across behavioral sessions.

204 We focused the rest of our analysis on the visual and timing strategies based on three ob-
205 servations. First, the lack of change in model evidence for the omission strategy. Second, we
206 observed a strong correlation between the post omission strategy and visual strategy in terms of
207 both the changes in model evidence, and their average weights (Fig. 2E). Third, after performing
208 PCA on the matrix of changes in model evidence, we found the top two principal components
209 explained 99.04% of the variance and are closely oriented with the timing and visual strategies
210 respectively (Supplemental Note 6).

211 Plotting the change in model evidence from the visual and timing strategies against each
212 other we find that there is a continuous spectrum of behaviors that mix the visual and timing
213 strategies together (Fig. 2F). We term the strategy index as the difference in the change of model
214 evidence between the visual and timing strategies. A positive strategy index value indicates the
215 session was well described by the visual strategy. A negative strategy index indicates the session
216 was well described by the timing strategy. Plotting the strategy index against the rewards earned
217 per session we see that all strategy mixes are able to earn a significant number of rewards per
218 session (Fig. 2G). However higher values of the strategy index tend to result in higher number of
219 earned rewards. Individual mice were fairly stable in their strategy preferences across multiple
220 behavioral sessions (Fig. 2H, up to 4 sessions per mouse performed during calcium imaging).
221 Mouse identity explains 72% of the variance in the strategy index across imaging sessions.
222 Consistent with this finding we did not observe mice switching between strategies within a
223 behavioral session. Further, strategy preferences emerged gradually over training (Supplemental
224 Note 7). Taken together we find individual mice develop unique strategy preferences between
225 the visual and timing strategies that are stable over many days.

226 Given that strategy preferences are stable over multiple days, the remaining analyses cate-
227 gorize each behavioral session by the dominant strategy (equivalently, the sign of the strategy
228 index). We refer to sessions best described by the visual strategy (positive strategy index)
229 as visual strategy sessions. Likewise, we refer to sessions best described by the timing strategy
230 (negative strategy index) as timing strategy sessions. Figure 2I illustrates 90 seconds of behavior
231 from each of the two dominant strategies. Supplemental Note 8 provides additional characteri-
232 zation of the behavior for each of the two strategies.

233

234 **Task strategy is distinct from task engagement**

235 Rather than switching strategies during a session, we observed that mice had clear patterns
236 of disengagement when they stopped licking altogether. To demonstrate this we generated
237 a contour plot of the licking bout rate and reward rate aggregated across all the behavioral
238 sessions (Fig. 3A). Mouse behavior is clearly divided between two regions. One region, which
239 we term disengaged behavior, has low licking rates and low reward rates. The other region,
240 which we term engaged behavior, is much broader, encompassing a wider range of licking and

241 reward rates. We define a simple threshold for disengagement as licking bout rates below 1
242 bout/10 s, and reward rates below 1 reward/120 s. On average, mice are engaged 60.1% of the
243 time. Figure 3B shows an illustrative example session in which the mouse transitions from task
244 engagement to disengagement.

245 In order to determine if task engagement was related to task strategy, we plotted the average
246 strategy weights across the same landscape of licking bout and reward rates. Both the visual
247 strategy weights (Fig. 3C) and timing strategy weights (Fig. 3D) are at their lowest values in
248 the disengaged region. In the engaged region, the visual strategy is highest in the upper left
249 when the ratio of rewards to licks is maximized. This can be understood as the visual strategy
250 efficiently transforming licking bouts into rewards. The timing strategy is highest in the lower
251 end of the engaged region, which can be understood as the timing strategy requiring more false
252 alarm licks to generate rewards. From this analysis we conclude that task engagement is separate
253 from each of the dominant strategies.

254 Next, we asked if the temporal pattern of engagement across each session was related to
255 task strategy (Fig. 3E). For both strategies, engagement is highest at the start of the ses-
256 sion and gradually decreases throughout the session, presumably as the mice become sated. A
257 slightly higher percentage of timing strategy sessions are in the engaged state at each time point,
258 presumably because the timing strategy requires more trial and error to earn water rewards.

259 Finally, we asked if the timing of licking was altered during disengaged periods by plotting
260 histograms of when each licking bout started with respect to the latency since the last image
261 presentation (Fig. 3F). By definition, the engaged periods have more licking bouts. However
262 we see the disengaged licking bouts have altered timing relative to stimulus presentations. The
263 engaged licking is time-locked to image onset, with the peak response time around 400ms.
264 Disengaged licking lacks this clear time-locking to image onset. This pattern holds true for both
265 behavioral strategies. Both visual and timing strategy sessions have clear time-locked responses
266 in engaged epochs (Fig. 3G), and both lack clear time-locked responses in disengaged epochs
267 (Fig. 3H). The fact that engaged licking in timing strategy sessions is time-locked to image
268 presentations demonstrates that mice performing the timing strategy understand that rewards
269 are tied to image presentations, and are synchronizing their timing-based guesses to image onsets
270 rather than randomly licking without regard to the stimulus.

271 We conclude that mice performing both strategies go through periods of engaged and dis-
272 engaged behavior, which is a separate dimension of behavior from their strategy preferences.
273 Mice performing both strategies gradually disengaged over the course of the one hour behav-
274 ioral session as they got sated by water rewards. Finally, mice performing both strategies have
275 image-locked licking while engaged, and randomly timed licking when disengaged.

276 **Strategy is reflected in neural activity across the Vip-Sst microcircuit**

277 We next wanted to assess whether the dominant behavioral strategy would be reflected in neural
278 activity. To answer this question we turned to two-photon calcium imaging recordings during
279 mouse behavior. We focused our analysis on two cortical visual areas, V1 and LM (Fig. 4A).
280 Calcium imaging was performed in transgenic mice expressing the calcium indicator GCaMP6f in
281 specific cell populations: excitatory neurons, Sst inhibitory neurons, and Vip inhibitory neurons.
282 Recent surveys of neural cell types have proposed a taxonomy in which excitatory neurons and
283 GABAergic neurons are classes, and Sst and Vip neurons are subclasses of GABAergic neurons
284 (Tasic et al. 2018). In this paper, for simplicity we refer to excitatory, Sst, and Vip as cell
285 classes. Each cell class was recorded in separate mouse populations. These three cell classes
286 are thought to form a cortical microcircuit whereby Sst and Vip reciprocally inhibit each other
287 (Fig. 4B). The dataset contains imaging while mice performed the task with both familiar and
288 novel stimuli. Novel stimuli have dramatic effects on neural activity (Garrett et al. 2023), so we
289 restricted our analysis to imaging during familiar image sessions. Our neural dataset contains
290

291 8,619 excitatory cells (21 imaging sessions, 9 mice), 470 Sst cells (15 imaging sessions, 6 mice),
292 and 1,239 Vip cells (21 imaging sessions, 9 mice). We performed all of our analyses on discrete
293 calcium events that were regressed from the raw fluorescence traces, thus removing the slow
294 decay dynamics of the calcium indicator GCaMP6f (Fig. 4C). The extracted calcium events are
295 of variable magnitude and correspond to a transient increase in internal calcium levels.

296 Our neural analysis examines how each cell class responds to three stimulus types: image
297 repeats, distracting image omissions, and image changes (Fig. 4D). We grouped cells by the
298 dominant strategy used by the mouse during the behavioral session in which they were recorded.
299 We first asked how each cell class responds to image repeats, and if strategy affects responses
300 to image repeats. Excitatory and Sst cells respond to each repeated image presentation with
301 no difference in the population average between strategies. Excitatory cells are image selective,
302 with each cell typically responding to only one of the 8 images presented during the session. In
303 contrast Sst cells are broadly image tuned, thus the population average for excitatory cells is an
304 order of magnitude smaller than Sst cells. Vip cells are suppressed by image presentations and
305 ramp their activity between image presentations. Notably, Vip cells from visual strategy sessions
306 showed significantly larger activity ramps between image presentations (Average calcium event
307 magnitude +/- hierarchically bootstrapped SEM, visual 0.0096 +/- 0.00094, timing 0.0070 +/-
308 0.00092, $p=0.025$). We assessed significance and report the standard error of the mean (hb.
309 SEM) by performing a hierarchical bootstrap (Saravanan et al. 2020). In summary, excitatory
310 and Sst cells showed no strategy differences in response to image repeats, while Vip cells from
311 visual strategy sessions showed increased activity between image repeats compared to cells from
312 timing strategy sessions.

313 We next asked if strategy affects how each cell class responds to image omissions. In response
314 to image omissions excitatory cells show an amplified response on the first image presentation
315 after the omission, compared with the pre-omission image, with no difference in the population
316 average between strategies. Sst cells showed significant strategy dependent changes in activity
317 during the second half of the omission interval. Cells from timing strategy sessions show in-
318 creasing activity ramping up over the omission interval, while cells from visual strategy sessions
319 show decreasing activity during the omission interval (Average calcium event magnitude +/-
320 hb. SEM, visual 0.0052 +/- 0.0021, timing 0.019 +/- 0.0054, $p=0.0037$). Sst cells from both
321 strategies show decreased responses on the first image presentation after the omission compared
322 to the pre-omission image. Vip cells show large ramps of activity during the omission interval
323 with significant differences between strategies (Average calcium event magnitude +/- hb. SEM,
324 visual 0.036 +/- 0.0038, timing 0.019 +/- 0.0022, $p=0.00$). In summary, Sst cells from visual
325 strategy sessions show lower activity following omissions compared to cells from timing strategy
326 sessions, while Vip cells from visual strategy sessions show increased ramping activity following
327 omissions compared to timing strategy sessions.

328 We then asked if strategy affects how each cell class responds to image changes, including both
329 hits (mouse licked) and misses (mouse did not lick). In response to image changes we see strategy
330 dependent differences across all three cell classes. Figure 4E shows summary quantification of
331 differences between hits and misses for each strategy.

332 We find excitatory cells from visual strategy sessions show greater activity in response to
333 hits compared to cells from timing strategy sessions (Average calcium event magnitude +/- hb.
334 SEM, visual hit 0.014 +/- 0.0017, timing hit 0.0097 +/- 0.0014, visual hit vs timing hit $p=0.04$).
335 Further, we find a significant difference between hits and misses for cells from visual strategy
336 sessions, but not for cells from timing strategy sessions (Average calcium event magnitude +/-
337 hb. SEM, visual hit 0.014 +/- 0.0017, visual miss 0.0081 +/- 0.0010, timing hit 0.0097 +/-
338 0.0014, timing miss 0.0080 +/- 0.00095, visual hit vs visual miss $p=0.0025$). For Sst cells, cells
339 from visual strategy sessions show lower activity during the interval after hits compared to cells
340 from timing strategy sessions (Average calcium event magnitude +/- hb. SEM, visual hit 0.0015

341 +/- 0.00074, timing hit 0.013 +/- 0.0032, p=0.00). Further we find lower Sst activity following
342 hits compared to misses for Sst cells from visual but not from timing strategy sessions (Average
343 calcium event magnitude +/- hb. SEM, visual hit 0.0015 +/- 0.00074, visual miss 0.0059 +/-
344 0.0021, timing hit 0.013 +/- 0.0032, timing miss 0.0098 +/- 0.0022, visual hit vs visual miss
345 p=0.010). For Vip cells, in the interval before the image change we find significant differences
346 in activation between the two strategies as well as between hits and misses for cells from visual
347 but not from timing strategy sessions (Average calcium event magnitude +/- hb. SEM, visual
348 hit 0.016 +/- 0.0022, visual miss 0.011 +/- 0.0011, timing hit 0.0070 +/- 0.00076, timing miss
349 0.0072 +/- 0.00087, visual hit vs visual miss p=0.037, visual hit vs timing hit p=0.00, visual
350 miss vs timing miss p=0.0003). In summary, cells from visual strategy sessions show differential
351 activity in all three cell classes between hits and misses, while cells from the timing strategy
352 shows no modulation between hits and misses. Further, we see strategy dependent differences
353 in neural activity in responses to hits across all three cell types: excitatory cells from visual
354 strategy sessions show greater activity after hits compared to cells from timing strategy sessions,
355 Sst cells from visual strategy sessions show lower activity following hits compared to cells from
356 timing strategy sessions, and Vip cells from visual strategy sessions show greater activity before
357 hits and misses compared to cells from timing strategy sessions.

358 Vip cells are known to be modulated by locomotion (Fu et al. 2014). This effect is seen in
359 our data most visibly in figure 4D when the mice stop running after image changes to consume
360 their water reward. With this in mind, we wanted to know whether the strategy differences we
361 observe could be due to differences in running speed or patterns. To answer this we looked at
362 the Vip response amplitude to images and omissions as a function of running speed (Fig. 4F,G).
363 Broadly, we observe Vip activity in cells from visual strategy sessions is equal to or greater
364 than cells from timing strategy sessions across all running speeds. From this we conclude that
365 strategy differences in Vip cell activity cannot be a result of different running speeds or patterns.

366 **Microcircuit disinhibition dynamics are amplified in the visual strategy**

367 In order to make sense of the diverse strategy differences we observe in figure 4 we now turn
368 to the Vip-Sst microcircuit as a unifying model (Fig. 5A). We first asked how the microcircuit
369 components respond as a system to each stimulus type. We thus examined the neural population
370 averages grouped by strategy allowing a direct comparison across cell classes (Fig. 5B). We
371 emphasize here each cell class was recorded in a separate population of mice. Viewing the neural
372 population averages in this manner highlights that excitatory and Sst cells are image responsive,
373 while Vip cells are inhibited by image presentations. Notably Vip cells show ramping between
374 image presentations. We can further condense this information by showing the three cell classes
375 in a 3D state space plot (Fig. 5C), or for clarity in a 2D state space between excitatory and Vip
376 cells. These state space plots reveal the dynamics of the three cell classes as a periodic cycle
377 corresponding to the rhythmic stimulus presentations where the two strategies differ primarily
378 in the Vip activation between image presentations. Importantly, in this periodic cycle excitatory
379 and Sst cells are tightly correlated, each responding to image presentations, while Vip cells are
380 suppressed by image presentations. Supplemental Note 9 shows 3D state space plots and all
381 2D state space combinations of cell classes. We will next consider image omissions and image
382 changes as perturbations to this underlying microcircuit cycle.

384 Previous work (Millman et al. 2020) found that Vip-Sst antagonism regulates the gain of
385 cortical circuits to broaden the range of stimulus contrast levels excitatory cells can encode.
386 Comparing the dynamics of Vip and Sst cells in response to image omissions we can see this
387 antagonism at work (Fig. 5E). When an image is omitted, the Vip cells continue their between-
388 image ramping until they are finally suppressed by the post-omission image. Sst cells have
389 smaller responses to the post-omission image compared to the pre-omission image and excita-
390 tory cells have larger responses to the post-omission image compared to the pre-omission image,

presumably a result of the increased Vip activation. We can interpret this ramping as Vip cells responding to the lack of visual stimulus by amplifying the gain of the cortical circuit via inhibition of Sst cells and disinhibition of excitatory cells. In the state space view of microcircuit dynamics, the image omission is a perturbation to the periodic repeating image cycle. In response to this perturbation, Vip cells activate, releasing excitatory cells from inhibition thereby amplifying the response to the post-omission image before returning to the periodic image cycle on subsequent images. Notably, these gain dynamics are amplified in cells from visual strategy sessions compared to cells from timing strategy sessions (Fig. 5E).

Image changes can also be understood as perturbations to the periodic image cycle. In response to both hits and misses excitatory cells show increased responses. For cells from visual strategy sessions we see notable differences between hits and misses in Vip activity before the image change (Fig. 5F,G). We do not observe these differences for cells from timing strategy sessions (Fig. 4E). One possible interpretation of these data is that mice performing the visual strategy are more likely to make the choice to respond or not based on visual cortex activity. On a trial by trial basis, a more active Vip population may prime excitatory cells for more robust change responses. Thus leading to increased Vip activity before hits compared to misses, increased excitatory activity on hits compared to misses, and decreased Sst activity after hits compared to misses. We emphasize here that the increased excitatory response on hits happens, on average, 200ms before the mouse responds and therefore cannot be interpreted as a reward response. In this interpretation, mice performing the timing strategy are less reliant on visual cortex activity to trigger responses, instead using some internal timing mechanism elsewhere in the brain. Thus, we see no differences in average Vip, Sst, or excitatory activity between hits and misses for timing mice. Increased Vip activity priming visual, but not timing, strategy mice to respond may also explain why visual strategy mice are more likely to respond to the post-omission image (Fig. 2E). In the state space view of microcircuit dynamics, the image change perturbs the ongoing periodic image cycle by elevating excitatory responses. For mice performing the visual strategy, but not the timing strategy, increased Vip activity can amplify excitatory responses and preferentially lead to behavioral responses.

In summary, when comparing between visual and timing strategy circuits, we can succinctly describe the differences in population response to image repeats, omissions, and changes as amplified Vip disinhibition dynamics. Excitatory and Sst cells respond in unison to repeating image presentations, while Vip cells are suppressed by each image presentation, instead ramping their activity between images. This between image ramping is elevated in cells from visual strategy sessions. When images are omitted, Vip cells continue to ramp their activity which in turn suppresses Sst and disinhibits excitatory cells during the post-omission image. This functionally allows Vip cells to calibrate the subsequent gain of excitatory cells, and this mechanism is heightened in cells from visual strategy sessions. Finally, for the visual strategy elevated Vip activity before image changes facilitates increased excitatory responses which in turn potentially leads to mouse licking responses.

Trial by trial neural activity is more correlated with behavioral choices for visual strategy mice

Following the interpretation suggested above that visual strategy mice are more reliant on visual cortical activity to drive choices, we next wanted to determine if the differences in neural activity between strategies were behaviorally relevant on an trial by trial basis. To answer this we used a random forest classifier trained on neural activity to predict either image changes versus repeats (change decoder), or hits versus misses (hit decoder). Decoding was performed on neural activity in the first 400ms after each stimulus presentation. This time window is before the average licking response, and thus largely avoids reward signals.

Across all three cell types, we found that image changes versus repeats could be decoded

441 equally well from cells from visual strategy sessions and timing strategy sessions (Fig. 6A). We
442 then asked to what degree the image change signals were correlated with animal behavior. Since
443 we observe differential activity on hits versus misses for cells from visual strategy sessions, but
444 not cells from timing strategy sessions, we reasoned that change signals in visual cortex should
445 be more correlated with behavior when mice are performing the visual strategy. We measured
446 the correlation between the decoder's predictions on image changes (change vs repeat) and the
447 animal's choice (hit vs miss). For excitatory, but not Vip or Sst cells, we find a stronger correla-
448 tion for cells taken from visual strategy sessions compared to timing strategy sessions (Fig. 6B).
449 For excitatory cells, the correlation between behavior and decoder predictions is more than twice
450 as strong for visual sessions compared to timing sessions. This demonstrates that while image
451 change information is equally present in neural activity from mice performing both strategies,
452 it is more correlated with animal choices in visual strategy sessions. This finding is consistent
453 with the interpretation that mice performing the visual strategy are more dependent on activity
454 in visual cortex to drive behavioral responses. Finally, we asked how well we could decode hits
455 versus misses. For excitatory and Vip cells, but not Sst cells, decoder performance was higher
456 for visual strategy sessions compared with timing strategy sessions.

457

458 **Engagement state has limited modulation of neural activity**

459 We next asked if we could observe neural correlates of task engagement. Similar to figure 4D,
460 we plotted the average neural activity aligned to either image omissions or image changes but
461 now additionally split by engaged and disengaged states (Fig. 7). The disengaged state does
462 not contain hits, so we restricted our comparison to misses. Excitatory cells from visual strat-
463 egy sessions, but not timing strategy sessions, show elevated responses to misses when engaged
464 compared to disengaged (Average calcium event magnitude +/- hb. SEM, visual engaged 0.010
465 +/- 0.0016, visual disengaged 0.0069 +/- 0.00088, $p = 0.032$). We do not observe any other sig-
466 nificant differences between average neural activity in engaged and disengaged states for either
467 dominant strategy across any cell type. Further, we do not see major differences in Vip activity
468 even when controlling for running speed differences during engagement periods (Supplemental
469 Note 10). Thus, we conclude that the effects of strategy are separate from task engagement.

470

471 **Both dominant strategies show robust effects of image novelty**

472 Our analysis to this point has examined neural activity when mice are shown familiar stimuli they
473 have seen many times. The Allen Institute Visual Behavior - 2p calcium imaging dataset also
474 contains neural activity in response to novel stimuli. Garrett et al. 2023 examined this data and
475 found exposure to novel stimuli dramatically altered neural activity, finding striking effects across
476 all three recorded cell classes. We sought to extend the results reported in Garrett et al. 2023 by
477 asking two questions. First, behaviorally, does strategy change with novel stimuli? Second, how
478 do cells from each dominant strategy respond to novel stimuli? Supplemental Note 11 answers
479 both questions. Analyzing behavior, we see a small but significant shift in strategy preference
480 towards the visual strategy on the novel image session. This shift manifests as most mice
481 slightly increasing their strategy index, rather than individual mice making dramatic changes in
482 strategy. Analyzing neural activity we see cells from both strategies show the effects of novelty
483 documented in Garrett et al. 2023. Further, on the novel session the primary effects reported in
484 figure 4 are still present. Namely, Vip cells from visual strategy sessions had increased activity
485 on image omissions, and before hits compared to cells from timing strategy sessions. As well as
486 increased excitatory activity for hits compared to misses for cells from visual strategy sessions
487 but not from timing strategy sessions. We conclude the effects of stimulus novelty are largely
488 separate from strategy preference.

Discussion

The Allen Institute Visual Behavior - 2p calcium imaging dataset (brain-map.org) is a large scale survey of neural activity in three neural cell classes in the context of a change detection task. We sought to identify behavioral strategies used by mice in this dataset. Using a dynamic logistic regression model we found that mice have unique mixtures of two strategies, a visual comparison strategy where mice respond to image changes, and a statistical timing strategy where mice respond at the expected duration between image changes. Individual mouse strategy preferences were relatively stable over multiple behavioral sessions and emerged gradually over training. Separately from strategy preference, we found mice have periods of task engagement and disengagement. Mice performing either strategy gradually disengaged from the task throughout each behavioral session. For both dominant strategies, engaged licking was time-locked to stimulus presentations, while disengaged licking was not time-locked to stimulus presentations.

We then analyzed neural activity based on the dominant strategy preference. We found a diversity of neural correlates of strategy across excitatory, Sst inhibitory, and Vip inhibitory cell classes. We found that this diversity of responses can be understood through the lens of the Vip-Sst disinhibitory circuit. In response to image omissions, Vip cells increase their activity to change the gain on excitatory cells. In visual strategy sessions, this Vip gain dynamic is amplified. Further, in visual strategy sessions, but not timing strategy sessions, Vip activity is elevated before hits compared to misses, suggesting Vip cells potentiate excitatory cells and bias the decision to respond to each image presentation in mice performing the visual strategy. Supporting the view that visual strategy mice are more reliant on visual cortical activity, we found stronger hit decoding from visual strategy sessions, and the performance of an image change decoder is more correlated with animal behavior in visual strategy sessions. Additionally, the visual strategy mice show increased post-omission licking compared to timing strategy mice, suggesting Vip omission activity potentiates excitatory responses on the post-omission image.

Despite clear effects of task strategy, we found only limited neural correlates of task engagement. Excitatory cells from visual strategy sessions show elevated responses to misses when engaged. This suggests the effects of strategy influence neural circuits on longer timescales. Additionally, we found the effects of strategy preference persist when the mice perform the task with novel stimuli, despite robust changes to population activity. Our findings demonstrate that behavioral strategy alters neural activity within visual cortex, and is mediated by specific cell classes.

Behavioral diversity

We note that it could have been possible to alter our training pipeline to push mice away from the timing strategy, skip over mice performing the timing strategy for neural imaging, or post-hoc exclude their data from neural analysis. Indeed, such practices are common in neuroscience laboratories where strict experimental control is demanded by the practicalities of limited experimental resources and a desire to clearly isolate single behaviors or computations. Recently there has been considerable discussion over the advantages of naturalistic behavior and tightly controlled laboratory tasks (Juavinett et al. 2018; Musall et al. 2019). Naturalistic behavior offers ethological relevance and behavioral richness, while laboratory tasks can isolate behaviors and yield reproducibility. Our findings demonstrate a middle ground, through the use of large scale brain observatories with a behavioral task that subjects can solve in multiple ways. By recording from many mice we find considerable behavioral richness across our population, but still harness the advantages of well defined stimuli and task structure. This approach complements the existing range of behavioral paradigms in the field.

How do behavioral strategies arise?

We found that strategy preferences emerge gradually over many days of training. How do mice

539 learn their strategy preferences? One possibility is mice could adopt one strategy or another
540 based on a myriad subtle biases such as visual ability, cognitive ability, or difficulty licking the
541 reward spout. Alternatively, mice could have been biased to one strategy based on variability
542 in early behavioral exploration. Given that the visual strategy can earn a greater number of
543 rewards per session we can consider the timing strategy as a local maximum in behavioral per-
544 formance that some mice might settle into early in training. Finally, it is possible that prior to
545 any task training, some mice could already have amplified Vip-Sst dynamics and thus be predis-
546 positioned to adopting the visual strategy. This predisposition could be the result of genetics,
547 or life experience. The learning processes that lead mice to each strategy may involve unique
548 behavioral states and neural mechanisms (Rosenberg et al. 2021; Meister 2022).

549 550 **How does strategy preference amplify Vip-Sst circuitry?**

551 We found that the visual strategy resulted in amplified Vip-Sst disinhibition dynamics. If strat-
552 egy preferences arise from outside visual cortex, then what mechanisms facilitate the diversity
553 of neural correlates we observe? Vip cells are known to be preferential targets of top-down
554 feedback (Kamigaki 2019; Ma et al. 2021). One possibility is that external feedback results in
555 higher tonic activation of Vip cells during visual strategy sessions. Alternatively, neuromodula-
556 tory input could alter intrinsic Vip firing patterns (F  r  zou et al. 2002; Fu et al. 2014; Pr  nneke
557 et al. 2020).

558 Strategy preference could also recruit different visual pathways and brain structures (Bolkan
559 et al. 2022). We found cells from visual strategy sessions, but not timing strategy sessions, show
560 differential activity between hits and misses. Further, we found a decoder trained to predict
561 image changes made predictions that were more correlated with the animal’s choices for visual
562 sessions compared to timing sessions. For excitatory cells, the correlation was more than twice
563 as strong. These results suggest that the timing mice may execute this task primarily through
564 other brain structures. We re-iterate here that licking bouts from timing mice are time-locked to
565 image presentations. This demonstrates timing strategy mice still use visual input, but perform
566 less processing of the visual stimulus. Retinal ganglion cells project to many sub-cortical struc-
567 tures (Martersteck et al. 2017), which could facilitate the simpler visual processing required for
568 the timing strategy.

569 570 **Engagement and novelty**

571 Mice performing both dominant strategies displayed periods of task engagement and disengage-
572 ment (Ashwood et al. 2022). Across both dominant strategies we observed limited modulation
573 of population activity with task engagement. This may be a puzzling finding, especially given
574 some similarities between task engagement and visual attention. However, we caution that task
575 engagement is a separate phenomena from visual attention and care should be taken before
576 taking inspiration from attentional mechanisms. With this reservation in mind, we do note that
577 Myers-Joseph et al. 2023 found that attention modulation operates distinctly from Vip disinhi-
578 bition. Consistent with our findings, Pho et al. 2018 found little modulation of neural activity
579 by engagement in V1 but significant modulation in posterior parietal cortex.

580 One possibility for a lack of engagement correlates is the nature of our stimuli. Our stimuli
581 are large full visual field images with relatively high contrast - they are not near perceptual
582 thresholds. Perhaps our stimuli are salient enough to evoke visual responses regardless of task
583 engagement. If our task operated at a perceptual threshold we might observe stronger modula-
584 tion of neural activity by task engagement.

585 The Allen Institute Visual Behavior - 2p calcium imaging dataset contains multiple behav-
586 ioral dimensions, including novel stimuli. We did not focus on novel stimuli, but Garrett et
587 al. 2023 found striking changes in neural activity in all three recorded cell classes. We found
588 strategy alters neural activity in distinct ways from novel stimuli. Since strategy differences

589 are present during both task engaged and disengaged states, it is likely the strategy effects we
590 observe are the result of long-term learning and firmly established in cortical circuits. This is
591 further supported by the persistence of strategy differences during the novel stimulus presenta-
592 tion. The neural correlates of strategy on this task are therefore not a fleeting activity pattern,
593 or a flexible state to be switched on and off, rather it appears to be a deeply ingrained change
594 in the cortical circuit that the mouse develops to solve the task consistently well.

595

596 **Future directions**

597 A naive view of sensory circuits might expect veridical encoding of the sensory world. However
598 our findings highlight that task strategy is mediated through changes in neural activity in sensory
599 cortex. This result raises general questions about how, when, and why cognitive states alter
600 sensory processing. Future studies should seek mechanistic understanding of how cognitive
601 states influence local circuit processing in visual cortex, how local circuit processing changes
602 with learning, and how cognitive states influence the propagation of sensory information up the
603 visual hierarchy into deeper brain structures.

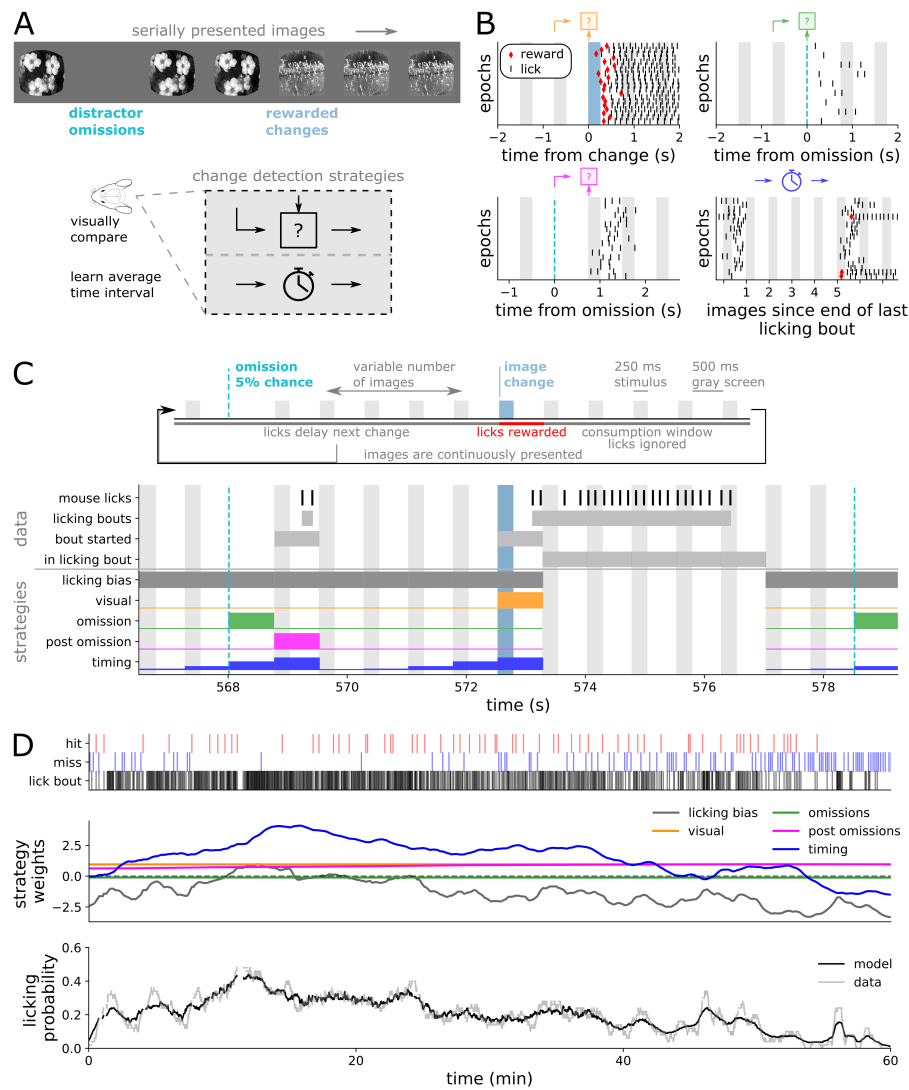


Figure 1: Quantifying strategies during a change detection task. (A) Head-fixed mice were shown a stream of natural images and were rewarded for licking in response to image changes. Mice could perform this task using multiple strategies, including visually comparing image presentations or learning statistical distributions of rewards. (B) Example lick rasters demonstrate multiple strategies. Each row is an epoch within one example session. Up to 20 examples for each strategy are shown. Gray bands show time of repeated image presentations. Blue bands show time of change image presentations. Dashed blue lines show time of omitted images. Red markers show time of rewards. Top left - licking aligned to image changes. Top right - licking aligned to image omissions. Bottom left - licking aligned to post-omission images. Bottom right - licking aligned to a fixed time interval from the last licking bout. (C) Diagram of task structure, data processing, and strategies. Images were presented for 250ms with 500ms gray screens interleaved. 5% of all images were randomly omitted. Image changes were drawn from a geometric distribution. Individual licks were segmented into licking bouts. Licking bouts were assigned to the preceding image presentation. The licking model predicts whether a licking bout starts during each image interval, and we therefore ignore image presentations where the mouse was already licking. For each strategy we show the probability of starting a licking bout during each image interval. (D) Top - Raster of licking bouts, hits, and misses for full 1-hour behavioral session. Middle - time-varying strategy weights for each strategy for this example session. Bottom - licking probability in the data and model prediction smoothed with a one minute boxcar.

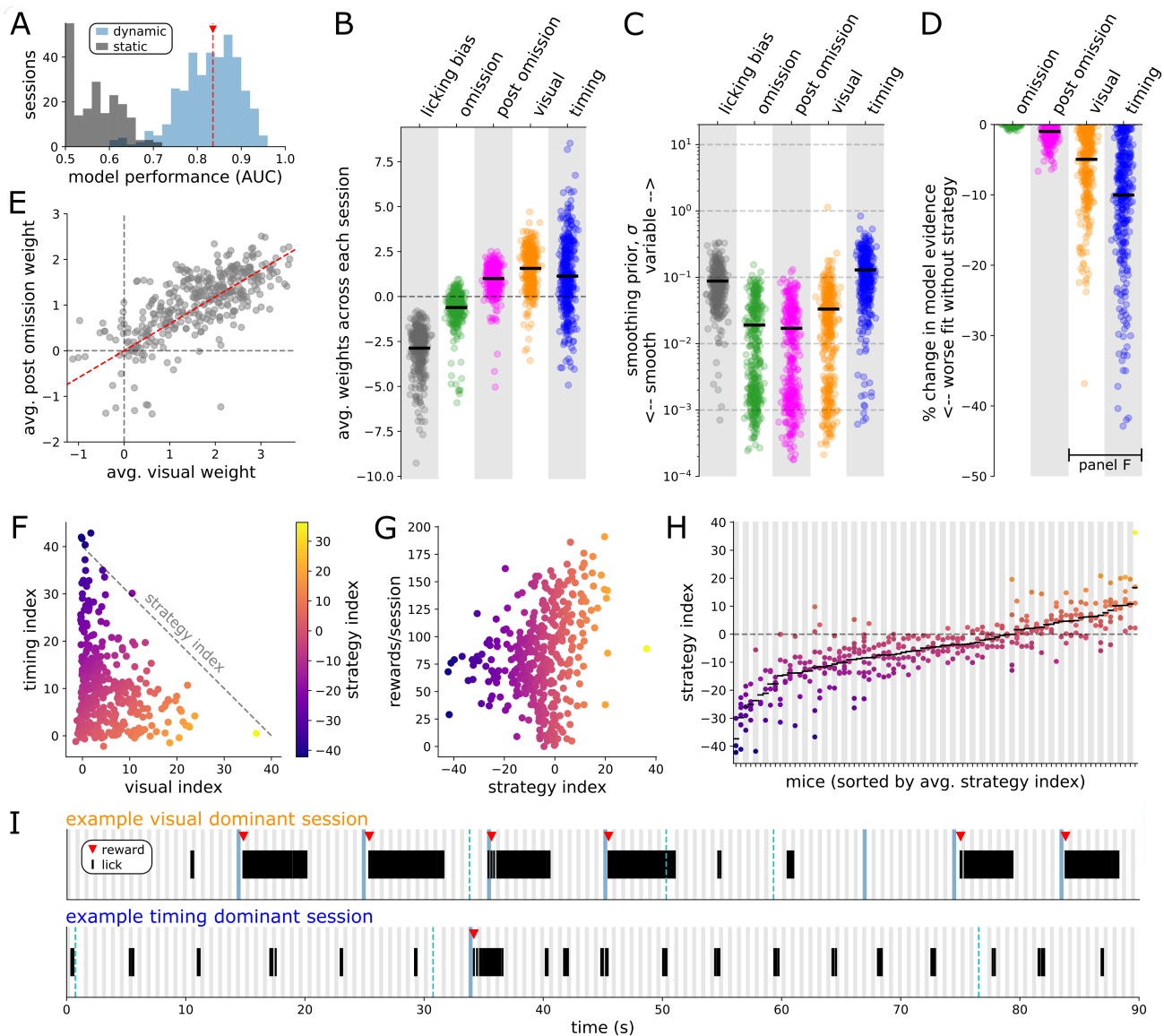


Figure 2: Licking model reveals distinct task strategies (A) Cross validated model performance. Histogram of area under the ROC curve for the dynamic model (blue) and static model (gray) for each session ($n=382$). The red line marks the average dynamic model performance (0.83). (B-H) Dots indicate individual sessions ($n=382$), and (B-D) black bars are population averages. (B) Average strategy weights. (C) Learned smoothing prior σ for each strategy. (D) Reduction in model evidence when removing each strategy. The absolute value for the visual and timing strategies is shown in panel F. (E) Average weights of the visual and post-omission strategies. Red line shows a linear correlation ($R^2 = 0.44$). (F) Scatter plot of the absolute value of the reduction in model evidence (termed here as an index) for the visual and timing strategies. The strategy index is defined as the counter-diagonal difference between visual and timing indices. (G) Rewards per session compared with the strategy index. (H) Mice were sorted by their average strategy index. Each session from a mouse is shown in the same column. (I) 90 seconds of illustrative behavior for two example sessions with either a visual dominant strategy (top) or timing dominant strategy (bottom). Gray bands show image repeats, blue bands mark image changes, and dashed blue lines mark image omissions.

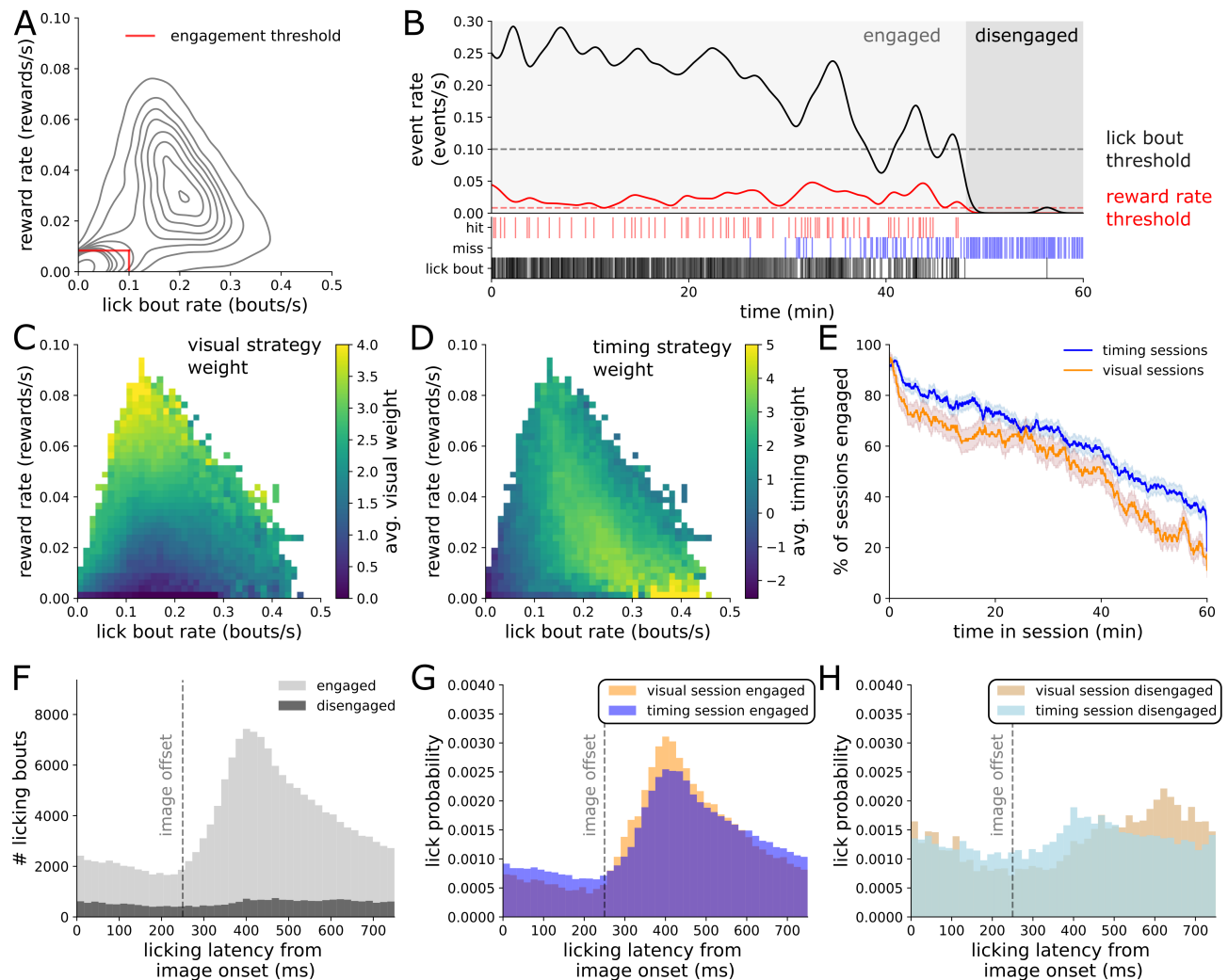


Figure 3: Strategy is distinct from engagement (A) Contour plot of reward rate and lick bout rate from all imaging sessions ($n=382$ sessions, 1,804,462 image intervals). Red line marks our threshold for classifying engaged and disengaged behavior (1 reward/120s, 1 lick bout/10s). 60.1% of image intervals are classified as engaged. (B) Example session showing lick bout rate (solid black), licking engagement threshold (dashed black), reward rate (red), and reward rate threshold (dashed red). (C, D) Average value of the visual and timing strategy weights across a range of licking and reward rates. Both panels show data from all sessions ($n=382$ sessions, 1.8 million image intervals) across a range of licking and reward rates. (E) Percentage of sessions in an engaged state at each point in the hour long behavioral session, split by dominant strategy. (F) Response latency histogram split by engaged and disengaged epochs. Response latency is defined as the time from the start of each licking bout to the most recent image onset. (G) Response latency histogram for engaged periods, split by visual or timing strategy sessions. (H) Response latency histogram for disengaged periods, split by visual or timing strategy sessions.

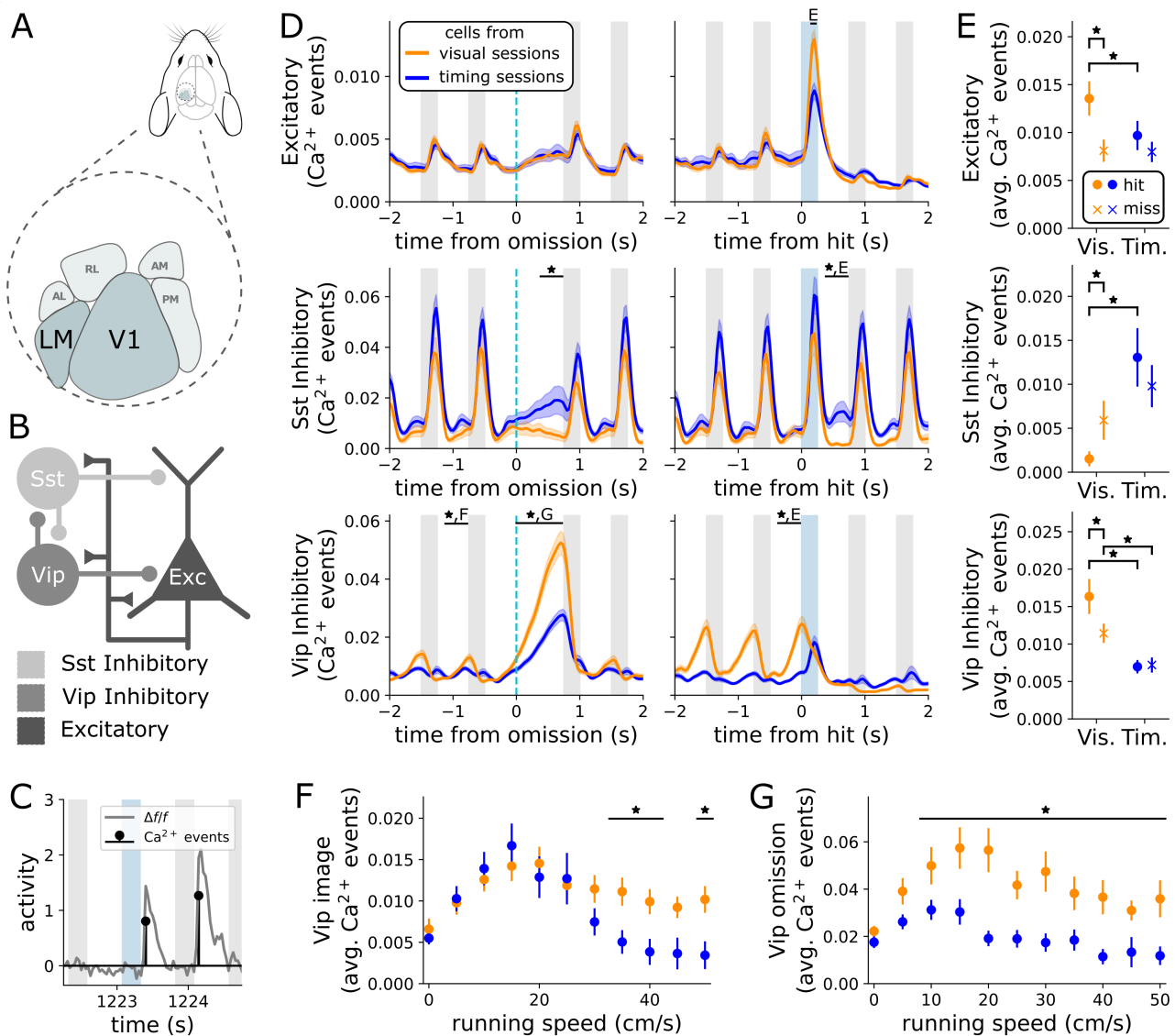


Figure 4: Neural correlates of behavioral strategy across multiple cell populations. (A) Two-photon calcium imaging was performed in visual areas V1 and LM. (B) Cartoon of Vip-Sst microcircuit. Vip and Sst inhibitory neurons reciprocally inhibit each other. (C) Discrete calcium events were regressed from the fluorescence traces. (D) Average calcium event magnitude of each cell class aligned to image omissions (left column), and hits (right column), split by dominant behavioral strategy (* indicates $p < 0.05$ from a hierarchical bootstrap over imaging planes and cells, corrected for multiple comparisons). (E) Average calcium event magnitude +/- hierarchically bootstrapped SEM in a interval around image changes split by strategy and whether the mouse responded. Excitatory and Sst cells show average events after image changes, (150, 250ms) and (375, 750ms) respectively. Vip cells show average events immediately before image changes (-375, 0 ms). * indicates $p < 0.05$ from a hierarchical bootstrap over imaging planes and cells, corrected for multiple comparisons. (F) Average calcium event magnitude +/- hb. SEM in the 750ms interval after image presentations split by running speed and strategy (* indicate $p < 0.05$ from a hierarchical bootstrap over imaging planes and cells, corrected for multiple comparisons). (G) Same as F after image omissions.

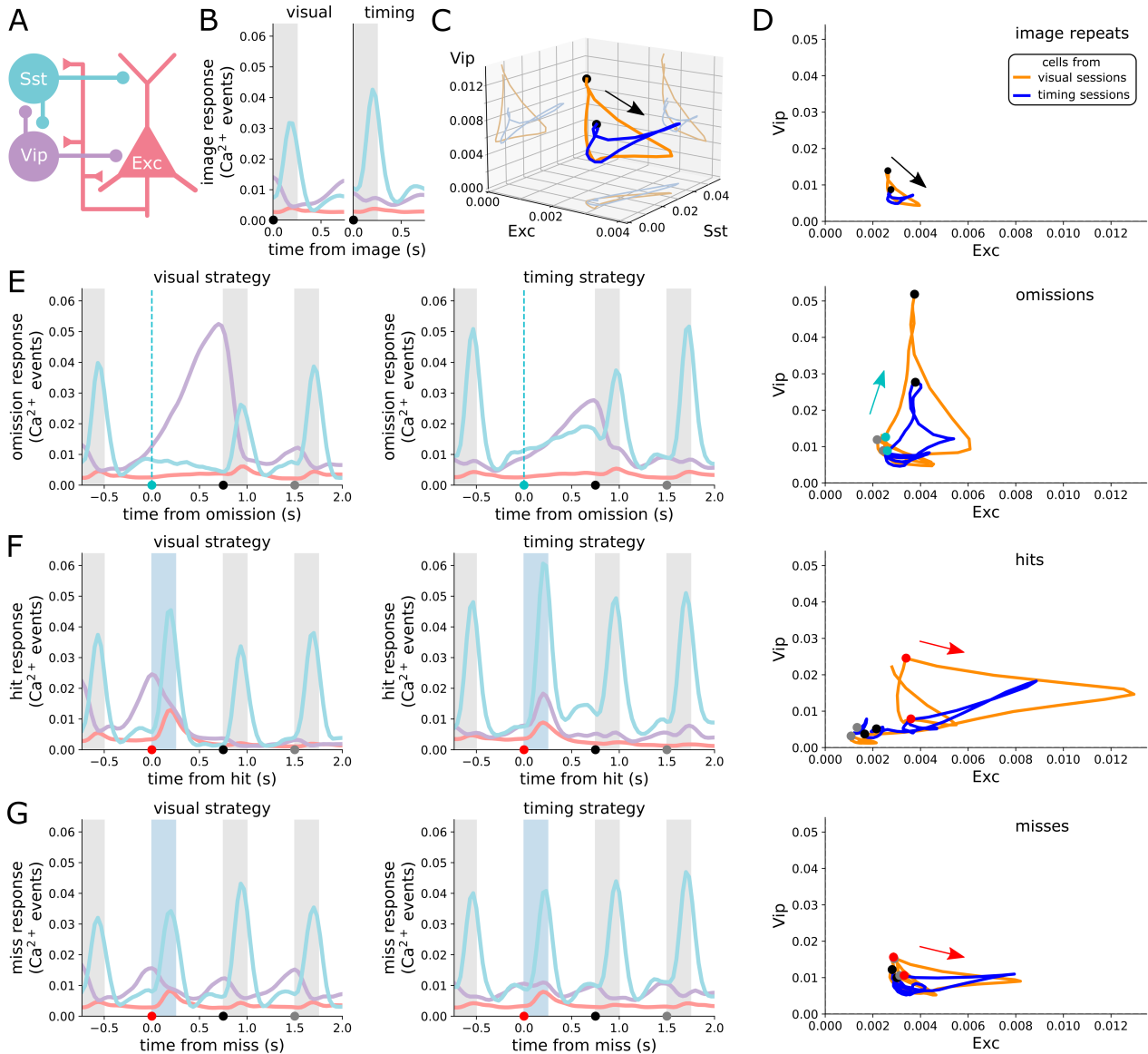


Figure 5: **Microcircuit disinhibition dynamics are amplified in the visual strategy** (A) Cartoon schematic of microcircuit. (B) Population average response to image repeats, grouped by strategy. (C) Population average response to image repeats plotted in 3D space. (D) Population average response to image repeats for excitatory cells against Vip cells. (C,D) Arrow marks forward progression of time. Black circle marks image onset in B. (E) Same as B,D for image omissions. (F) Same as B,D for hits. (G) Same as B,D for misses.

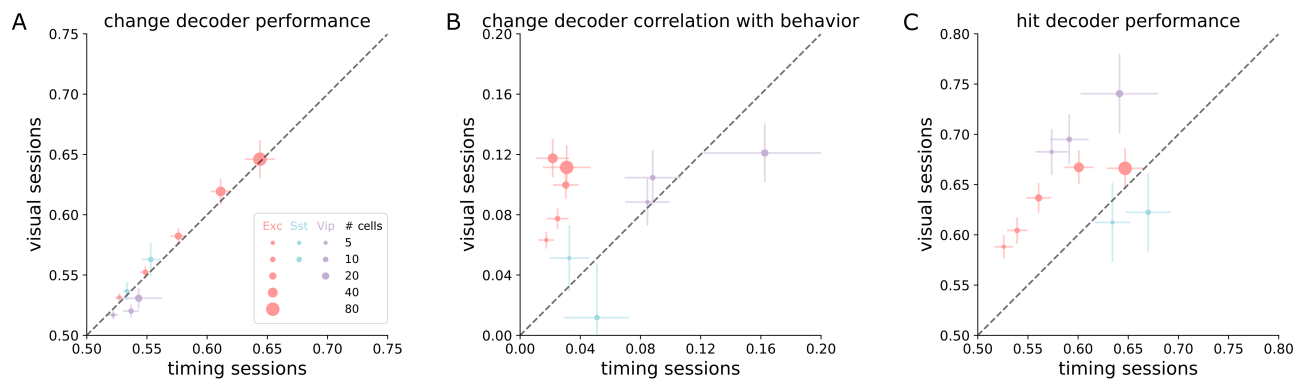


Figure 6: Stronger behavioral choice signals in cells from visual strategy sessions. (A-C). Decoding was performed on neural activity in the first 400ms after image presentation. Error bars are SEM over imaging planes. Each cell type is plotted as a separate color, with marker size indicating the number of cells used for decoding from each imaging plane. (A) Cross validated random forest classifier performance at decoding image changes and repeats (% correct). (B) Correlation between decoder prediction on image changes (change vs repeat) and animal behavior (hit vs miss). (C) Cross validated random forest classifier performance at decoding hits and misses (% correct).

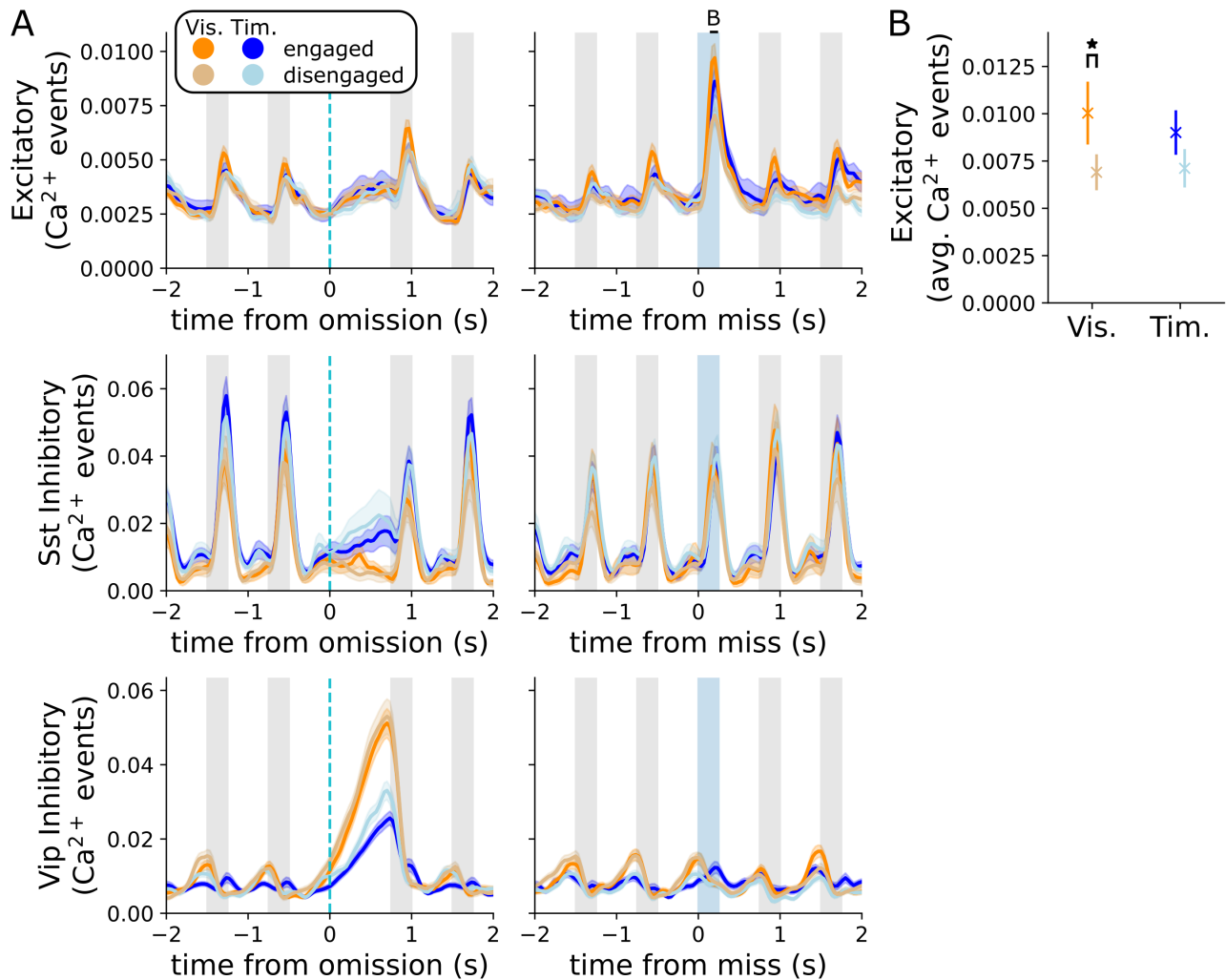


Figure 7: **Task engagement has minor effects on neural population activity.** (A) The average activity of cells from each dominant task strategy, split by epochs of task engagement and disengagement, aligned to either image omissions (left), or image change misses (right). Error bars are +/- SEM. (B) Average calcium event magnitude +/- hierarchically bootstrapped SEM in a interval (150ms, 250ms) around image changes split by strategy and whether the mouse responded. * indicates $p < 0.05$ from a hierarchical bootstrap over imaging planes and cells, corrected for multiple comparisons.

604 **Methods**

605 **Data selection**

606 The collection and processing of all data in the study was previously described in Garrett et al.
607 2023, and is available at <https://portal.brain-map.org/explore/circuits/visual-behavior-2p>. For our behavioral analysis we used all active behavioral sessions from mice in the
608 **avior-2p**. For our behavioral analysis we used all active behavioral sessions from mice in the
609 V1 and LM datasets across all image set experience levels (familiar images, novel images, and
610 repeated exposure to novel images). For all analyses we combined mice trained on image sets
611 A and B. For neural analysis we used neurons recorded during familiar image set presentations
612 on the multi-plane imaging rig. Except where noted we combined across cells from V1 and LM
613 and across cortical depths.

614 **Behavioral data processing**

615 We performed all of our behavioral analysis after assigning behavioral events to each image
616 presentation interval. By image presentation interval we refer to the 750ms interval beginning
617 with each image presentation. For image omissions we used the 750ms following the time of the
618 omission, when the image should have been presented. Licks were segmented into licking bouts
619 using an inter-lick interval of 700ms. This threshold was determined by visual inspection of the
620 histogram of inter-lick intervals. The start and end of each licking bout was then assigned to an
621 image presentation interval.
622

623 **Strategy model**

624 The strategy model predicts whether a licking bout started on each image presentation interval.
625 We thus excluded from our model fits any image presentation intervals where a licking bout was
626 on-going at the start of the interval. The licking bias strategy vector was defined as a 1 on every
627 interval. The visual, omission, and post-omissions strategy vectors were defined as 1 on intervals
628 with the respective stimulus and 0 otherwise. The timing strategy vector was a number between
629 0 and 1 based on a sigmoidal function of how many image intervals since the end of the last
630 licking bout. See supplemental note 3 for details on the timing strategy regressor. Except for
631 the licking bias, all strategy vectors were then mean-centered.
632

633 **Fitting the strategy model**

634 We fit the strategy model using the PsyTrack package (Roy et al. 2018; Roy et al. 2021, <https://github.com/nicholas-roy/psytrack>). The PsyTrack package fits the model through an
635 empirical Bayes procedure. The hyper-parameters are first selected by maximizing the model
636 evidence. Then the strategy weights were determined by the MAP estimate. The model hyper-
637 parameters and strategy weights were fit separately for every behavioral session.
638

639 Model performance was determined using the cross-validated model predictions as a classifier
640 to determine whether a mouse initiated a licking bout on each image interval. The receiver op-
641 erator curve determines the rate of true positives against false positives as a function of different
642 classifier thresholds. The area under the curve provides a summary statistic to compare mod-
643 els. Behavioral sessions were classified as visually dominant or timing dominant by determining
644 which strategy lead to the greater decrease in model evidence when that strategy was removed.
645

646 **Task Engagement**

647 Task engagement periods were determined by applying a threshold to the reward rate and lick
648 bout rate. Task engagement was determined for each image presentation interval. Both rates
649 were calculated by annotating which image presentations intervals had rewards and lick bout
650 initiation. We then smoothed across image presentations with a filter. We used a Gaussian
651 filter with standard deviation of 60 images. We then converted both rates into units of events
652 per second. We set the thresholds of 1 reward per 120 seconds and 1 lick bout per 10 seconds
653

654 through visual inspection of the behavioral landscape in figure 3A. If either rate was above its
655 threshold, then the interval was labeled engaged.

656

657 **Neural data**

658 For all analysis of neural data we used the detected calcium events as described in Garrett et al.
659 2023 and <https://portal.brain-map.org/explore/circuits/visual-behavior-2p>. This
660 process produces, for each cell, a set of calcium events each with a time and magnitude. Except
661 where noted we used familiar image set sessions collected on the multiplane calcium imaging rig.

662 To generate the population averages traces we compute the behavioral event triggered re-
663 sponse for each cell to each behavioral event and then average across all cells in each population.
664 We compute the behavioral event triggered response by isolating the calcium events around the
665 triggering behavioral event, then linearly interpolating onto a consistent set of 30hz timestamps
666 relative to the triggering behavioral event. This produces a vector of calcium event magnitudes
667 for each cell relative to each behavioral event (omission, image change, or repeat).

668 To generate the average calcium response across a time interval, we first compute the event
669 triggered response for each cell as described above. We then average across all time points in
670 the same image interval, producing a single scalar for each cell on each image interval. Average
671 calcium responses were computed for either the entire image interval (50, 800ms), the first half
672 of each image interval (50, 425ms), the second half of each image interval (425, 800ms), or a
673 more narrow stimulus locked window for excitatory cells (150, 250ms). We used a 50ms delay
674 for the image interval, (50, 800ms) rather than (0, 750ms), to account for signal propagation to
675 visual cortex.

676

677 **Hierarchical bootstrap analysis**

678 To determine significance for average calcium response metrics we applied a hierarchical boot-
679 strap method (Saravanan et al. 2020). On each bootstrap iteration we sampled with replacement
680 from first imaging planes, and then for each imaging plane we sampled with replacement from
681 cells from that plane. Averaging across all of these cells produces one bootstrap sample. For
682 all of our analyses, we used this procedure to generate 10,000 samples. The standard deviation
683 of this set of samples produces an estimate of the standard error of the mean. To performance
684 hypothesis testing we assigned samples from each condition into random pairs and performed
685 pairwise comparisons to determine what fraction of samples from each condition was greater or
686 less than the other condition. In this context an imaging plane is a specific cortical area and
687 depth from one behavioral session, so by sampling imaging planes we are effectively sampling
688 over sessions and mice. We corrected for multiple comparisons through the Benjamini-Hochberg
689 procedure (Benjamini et al. 2001).

690

691 **Running speed**

692 Running speed traces were processed in the same manner as calcium event traces. For each
693 behavioral session, we computed the event triggered running trace by isolating running time-
694 points around the triggering behavioral event then linearly interpolating onto a common 30hz
695 timeseries. We then averaged across all points in the relevant time window.

696

697 **Decoding analysis**

698 To decode task signals on an image by image basis we used a random forest classifier to predict
699 either image changes versus repeats (change decoder), or hits versus misses (hit decoder). We
700 iterated over the number, n , of simultaneously recorded neurons used in the decoding analysis.
701 For each imaging plane we sampled neurons and performed decoding until there was a 99%
702 probability all neurons had been used in decoding. For each sample we took n neurons without
703 replacement and concatenated their neural activity on each image presentation to make a $k \times nt$

704 matrix X . Here k is the number of images, and t is the number of timesteps from each neuron
705 on each image. The change decoder used each image change and the image repeat immediately
706 before the image change. The hit decoder used all image changes. We then performed 5-fold
707 cross validated decoding using the RandomForestClassifier package from *sklearn*. We evaluated
708 decoder performance as the percentage of test-set images correctly classified. We averaged the
709 performance of all samples from the same imaging plane and report summary statistics as the
710 mean \pm SEM over imaging planes. We computed the correlation between the change decoder's
711 predictions and the animal's choices using the phi coefficient.

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716 for developing the dynamic logistic regression model, the associated code package PsyTrack, and
717 helpful discussions.

718 Author contributions

719 AP conceived of the project, performed behavioral and neural analysis, and wrote the paper. NP
720 and DO performed behavioral analysis. DO, MG, PG, SO, and CK oversaw task development
721 and data collection. AA oversaw the project.

722 Data availability

723 All data used in this study is publicly available at [https://portal.brain-map.org/explore](https://portal.brain-map.org/explore/circuits/visual-behavior-2p)
724 [/circuits/visual-behavior-2p](https://portal.brain-map.org/explore/circuits/visual-behavior-2p)

725 Code availability

726 The behavioral analysis code is available at [https://github.com/alexpiet/licking_behav](https://github.com/alexpiet/licking_behavior/)
727 [ior/](https://github.com/alexpiet/licking_behavior/). The strategy model fits are available at [https://figshare.com/projects/Allen_Ins](https://figshare.com/projects/Allen_Institute_Visual_Behavior_Strategy_Paper/160972)
728 [titute_Visual_Behavior_Strategy_Paper/160972](https://figshare.com/projects/Allen_Institute_Visual_Behavior_Strategy_Paper/160972). The neural analysis code is available at
729 https://github.com/AllenInstitute/visual_behavior_glm.

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853 Supplemental Materials

854 The supplementary materials contains extended figures and control analyses for several as-
855 pects of the study:

- 856 1. Mouse behavior
- 857 2. Segmenting licks into licking bouts
- 858 3. Constructing the timing strategy
- 859 4. Model validation
- 860 5. Strategy characterization
- 861 6. PCA on model strategies
- 862 7. Strategy over training
- 863 8. Strategy behavior over time
- 864 9. Microcircuit dynamics
- 865 10. Running speed and task engagement
- 866 11. Transition to the novel image set

867 Supplemental Note 1 - Mouse behavior

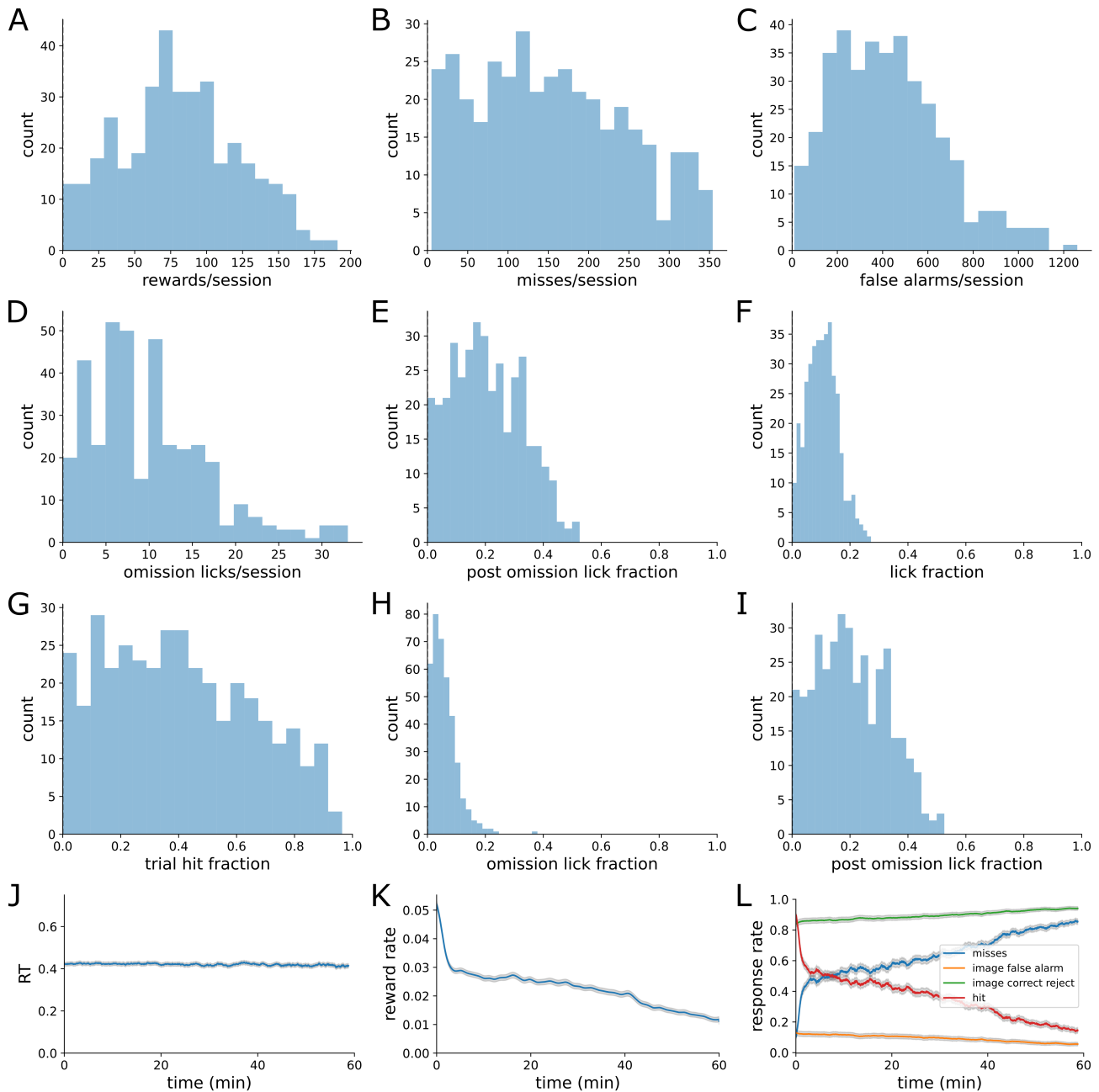


Figure 8: **Quantification of mouse behavior.** (A) Histogram of rewards/session. (B) Histogram of misses/session. (C) Histogram of false alarms / session. (D) Histogram of omissions with licks/session. (E) Histogram of post-omission-licks/session (F) Histogram of average lick fraction per session. (G) Histogram of fraction of image changes with licks per session. (H) Histogram of fraction of omissions with licks per session. (I) Histogram of fraction of post-omission images with licks per session. (J) Average Response latency over time. (K) Average reward rate over time. (L) Hit, Miss, False alarm, and correct reject rates over time.

868 Supplemental Note 2 - Segmenting licks into licking bouts

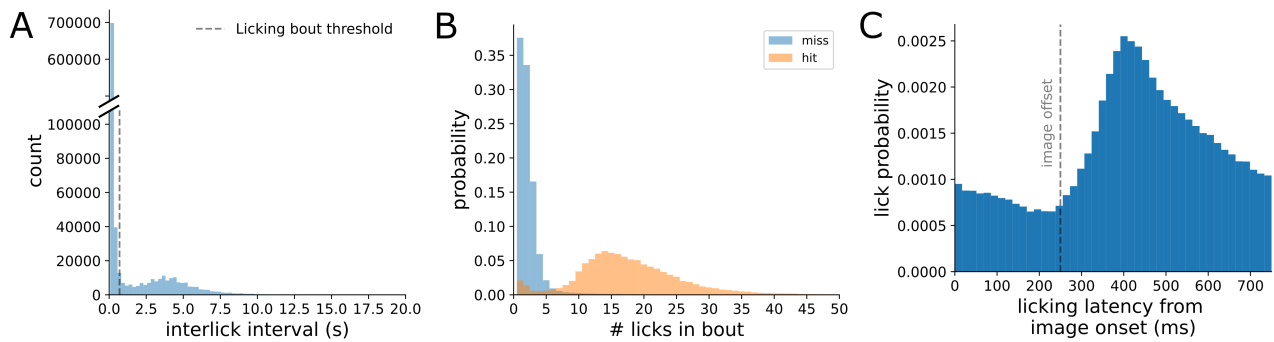


Figure 9: **Licks were segmented into licking bouts and aligned to image onset.** (A) Histogram of interval between successive licks ($n = 936,136$ licks from 382 imaging sessions). Dashed line indicates 700ms threshold used to separate licks within the same licking bout (< 700 ms) and licks in separate licking bout (> 700 ms). (B) Histogram of the number of licks in each licking bout separated by whether the licking bout earned a reward (hit) or did not (miss) ($n = 190,410$ licking bouts from 382 imaging sessions). (C) Histogram of the response latency for the start of each licking bout with respect to the most recent image onset ($n = 190,410$ licking bouts from 382 imaging sessions).

869 Supplemental Note 3 - Constructing the timing strategy

870 A subset of 45 sessions were used to construct the timing regressor. The strategy model
 871 was fit with 10 timing regressors, each using 1-hot encoding for different length delays since the
 872 image with the end of the last licking bout. Then a four parameter sigmoid was fit to the average
 873 weights of each of these 1-hot timing regressors. The equation of the four parameter sigmoid
 874 used to construct the timing regressor is given by:

$$y(t) = y_{min} + \frac{y_{max} - y_{min}}{1 + (t/a)^b}. \quad (4)$$

875 Here, y_{min} and y_{max} scale the vertical limits of the sigmoid, a controls the midpoint of the
 876 sigmoid, and b influences the slope of the sigmoid. The slope of the sigmoid at the midpoint is
 877 given by $-b/4a$. The parameters used in the full model were: $y_{min}=-1$, $y_{max}=0$, $a = 4$, $b = -5$.
 878 The timing regressor for each session was mean-centered.

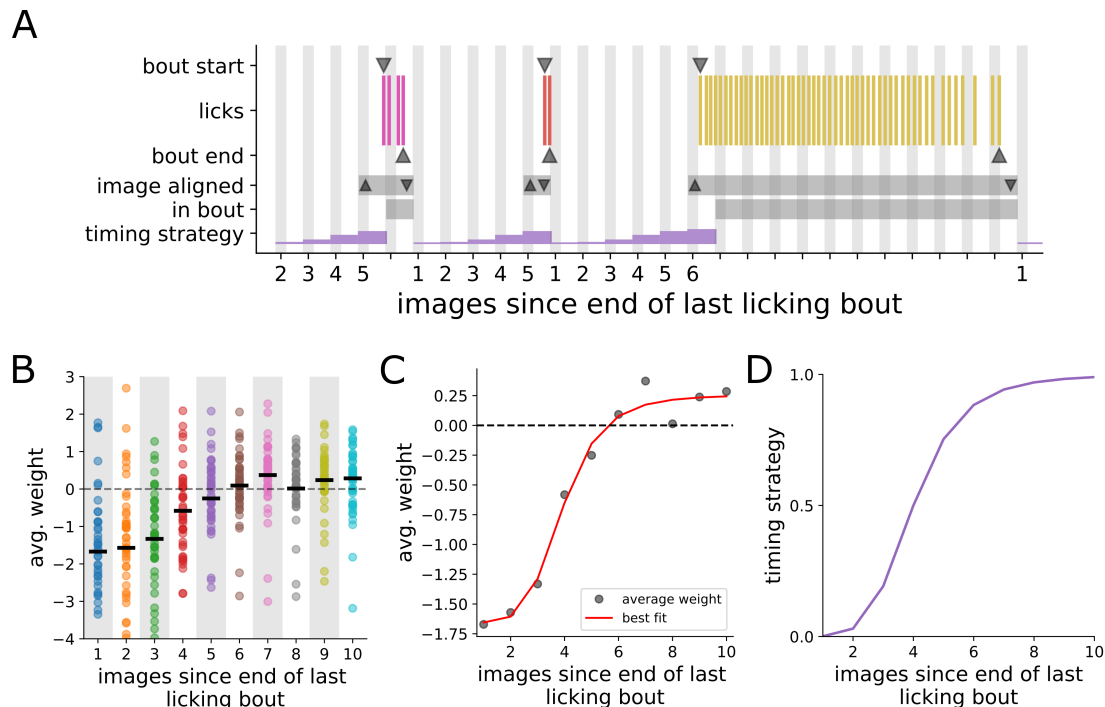


Figure 10: **Constructing the timing regressor.** (A) Schematic illustrating how timing is measured. Shaded bars indicate the time of stimulus presentations. Tick marks indicate the time of each lick. Individual licking bouts are colored separately. Down arrows (∇) indicate the start of each licking bout. Up arrows (Δ) indicate the end of each licking bout. Our model predicts whether the mouse will start a licking bout on each image presentation. Therefore images where the mouse was already in a licking bout are excluded from the fitting process. Consequently, our timing regressor starts measuring how many images have been presented since the end of the last licking bout starting at 1. The timing strategy is a sigmoidal function of time since the end of the last licking bout. Note the timing strategy is undefined on image when the mouse was already in a licking bout. (B) Average weight of each timing regressor (dots, $n=45$ sessions) Black bars indicate the average across sessions. (C) A four parameter sigmoid was fit to the average regressor weights from panel A (gray dots). The best fitting sigmoid is shown in red. (D) The timing strategy uses the midpoint and shape parameters from panel C, but scales the sigmoid to unit height. The strategy vector is later mean-centered.

879 Supplemental Note 4 - Model validation

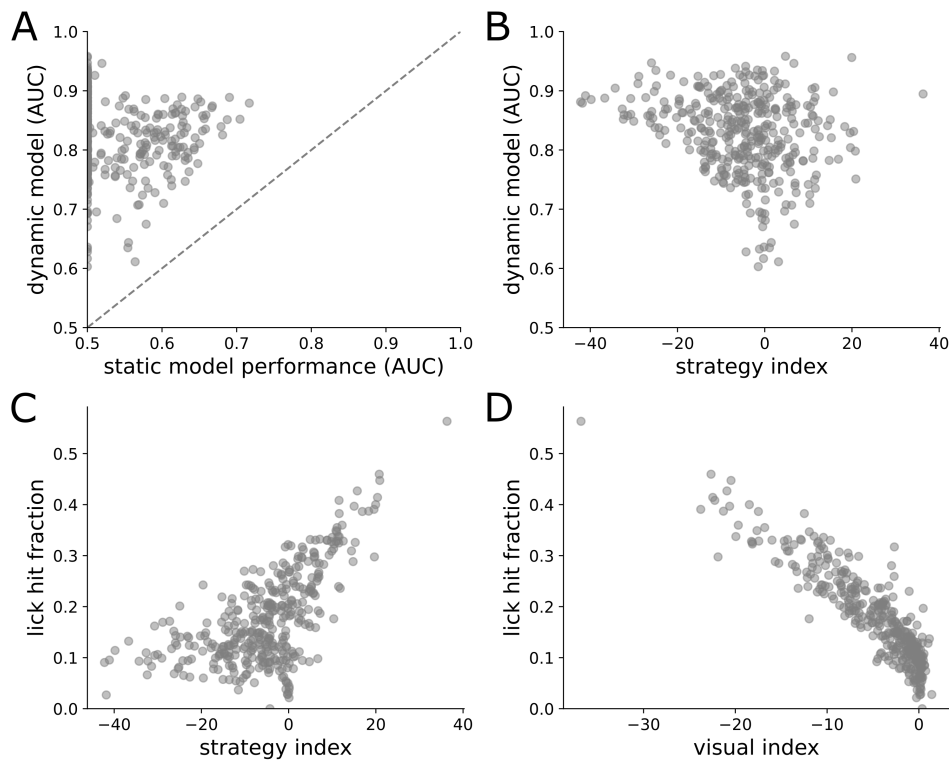


Figure 11: **Model validation.** (A) Scatter plot of area under ROC curves for each session for the dynamic model compared to static logistic regression (n=382 imaging sessions). Dashed line marks unity. (B) Scatter plot of area under ROC curves for each session for the dynamic model compared to the strategy index. (C-D) The lick hit fraction is the fraction of licking bouts that resulted in a reward. (C) Lick hit fraction compared to the strategy index. (D) Lick hit fraction compared to the visual strategy index.

880 Supplemental Note 5 - Strategy characterization

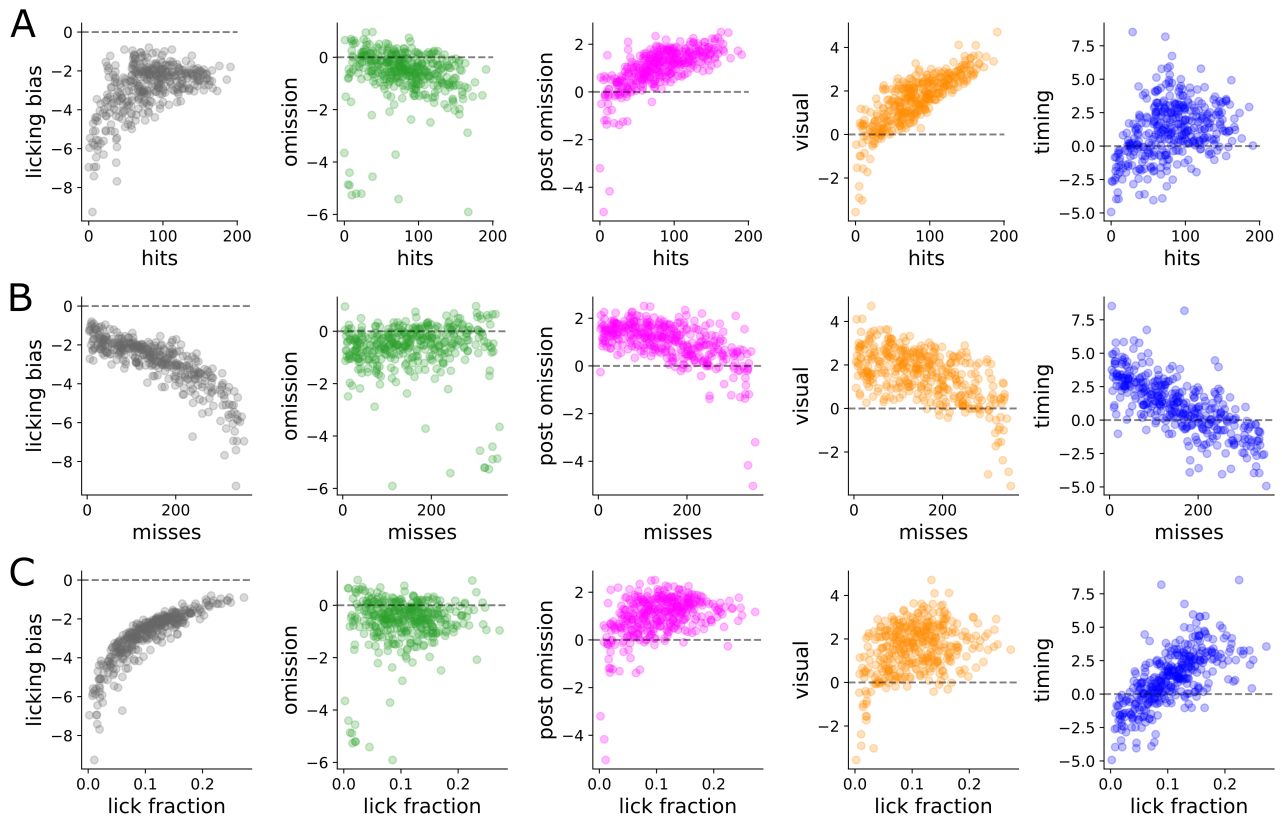


Figure 12: **Average strategy weights are correlated with task events.** Scatter plot between the average weight of each strategy and task events. Hits (A) are image changes with a reward, misses (B) are image changes without a reward, and lick fraction (C) is the fraction of images with a lick bout start.

881 Supplemental Note 6 - Principal Components Analysis

882 To assess the variability of strategies across our behavioral dataset we performed PCA on the
883 matrix of strategy indices containing 382 imaging sessions. Examining the component vectors
884 we find that the first component is primarily aligned with the timing strategy, while the second
885 is primarily aligned with the visual strategy. We find that these top two components contain
886 99.04% of the total variance (72.13% and 26.90%, respectively). Indeed, 98.24% of all variance
887 is contained in just the timing and visual strategy indices. This finding motivates our use of
888 the strategy index, which is simply the difference between the visual and timing indices. The
889 strategy index contains 59.95% of the total variance, and has a strong correlation with the top
890 principal component ($R^2 = 0.88$).

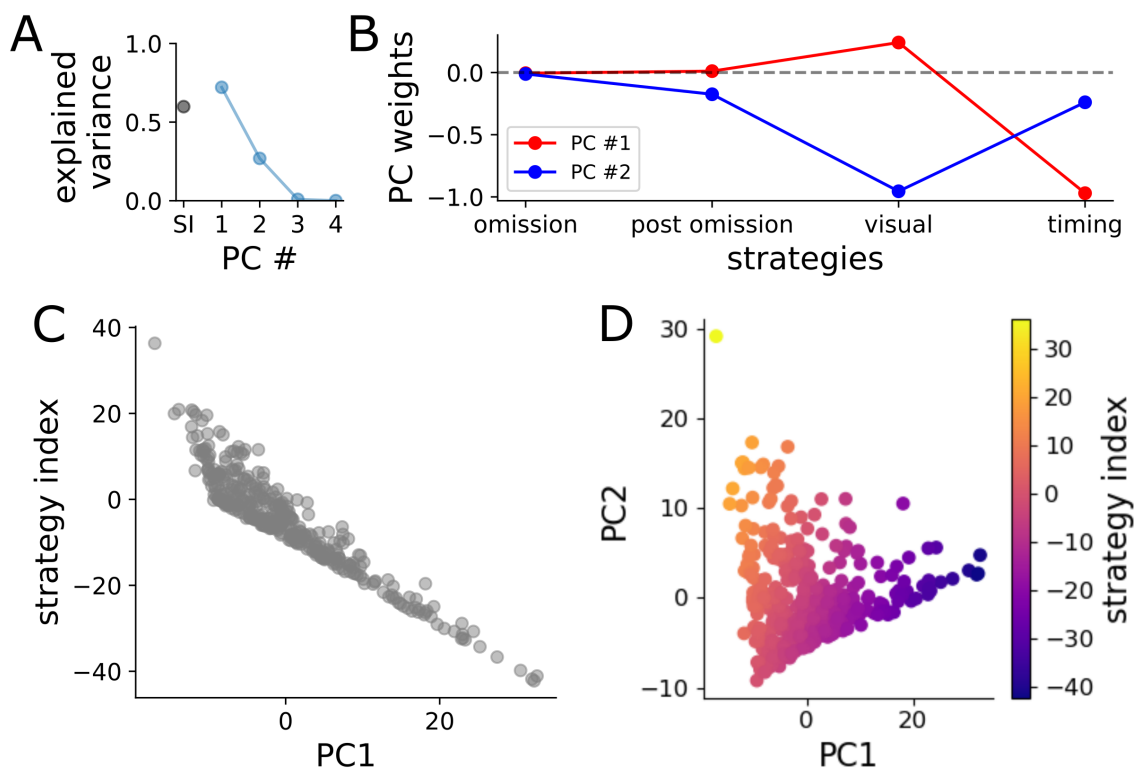


Figure 13: **Principal Components Analysis (PCA) on strategy index.** (A) Variance along each principal component (PC #), as well as the variance along the strategy index (SI). (B) The top two principal components are aligned with the timing and visual strategies, respectively. (C) Scatter plot between each session projected onto the first principal component and the strategy index. (D) All sessions (n=382 imaging sessions) projected onto the first two principal components and colored by the strategy index.

Supplemental Note 7 - Strategy over training

To examine how strategy preferences emerge with training, we classified mice by their dominant strategy (visual or timing) based on their behavior during imaging. We then fit our strategy model to the training sessions and examined how their strategy preferences changed over training. The training pipeline consisted of 7 stages before imaging:

- Training 0 - Mice learned to lick for rewards
- Training 1 - Mice earned rewards when a static grating changed orientation
- Training 2 - Static gratings were interleaved with a gray screen
- Training 3 - Static gratings are replaced with natural images
- Training 4 - Rewards decrease in size, and free rewards are no longer given when the mouse misses 10 changes in a row
- Training 5 - Performance must be consistently above a minimum threshold
- Habitation - Mice performed the task on the imaging rig
- Imaging - Mice performed the task with familiar images, then with novel images. Imaging was also performed during passive viewing of the same stimulus, which was not analyzed here.

We did not fit the model to training stages 0 and 1 because the stimulus was continuous and not periodically presented. In general we find strategy preferences emerge slowly over the training stages. Visual dominant mice significantly increased their use of the visual strategy over training (Fig. 13B), while decreasing their use of the timing strategy (Fig. 13C). Timing dominant mice showed less change in strategy use over training. Both strategies show decreases in the number of licking bouts (Fig. 13G), increases in the fraction of licking bouts that result in a reward (Fig. 13H), increases in the number of missed image changes (Fig. 13E), decreases in the fraction of the session they are engaged (Fig. 13F), while maintaining or slightly increasing the rewards per session (Fig. 13D). As mice increase their lick hit fraction, they need to lick less often to earn the same number of rewards. By increasing their lick hit fraction, this means they are licking on image changes more often rather than licking early which delays the next image change. Increasing their lick hit fraction means they can earn more rewards in less time, and thus they disengage earlier and miss more image changes while they are disengaged.

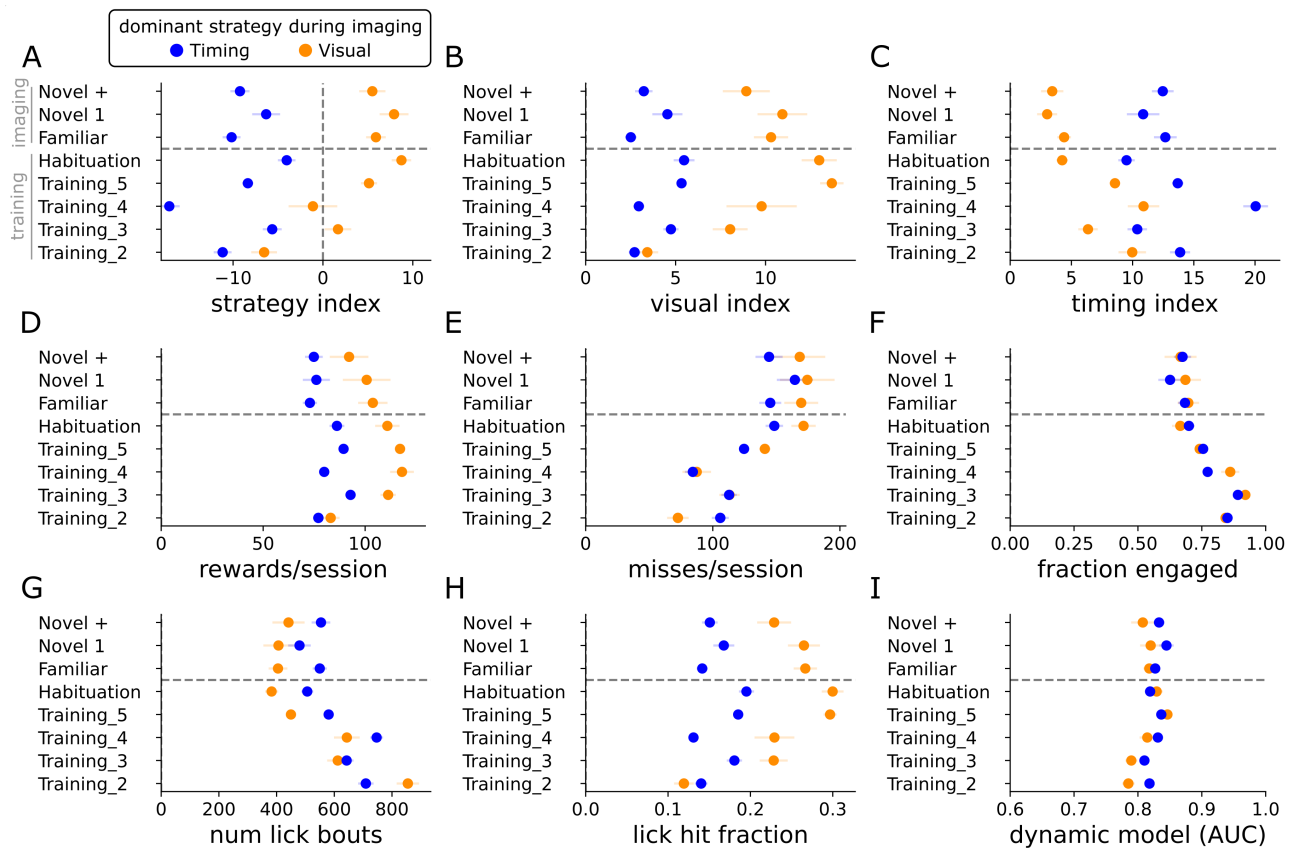


Figure 14: **Strategy over training** Metrics as described in Supplemental Note 1. Each dot shows mean \pm SEM for each strategy group.

920 **Supplemental Note 8 - Strategy behavior over time**

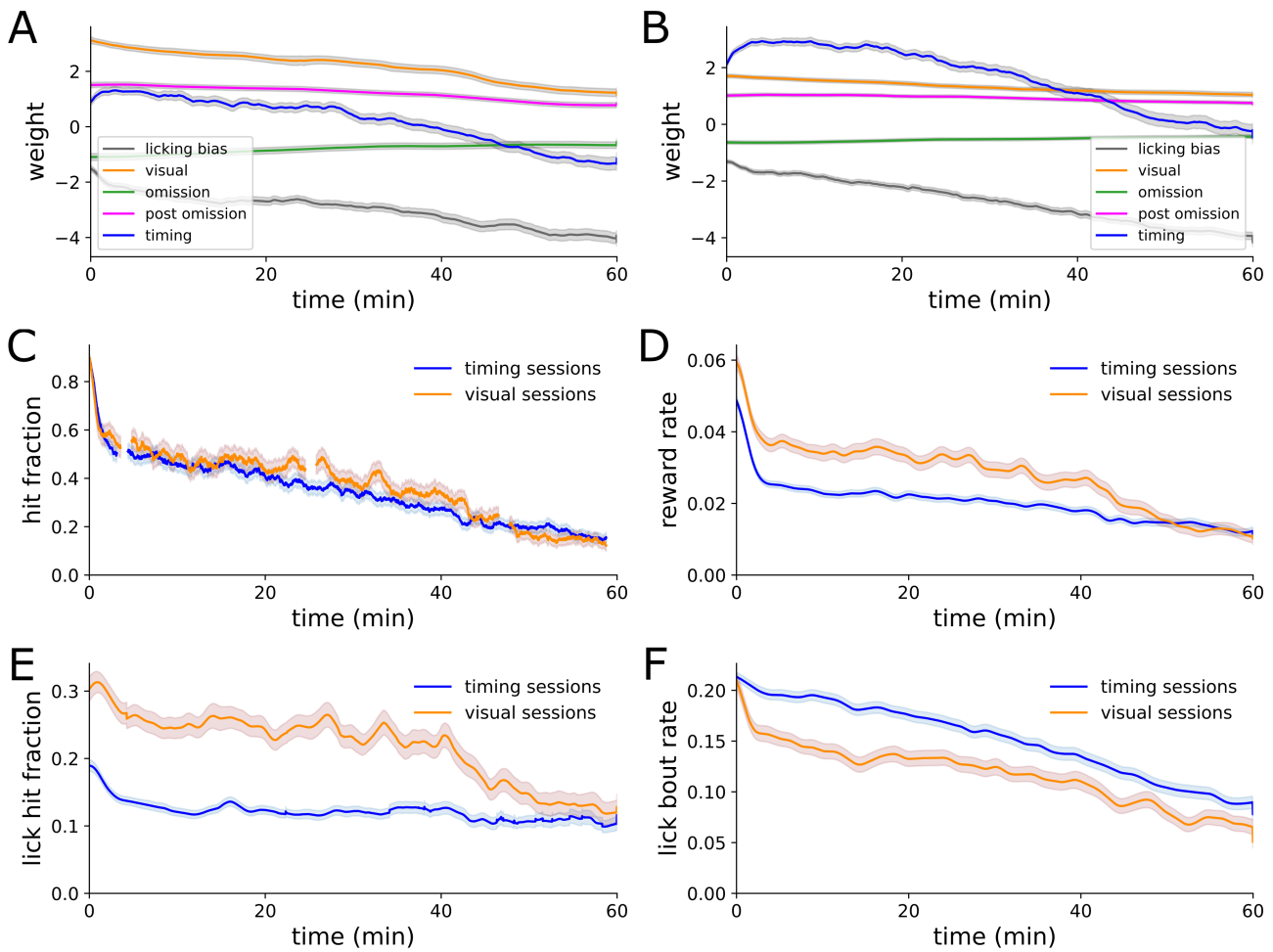


Figure 15: **Strategy behavior over time.** (A) Average strategy weights over time for visual strategy sessions (n = 116 sessions). (B) Same as A but restricted to timing strategy sessions (n=260 sessions). (C) Hit fraction split by visual or timing strategy sessions. (D) Reward rate split by visual or timing strategy sessions. (E) Lick hit fraction split by visual or timing strategy sessions. (F) Lick bout rate split by visual or timing strategy sessions.

921 Supplemental Note 9 - Microcircuit dynamics

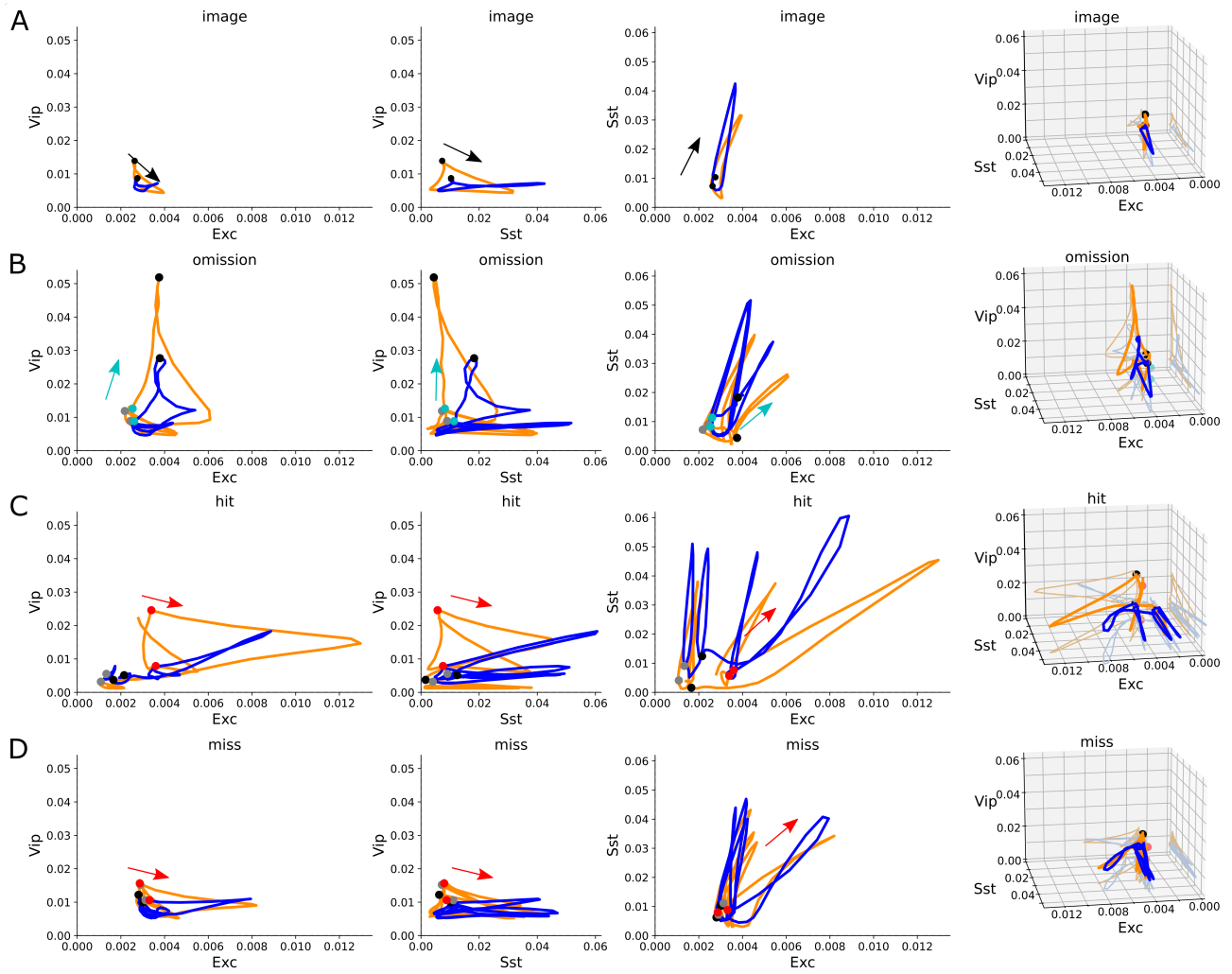


Figure 16: **Microcircuit dynamics** Average population activity of different cell classes plotted against each other, similar to figure 5D. In response to (A) image repeats, (B) image omissions, (C) hits, and (D) misses. NOTE - need to polish, remove Vip-Sst vs Exc column, add 3D plots.

922 **Supplemental Note 10 - Running speed and task engagement**
923

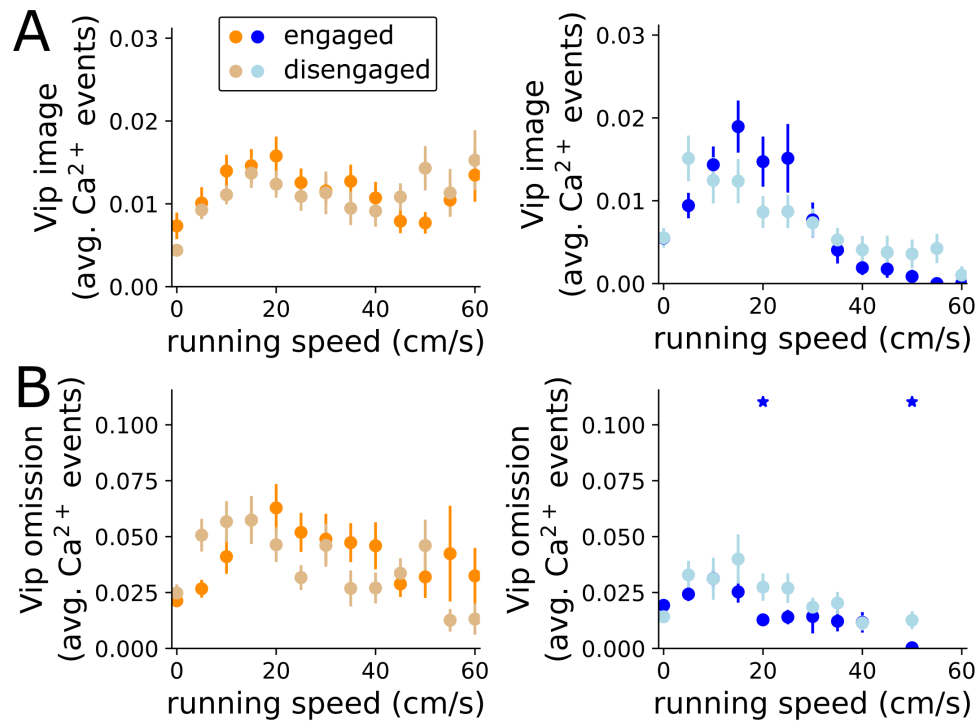


Figure 17: **Running speed and task engagement.** Similar to 4F,G. Vip activity in response to images and omissions across running speeds split by dominant strategy and task engagement. Stars indicates $p < 0.05$ after a hierarchical bootstrap across imaging planes and cells, then corrected for multiple comparisons.

924 Supplemental Note 11 - Transition to the novel image set

925 The mice were trained on one set of 8 images, we refer to this as as the familiar image set.
926 After imaging during the familiar image set, the mice were transitioned to a new set of 8 images
927 termed here as novel image set. We compare how this transition influenced mouse strategy.
928 The familiar session is the last session using the familiar image set. Novel is the first exposure
929 to the new image set. Novel+ is a repeated exposure to the new image set. The transition to
930 novel stimuli is explored in-depth in Garrett et al. 2023. We make two notes here relevant to
931 task strategy. First, there is a small but significant shift in the strategy index on novel sessions
932 towards more visual strategy. Second, both strategies show the neural effects of novelty explored
933 in Garrett et al. 2023. Thus any differences in strategy cannot explain the effects of novelty.
934 Broadly, during the novel session we see increased Vip activation in response to image repeats,
935 omissions, and before hits.

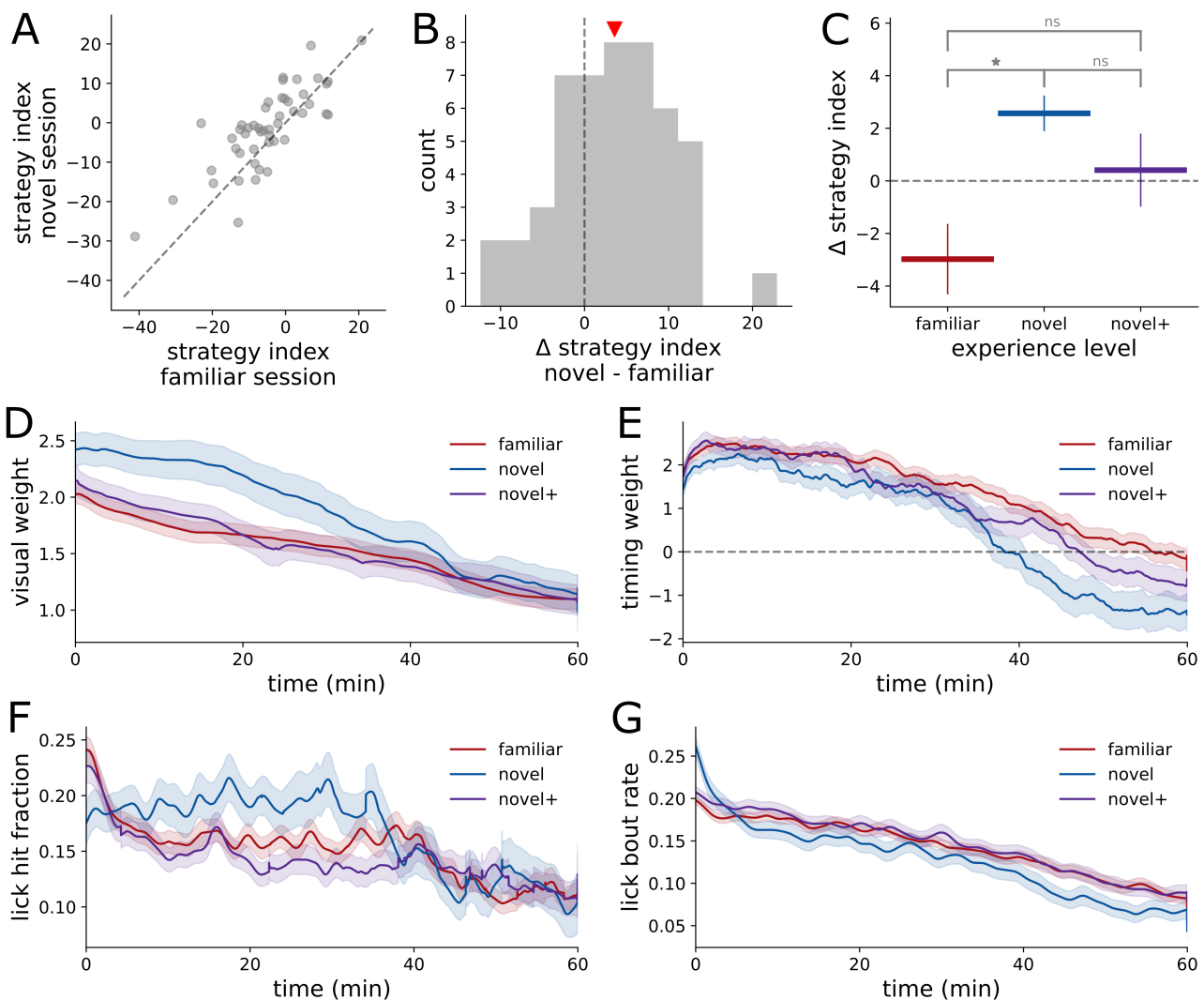


Figure 18: **Stimulus novelty has a small influence on strategy.** (A) Scatter plot of the strategy index for familiar and novel sessions. Each dot is a pair of sessions from the same mouse. (B) Histogram of the difference between strategy index on the novel session compared to the familiar session. (C) Average value of the strategy index across all mice relative to each mouse's average strategy index value. Significance determined with a paired t-test, $p < 0.05$. (D) Visual strategy weight over time split by experience level. (E) Same as D but for the timing strategy weight. (F) Lick hit fraction over time split by experience level. (G) Lick bout rate split by experience level.

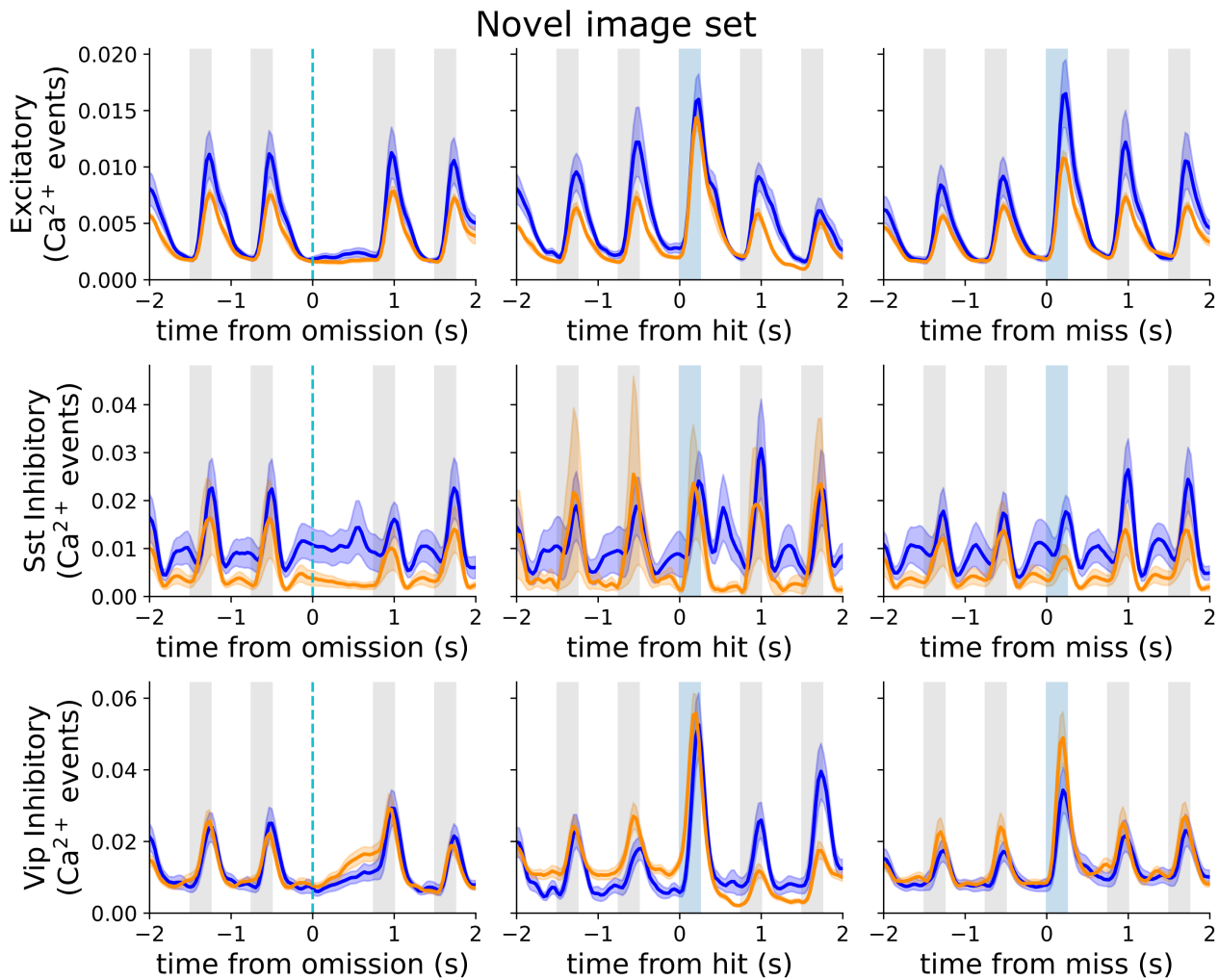


Figure 19: **Both dominant strategies show robust changes to novel stimuli** Average population activity on sessions with novel stimuli for each cell class split by strategy aligned to either image omissions (left), hits (center), or misses (right). Compare with figure 4D, which show population activity on sessions with familiar stimuli.