Title:

Frontal Cortex Gates Distractor Stimulus Encoding in Target Sensory Cortex

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Abstract:

Suppressing behavioral responses to distractor stimuli is a fundamental cognitive process, essential for performing goal-directed tasks. A common framework for the neuronal implementation of distractor suppression is the attenuation of distractor stimuli from early sensory to higher-order processing. However, details of the localization and mechanisms of attenuation are poorly understood. In this study, we trained mice to selectively respond (lick) to whisker deflections from one whisker field and ignore identical deflections from the opposite whisker field. We found that suppression of frontal cortex, aligned to the target stimulus or the distractor stimulus, increases responses to distractors (false alarms). By simultaneously recording spiking activity in the mouse whisker region of primary somatosensory cortex (S1), we found that frontal cortex selectively suppresses the neuronal encoding of distractor stimuli in target-aligned S1. Frontal cortex decorrelates the encoding of target and distractor stimuli in single units, thereby increasing stimulus selectivity across the population of target-aligned S1 neurons. Even before stimulus onset, effects of frontal cortex on S1 were robust and context-dependent, indicating proactive modulation. Overall, our study provides important mechanistic details about the roles of frontal cortex in gating sensory responses in sensory cortex.

Key words: frontal cortex; sensory cortex; sensorimotor interaction; top-down; sensory gating; inhibitory control

Major findings (declarative statements):

1. Behavior: Suppressing either target-aligned or distractor-aligned frontal cortex increases behavioral responses to distractor stimuli.

2. Population neuronal encoding: Suppressing target-aligned frontal cortex increases distractor stimulus encoding in target-aligned S1.

3. Single unit neuronal encoding: Frontal cortex decorrelates encoding of target and distractor stimuli in target-aligned sensory cortex.

4. Proactive modulation: Frontal cortex modulation of sensory cortex pre-stimulus is robust and context-dependent.

Introduction:

To achieve our goals, we must respond to task-relevant target stimuli and not respond to task-irrelevant distractors. The ability to suppress responses to distractor stimuli is a component of impulse control, which is a core cognitive process. Impairments in distractor response suppression underlie some of the behavioral and cognitive dysfunctions in neuropsychiatric disorders such as attention-deficit/hyperactivity disorder (ADHD), obsessive–compulsive disorder, and substance abuse disorder (Chamberlain & Sahakian, 2007; Hester & Garavan, 2004).

Frontal cortex is an essential mediator of distractor response suppression. Wide-ranging studies across multiple species and sensory modalities have shown that disruptions of frontal cortex impair the ability to suppress behavioral responses to distractor stimuli (including the rhinal sulcus [Eichenbaum et al., 1983], prefrontal cortex (Konorski, 1972; Li et al., 2020), frontal lobe [Leimkuhler & Mesulam, 1985; Markowitsch & Pritzel, 1977; Picton et al., 2007; Salmaso & Denes, 1982], frontal pole [Eichenbaum et al., 1974] , orbital frontal cortex [Buia & Tiesinga, 2008; Kolb et al., 1974], inferior frontal convexity [Iversen & Mishkin, 1970], motor cortex [Zagha et al., 2015], left or right inferior frontal gyrus [Swick et al., 2008], cingulate cortex [Bussey et al., 1997; Hvoslef-Eide et al., 2018]). In healthy human subjects, enhanced activation in the frontal cortex correlates with enhanced distractor response suppression (Carter et al., 1998; Li et al., 2006; Rubia et al., 2001). And yet, the mechanisms by which frontal cortex mediates distractor response suppression are poorly understood.

There are many possible mechanisms by which frontal cortex may suppress responses to distractors. One set of hypotheses is that frontal cortex attenuates the generation and propagation of distractor-evoked neuronal activity in sensory cortices (Desimone & Duncan, 1995; Gilbert & Li, 2013; Zagha, 2020). In a pioneering study, Moran and Desimone (1985) showed that when target and distractor stimuli are presented within the receptive field of a higher order sensory neuron, spiking responses to the distractor stimulus are highly reduced. While it has been proposed that top-down signals from frontal cortex may contribute to this selectivity (Desimone & Duncan, 1995), experimental evidence for this is lacking. More recent studies have also shown modulations of the spatial tuning of receptive fields during selective detection (Fritz et al., 2003; Fritz et al., 2010; Niebergall et al., 2011; Womelsdorf et al., 2008). Alternatively, other studies have emphasized the potential roles of frontal cortex in enhancing neuronal responses to target stimuli and suppressing neuronal responses to spatially-offset distractor stimuli, through center-surround interactions (Angelucci et al., 2002; Hupé et al., 1998; Keller et al., 2020; Moore & Armstrong, 2003; Nassi et al., 2013; Zhang et al., 2014). However, many details regarding the functional relationships between frontal and sensory cortex remain unresolved, due to the lack of experimental data from combined recording and perturbation experiments in subjects while they are performing target-distractor discrimination tasks. This study explores the following unresolved questions regarding frontal cortex contributions to distractor response suppression. 1) What are the consequences of suppressing target-aligned versus distractor-aligned frontal cortices on behavioral responses to target and distractor stimuli? 2) What are the consequences of suppressing target-aligned versus distractor-aligned frontal cortices on single unit spiking responses to target and distractor stimuli in sensory cortex, during task performance? 3) To what extent are the impacts of frontal cortex on sensory cortex context-dependent (awake behaving vs. anesthetized, task engaged vs. task unengaged) and/or proactive (impacting sensory cortex even before stimulus onset)?

In this study, we trained mice in a selective whisker detection task, in which they learn to respond to rapid stimuli in one whisker field (target) and ignore identical stimuli in the opposite whisker field (distractor). Given the lateralization of the sensorimotor system in the mouse brain, this task establishes clear assignments of target-aligned and distractor-aligned hemispheres, contralateral to the site of sensory stimulation. Using this task, we previously demonstrated similar target and distractor stimulus encoding in the whisker region of primary somatosensory cortex (S1), yet highly attenuated propagation of distractor stimulus responses to frontal cortex (Aruljothi et al., 2020; Zareian et al., 2022). Here, we focus on top-down inputs onto S1 from whisker motor cortex (wMC), which is the frontal cortex region most robustly connected with S1. Stimulation and suppression studies have found robust yet varied impacts of wMC activity on S1, including through excitation (Jung et al., 2022; Lee et al., 2008; Manita et al., 2015; Petreanu et al., 2012; Rocco & Brumberg, 2007; Xu et al., 2012; Zagha et al., 2013), inhibition (Kinnischtzke et al., 2014; Zagha et al., 2016), and dis-inhibition (Lee et al., 2013). The impacts of wMC on S1 in the context of distractor suppression is unknown.

Results:

Performance in a selective detection task

Mice were trained to respond to target stimuli in one whisker field and ignore distractor stimuli in the opposite whisker field (Fig 1 A,B,C). Given the lateralization of the mouse whisker representation, this task establishes target-aligned and distractor-aligned cortices that are symmetric across hemispheres and contralateral to the site of stimulus delivery. Performance in this task was quantified based on behavioral responses on target trials (hit rate), on distractor trials (false alarm rate), and on catch trials (spontaneous response rate). Mice were considered expert in this task once they achieved a discrimination d prime (separation of hit rate and false alarm rate) greater than 1, for three consecutive days. Optogenetic perturbations and electrophysiological recordings were performed in expert mice while performing the selective detection task. Two stimulus amplitudes were applied in each session (equal for target and distractor trials): 'large' amplitude stimuli near the saturation of the hit rate psychometric curve and 'small' amplitude stimuli within the dynamic range. Unless otherwise indicated, our data analyses refer to the large amplitude stimuli.

Either target-aligned or distractor-aligned wMC suppression increases false alarms

We tested the impacts of wMC optogenetic suppression on task performance. Focal suppression was achieved by optical activation of GABAergic interneurons in either target-aligned or distractor-aligned wMC (Fig 1 D,F). Suppression was initiated 100-200 ms before stimulus onset, and was robust and stable throughout the post-stimulus lockout window (Fig 2A, Fig 3A). Control trials (light-off) and wMC suppression trials (light-on) were randomly interleaved. Interestingly, suppression of target-aligned or distractor-aligned wMC increased large (Fig 1G) and small (Supplementary Fig 1A,B) stimulus false alarm rates (target-aligned: large stimulus false alarm rate: n=28 sessions, light-off: 0.33±0.02, light-on: 0.54±0.04, paired test: $p=2.70\times10^{-7}$, MI=0.26±0.04, one sample t test: $p=6.00\times10^{-7}$; distractor-aligned: large stimulus false alarm rate: n=19 sessions, light-off: 0.26±0.03, light-on: 0.46±0.05, paired test: $p=5.00\times10^{-4}$, MI=0.27±0.06, one sample t test: $p=2.75\times10^{-4}$). Across the same sessions we did not observe significant changes in large stimulus hit rates (target-aligned: hit rate: n=25 sessions, light-off: 0.95±0.03, light-on: 0.96±0.02, paired test: p=0.67, MI=0.01±0.01, one sample t test: p=0.434, distractor-aligned: hit rate, n=15 sessions, light-off: 0.93±0.02, light-on: 0.93±0.02, paired test: p=0.92, MI=0.00±0.01, one sample t test: p=0.8876) (Fig 1G) or spontaneous response rates (Supplemental Fig 1). Suppression of target-aligned or distractor-aligned wMC caused trends towards increased small amplitude hit rates (with statistical significance depending on calculation method, Supplementary Fig 1A,B). These data support wMC function in suppressing behavioral responses, most robustly for distractor stimuli.

To determine the specificity of this effect, we additionally tested the impacts of S1 optogenetic suppression on task performance (Fig 1E). Suppression of target-aligned S1 resulted in significantly decreased small amplitude hit rates (Supplementary Fig 1C) and trends towards decreased hit rates and false alarm rates for large amplitude stimuli (Fig 1G). Decreased response rates during S1 suppression contrast with increased response rates during wMC suppression. These data suggest different functions of S1 and wMC in this task, with S1 promoting and wMC suppressing behavioral responses.

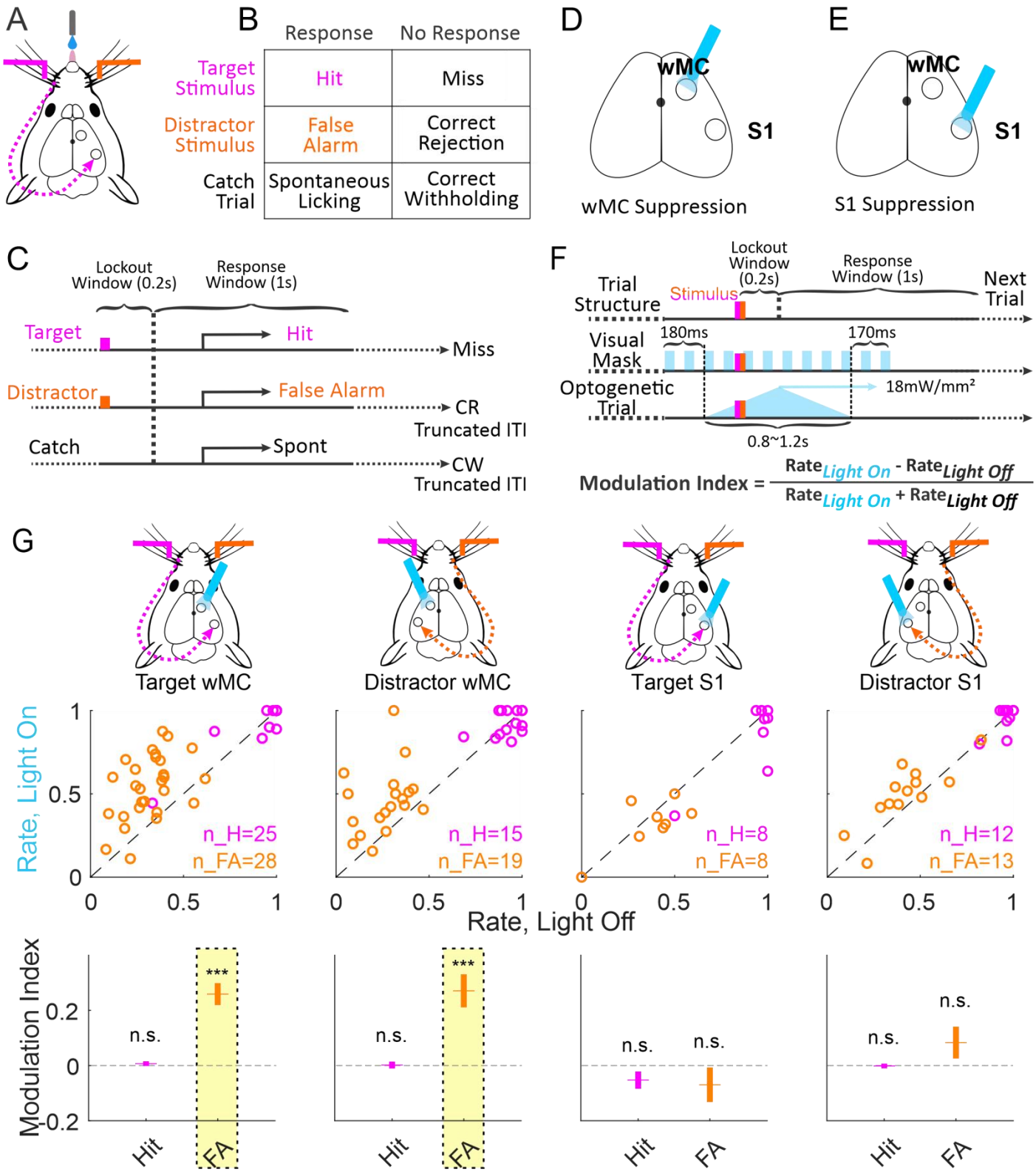

Figure 1: Suppressing either target-aligned or distractor-aligned wMC increases false alarm (FA) rates. (A) Illustration of the behavioral task setup. Mice are head-fixed in the behavioral rig with piezo-controlled paddles within their whisker fields bilaterally. Stimulus-triggered neural responses propagate to S1 in the contralateral hemisphere. (B) Task trial types and outcomes: for each trial there can be a target stimulus (hit or miss), a distractor stimulus (false alarm or correct rejection), or no stimulus catch trial (spontaneous licking or correct withholding). (C) Task structure: after whisker stimulus onset there is a 0.2s lockout window, followed by a 1s response window. Responding outside of the response window is punished by a time-out (resetting the inter-trial interval, ITI). Correct rejection and correct withhold are rewarded by a shortened ITI and subsequent target trial. Hits are rewarded with water dispensed from the central lick port. (D, E)

Illustration of the optogenetic suppression design, in VGAT-ChR2 transgenic mice. Optogenetic suppression (blue light on) of wMC or S1 was performed on 33% of trials, randomly interleaved with control (light off) trials. (F) Features of optogenetic stimulation: the optogenetic light (blue triangle) starts ramping up before the whisker stimulus, peaks after stimulus onset, and ramps down during the response window. A 10 Hz pulsing visual mask, present on all trials, fully covers the duration of optogenetic suppression. Modulation index is used to quantify changes in response rates, with positive modulation indices indicated higher response rates during optogenetic suppression. (G) Hit rates and false alarm rates for optogenetic light on trials and control light off trials across all sessions for suppression of target-aligned wMC (1st column), distractor-aligned wMC (2nd column), target-aligned S1 (3rd column), and distractor-aligned S1 (4th column). The top row indicates the site of optogenetic suppression. The middle row displays hit rates (magenta) and false alarm rates (orange), each circle reflecting one behavioral session. The bottom row displays the modulation indices calculated based on the middle row data. All the p values are indicated as: n.s. ($p>=0.05$), *($0.01<=p<0.05$), **($0.001<=p<0.01$), or ***($p<0.001$) throughout the article.

Suppressing target-aligned wMC increases distractor stimulus encoding in target-aligned S1

One of the main output projections from wMC is to S1, through both the direct feedback pathway and indirect cortico-thalamo-cortical pathways (Aronoff et al., 2010; Manita et al., 2015; Mao et al., 2011; Sato & Svoboda, 2010; White & DeAmicis, 1977). Therefore, we sought to determine the consequence of wMC suppression on sensory encoding in S1. We recorded spiking activity of single units in layer 5 S1 during task performance, with and without optogenetic wMC suppression (Fig 2A). wMC suppression reduced baseline firing rates for all conditions (Fig 2B, characterized further below and in Fig 4). Here we focus on the effects of wMC suppression on stimulus encoding, as determined by population neurometric analyses (Fig 2C). Specifically, we conducted these analyses to assess how target-aligned wMC suppression changes target-aligned S1 encoding for target and distractor stimuli (Fig 2D-F), and how distractor-aligned wMC suppression changes distractor-aligned S1 encoding for distractor and target stimuli (Fig 2G-I).

We first report stimulus encoding with wMC intact (control trials, black and gray data in Fig 2E,F,H,I). We refer to preferred stimuli (target stimuli for target-aligned S1, distractor stimuli for distractor-aligned S1) and unpreferred stimuli (distractor stimuli for target-aligned S1, target stimuli for distractor-aligned S1). Target-aligned and distractor-aligned S1 encoded their preferred stimuli robustly and at short latency, peaking at 40~45 ms post-stimulus (Fig 2E,H). Additionally, distractor-aligned S1 showed robust encoding of unpreferred (target) stimuli, peaking at approximately 60~80 ms post-stimulus (Fig 2I). This longer latency is consistent with a longer pathway for unpreferred stimuli to reach S1. In marked contrast, we observed a slight negative encoding of distractor stimuli in target-aligned S1 (-0.02±0.02, averaged over the 100 ms window, n=17 sessions; significant during 60-85 ms post stimulus window, indicated by the green bar: one sample t test for all 17 sessions in each sliding window, 60-80ms: $p=0.05$; 65-85ms: $p=0.04$) (Fig 2F). Accordingly, unpreferred stimulus encoding in distractor-aligned S1 was significantly larger than in target-aligned S1 (two sample t test, $p=9.54\times10^{-7}$ [neurometric averaged across 100 ms]). Thus, ignoring distractor stimuli is correlated with reduced encoding of distractor stimuli in target-aligned S1 (compared to the encoding of target stimuli in distractor-aligned S1).

Next, we report the effects of wMC suppression on S1 stimulus encoding (blue and dark green data in Fig 2E,F,H,I). wMC suppression marginally increased target stimulus encoding in target-aligned S1 (Fig 2E), which we interpret as wMC marginally suppressing target stimulus encoding under control conditions. wMC suppression did not significantly impact distractor-aligned S1 encoding of distractor (preferred) (Fig 2H) or target (unpreferred) stimuli (Fig 2I). However, wMC suppression did significantly increase target-aligned S1 encoding of distractor (non-preferred) stimuli (Fig 2F) (two sample t test, $p<0.05$ during 30-100 ms post stimulus window). This effect was present from 30-100 ms post-stimulus, well before the response time (minimum 200 ms), and similar to the latency of unpreferred stimulus encoding in distractor-aligned S1. From these data, we conclude that the main impact of wMC on sensory encoding is to suppress the 'spillover' of

distractor stimulus responses into target-aligned S1. Moreover, this neurometric finding is consistent with, and indeed may contribute to, the increased false alarm rates during wMC suppression (Fig 1G).

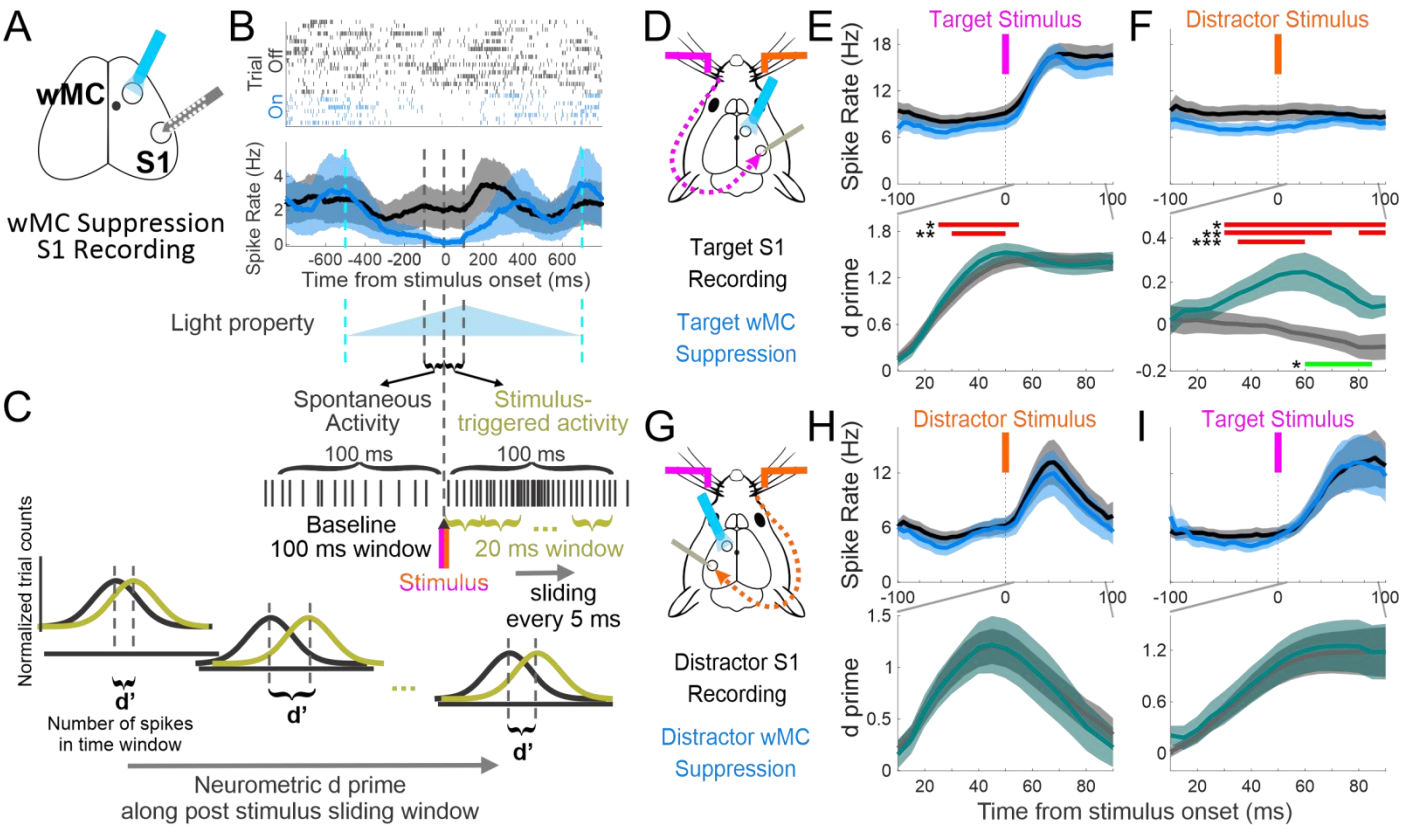

Figure 2: Suppressing target-aligned wMC increases distractor stimulus encoding in target-aligned S1. (A) Illustration of simultaneous optogenetic suppression in wMC and extracellular silicon probe recordings in S1. (B) The effects of wMC suppression on S1 multi-unit spiking activity, demonstrated from one anesthetized recording session (only catch trials are shown). Top plot: raster plots of neuronal spiking for multiple trials. Middle plot: averaged neuronal spike rates from the data above. Black, light off control trials; blue, light on optogenetic suppression trials. Bottom plot: time course of optogenetic stimulation. (C) Illustration of our method of calculating neuronal d prime (d'). In non-catch trials, a whisker stimulus is introduced during the late ramping up phase of optogenetic suppression. Neuronal activity from 100ms windows before and after whisker stimulus onset are assigned as spontaneous activity (stimulus absent) and stimulus-triggered activity (stimulus present), respectively. To generate a neurometric time series, we use a 20 ms sliding window across the 100ms post-stimulus period (with duration-matched samples from the pre-stimulus window, see Methods). (D) Experimental design illustration for [E, F]: recording in target-aligned S1, suppression of target-aligned wMC, target stimulus is preferred and distractor stimulus is unpreferred. (E, F) Neuronal activity (top) and d prime (bottom) of target-aligned S1 neurons during control trials (light off, black/gray) and wMC suppression trials (light on, blue/dark green) in response to target [E] or distractor [F] stimuli. The d prime time series only reflects the post-stimulus window. Data are grand averages, combined from all recording sessions. The red bars indicate the epochs in which d prime during wMC suppression is significantly different from control trials. The green bar in [F] indicates the epoch in which d prime in control trials is significantly below zero. (H, I) As same as [E, F] but for distractor-aligned S1 neurons during distractor-aligned wMC suppression. Note, the most robust effect of wMC suppression is increased distractor stimulus encoding in target-aligned S1 [F]. For neuronal activity perturbations across all stimulus categories, see Supplemental Fig 2.

Target-aligned wMC decorrelates target and distractor stimulus encoding in target-aligned S1 excitatory neurons

In the analyses described above we report population activity (from summed single units). Here, we conducted single unit analyses, segregated into putative excitatory and inhibitory neurons based on opto-tagging (Fig 3A and Supplemental Fig 3). Below, we focus our analyses on putative excitatory neurons, as the output of S1.

First, we present the activity of one example excitatory neuron in target-aligned S1 (Fig 3B). In control (light off) conditions (Fig 3B, left), this neuron responds robustly to target stimuli, but not to distractor stimuli. During wMC suppression (Fig 3B, right), responses to target stimuli are maintained, yet now we observe increased responses to distractor stimuli. We interpret this finding as reduced stimulus selectivity, in which this neuron increases its apparent receptive field size to now include distractor (unpreferred) inputs. This suggests that an important function of wMC is to gate out distractor stimulus responses from target-aligned S1 neurons.

We recognize two potential mechanisms by which wMC may gate distractor stimulus responses in target-aligned S1 (Fig 3C). First, there could be a shift of the entire population, such that throughout the distribution of S1 neurons there is a proportional reduction of distractor encoding (Gating model 1, Fig 3C, middle). Second, there could be a rotation in the distribution of S1 neurons, such that encoding of target and distractor stimuli are decorrelated in individual neurons (Gating model 2, Fig 3C, bottom). To distinguish between these mechanisms, we plotted the distribution of preferred (contralateral) and unpreferred (ipsilateral) stimulus encoding (neuronal d' over a 0-100ms post stimulus window compared to pre-stimulus, see Methods) from target-aligned S1 neurons, distractor-aligned S1 neurons, and from S1 neurons in naïve, anesthetized mice (Fig 3D-G). We first describe stimulus selectivity profiles in control light off conditions. In anesthetized mice (Fig 3D,G, green), S1 neurons displayed a slight positive correlation, such that the neurons with the strongest encoding of preferred stimuli also positively encode unpreferred stimuli (95% confidence interval of the slope of the linear fit: 0.07-0.21, for n=200 single units). During task performance, distractor-aligned and target-aligned S1 neurons displayed remarkably different stimulus selectivity profiles. Distractor-aligned S1 neurons were less selective than the anesthetized population, with a more positive slope to the linear fit of their stimulus response correlations (95% confidence interval of the slope of the linear fit: 0.23-0.57, for n=117 single units) (Fig 3E,G, orange). In contrast, target-aligned S1 neurons were more selective than the anesthetized population, with a flat, trending to negative, slope to the linear fit of their stimulus response correlations (95% confidence interval of the slope of the linear fit: -0.10-0.01, for n=197 single units) (Fig 3F,G, pink). That is, across target-aligned S1 neurons, target and distractor stimulus encoding is decorrelated.

Next, we tested the impact of wMC suppression on stimulus selectivity, starting with target-aligned S1. As shown in Fig 3F (blue), wMC suppression caused a rotation in the stimulus selectivity of target-aligned S1 neurons, such that now there was a positive slope to the population stimulus response correlation (95% confidence interval of the slope of the linear fit: 0.08-0.19). Thus, wMC contributes to sensory selectivity and distractor suppression in target-aligned S1. Moreover, this rotation in stimulus correlation space (Fig 3F bottom) is consistent with the 'Gating 2' model shown in Fig 3C, as opposed to a shift in distractor stimulus encoding across the population ('Gating 1' model). During wMC suppression, due to the positive correlation across single units for sensory encoding of target and distractor stimuli, it would be difficult for a down-stream reader to distinguish between a small target stimulus and a large distractor stimulus, and thus could account for the increased false alarm rates.

wMC suppression also caused a positive rotation in the stimulus selectivity space for the other conditions- significant for anesthetized recordings (Fig 3D), and a non-significant trend for distractor-aligned S1 (Fig 3E). These data may suggest that suppression of unpreferred stimuli is a general, non-context dependent, function of wMC. However, further analyses indicate that stimulus selectivity and its modulation by wMC is indeed task modulated and context dependent. First, the effects of wMC suppression were different for putative inhibitory neurons (Supplemental Fig 4A,B). In anesthetized mice, there was a trend for wMC suppression to increase the slope of stimulus correlation (reflecting reduced selectivity) of putative inhibitory neurons. Yet, there was a trend in the opposite direction for putative inhibitory neurons in target-aligned and distractor-

aligned S1 during task performance (reduced slope, increased stimulus selectivity) (Supplemental Fig 4A). Moreover, when mice were unengaged from the task, differences in stimulus selectivity were less pronounced between target-aligned and distractor-aligned S1 (Supplemental Fig 4C-F). Importantly, when mice were unengaged, wMC suppression in target-aligned S1 did not change stimulus selectivity (Supplemental Fig 4C). Altogether, these data suggest that asymmetric modulation of stimulus selectivity in S1 is a robust feature of selective detection, and that wMC contributes to this modulation, specifically in excitatory neurons during task engagement. The wMC-mediated decorrelation of target and distractor encoding in target-aligned S1 neurons, in particular, is likely to be critical for distractor response suppression in this task.

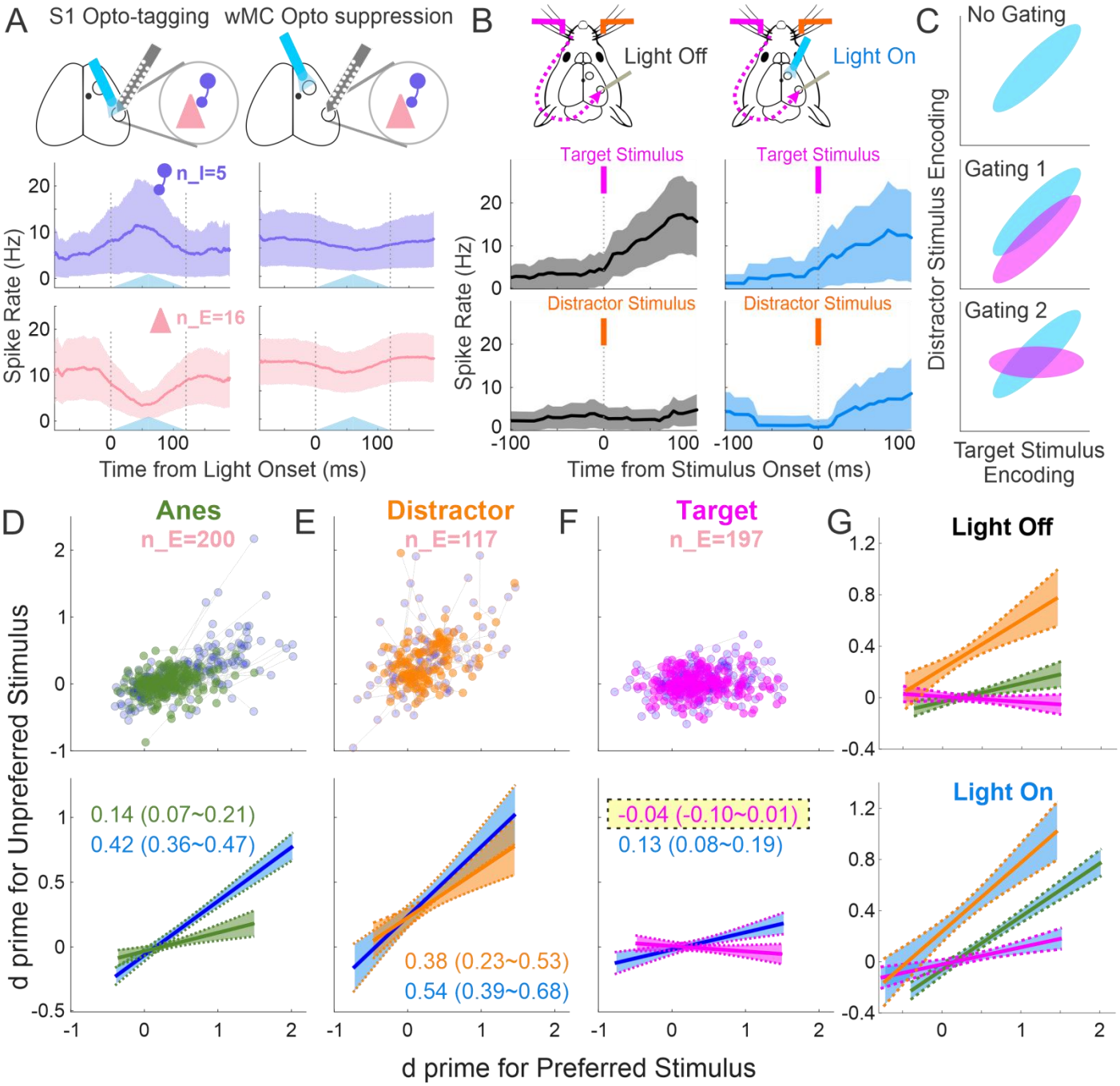

Figure 3: Asymmetric stimulus selectivity in target-aligned and distractor-aligned S1 and its modulation by wMC. (A) Example responses of S1 putative excitatory and inhibitory neurons to S1 opto-tagging (left) and wMC optogenetic suppression (right). Top row: for S1 opto-tagging, a light fiber is positioned above the S1 recording probe. For wMC suppression, a second light fiber is positioned above wMC. Middle and bottom plots: the traces of average spiking activity recorded

from one example session. Purple traces indicate activity of putative inhibitory neurons during S1 opto-tagging (left) and the same neurons during wMC opto suppression (right). Pink traces indicate activity of putative excitatory neurons during S1 opto-tagging (left) and the same neurons during wMC opto suppression (right). The blue triangles reflect the time course of optical stimulation. (B) Target and distractor evoked responses of an example excitatory neuron in target-aligned S1. Left: during light off control trials, this neuron displays a large stimulus-triggered response after target stimuli (top) but no response after distractor stimulus (bottom). Right: in light on wMC suppression trials, the same neuron displays robust stimulus-triggered responses for both target (top) and distractor (bottom) stimuli. (C) Illustration of potential mechanism of distractor stimulus gating plotted in stimulus selectivity space, with target stimulus encoding on the x-axis and distractor stimulus encoding on the y-axis. Blue distributions reflect a population of target-aligned S1 neurons without distractor gating. Pink distributions reflect the same population of neurons with distractor gating. Top: without gating, neurons in S1 robustly encode both target and distractor stimuli. Middle: one potential mechanism of gating is for the population to display the same stimulus selectivity correlation, yet with reduced distractor encoding throughout the population. Bottom: a second potential mechanism of gating, with a rotation in the selectivity space resulting in a decorrelation of target and distractor encoding throughout the population. (D-F) Putative excitatory neurons recorded (D) under anesthesia, (E) in distractor-aligned S1 in awake performing mice, and (F) in target-aligned S1 in awake performing mice. In each plot, the top scatter plot shows single neurons' d prime for the preferred stimulus (contralateral to the recording site) vs. the unpreferred stimulus (ipsilateral to the recording site). The green, orange and magenta dots indicate the values with intact wMC (control, light off) and the blue dots indicate the values in each condition when the wMC is suppressed (light on). The lines connect the same neuron's d primes under light off and light on conditions. The bottom plots show the linear fits of the single unit data above. The numbers indicate the slopes of the fitted lines [fit (95% confidence interval)]. (G) The overlay of the light off control (top) and light on wMC suppression (bottom) linear fits from the second row of [D-F].

wMC proactively modulates S1 activity in a context-dependent manner

Top-down modulations of sensory cortex can occur in two fundamentally different ways. Top-down modulations may be stimulus-evoked and reactively exert a functional feedback signal (Angelucci et al., 2002; Hupé et al., 1998; Manita et al., 2015; Moore & Armstrong, 2003; Nassi et al., 2013). Alternatively, top-down modulations may be in place before a stimulus arrives, proactively setting the initial condition for goal-directed sensory processing (Zagha, 2020). These last set of analyses were to determine whether there is evidence for proactive (pre-stimulus) wMC modulation of S1 spike rates (SR). For these analyses, we considered the last 100 ms pre-stimulus, in which we could achieve a relatively stable baseline during wMC optogenetic suppression (Fig 2B, Fig 4A). We calculated the pre-stimulus modulation index for each neuron as MI= (light_on_SR – light_off_SR) / (light_on_SR + light_off_SR). As such, MI < 0 indicates that wMC suppression reduces spiking (alternatively, that wMC normally drives spiking) in that neuron.

For conditions of anesthetized, awake target-aligned, and awake distractor-aligned, wMC robustly drives pre-stimulus spiking in S1 neurons (Fig 4B-D). This effect was not present in wild type control mice lacking channelrhodopsin expression, and therefore is unlikely to be due to artifacts of optogenetic stimulation (modulation index of each group, one sample t test p values of each group, and two sample t test p values between groups: wild-type: 0.02±0.02, p=0.21; VGAT: -0.21±0.01, $p=7.83\times10^{-112}$; WT vs. VGAT: 5.97×10^{-14}) (Fig 4B). Interestingly, wMC modulation of S1 pre-stimulus activity under anesthesia was larger than during task performance (modulation index of each group, one sample t test p values of each group, and two sample t test p values between groups: anes: -0.42±0.02, $p=4.87\times10^{-82}$; awake: -0.12±0.01, $p=1.44\times10^{-26}$; anes vs. awake $p=4.72\times10^{-49}$) (Fig 4C). The modulation indices were similar in awake target-aligned and distractor-aligned S1 (modulation index of each group, one sample t test p values of each group, and two sample t test p values between groups: target: -0.12±0.01, $p=2.03\times10^{-20}$; distractor: -

0.13±0.02, $p=8.47\times10^{-9}$; target vs. distractor: 0.6457) (Fig 4D), indicating similar levels of overall wMC drive.

To gain further insights into changes in local circuits, we analyzed wMC modulation separately for putative excitatory and inhibitory S1 neurons. Both excitatory and inhibitory S1 neurons were significantly driven by wMC in anesthetized and awake mice, both target-aligned and distractor-aligned (paired t test: anesthetized excitatory: $p= 8.60\times10^{-17}$; anesthetized inhibitory: $p= 8.91\times10^{-8}$; awake excitatory: $p=3.10\times10^{-12}$; awake inhibitory: $p=9.70\times10^{-6}$; target-aligned excitatory: $p=1.19\times10^{-11}$; target-aligned inhibitory: $p=2.26\times10^{-4}$; distractor-aligned excitatory: p=0.02; distractor-aligned inhibitory: p=0.01) (Fig 4 E-G). For each condition, we calculated the E/I modulation ratio, as the MI of excitatory neurons divided by the MI of inhibitory neurons. E/I ratio for anesthetized and target-aligned conditions were remarkably balanced, yielding ratios near 1. In contrast, the distractor-aligned E/I ratio was 0.40, reflecting a preferential drive of wMC to putative inhibitory neurons. Two-way ANOVA analyses supported these conclusions, yielding a significant main effect for behavioral context comparing anesthetized and awake behaving conditions (anesthetized vs. awake, $p=1.23\times10^{-24}$) (Fig 4F), and a main effect for cell-type (p=0.03) and an interaction effect between alignment and cell-type (p=0.02) comparing target-aligned and distractor-aligned conditions (Fig 4G). These data indicate that wMC modulation of S1 is proactive (influencing pre-stimulus activity levels) and context-dependent (for anesthesia vs. awake behaving and target vs. distractor alignment).

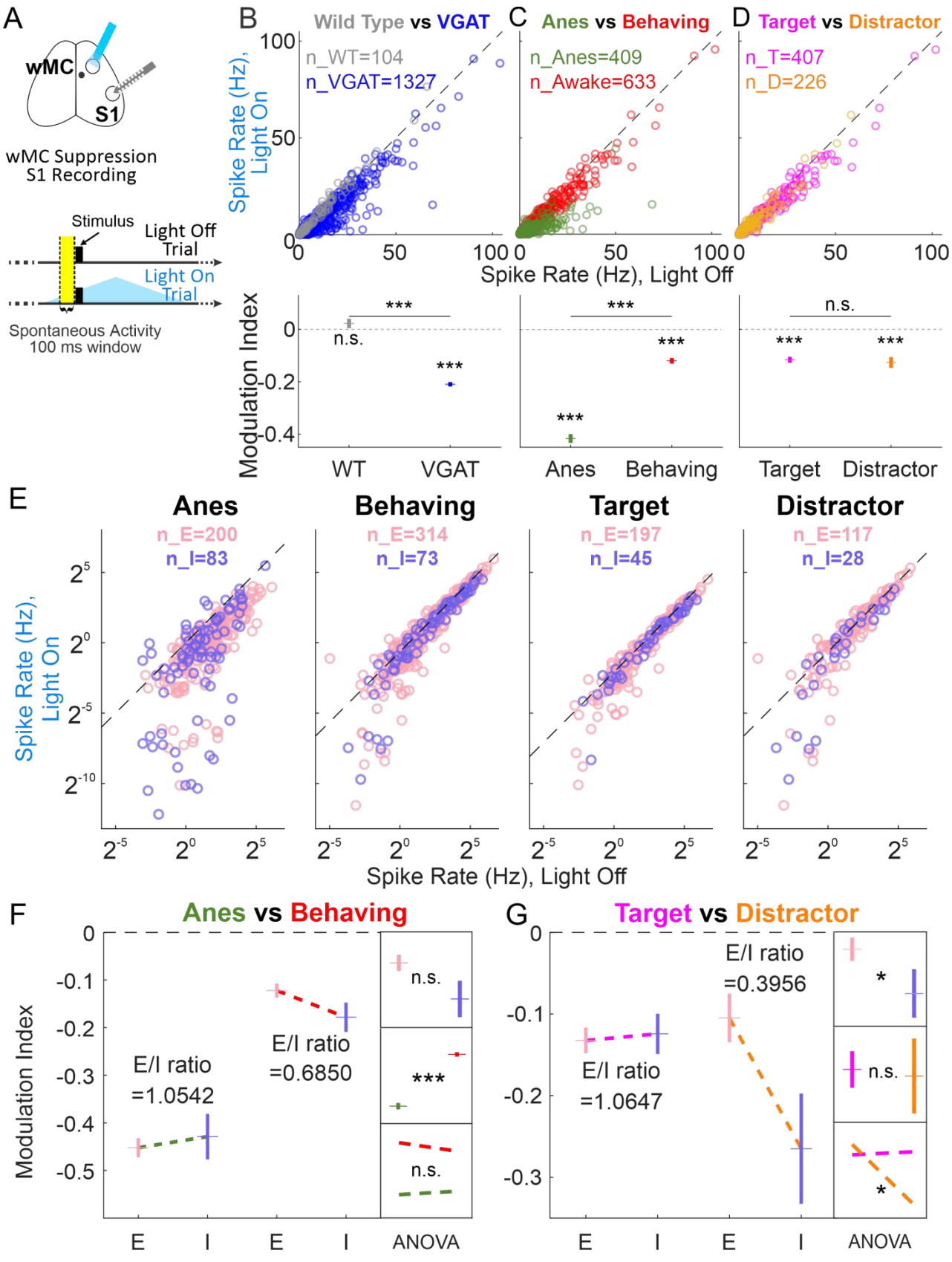

Figure 4: wMC proactively drives S1 excitatory and inhibitory neurons in a context-dependent manner. (A) wMC suppression is performed with S1 silicon probe recordings (top), as described previously. Neuronal activity within the 100 ms pre-stimulus window (highlighted) is used to determine pre-stimulus wMC modulation. (B) Top: S1 pre-stimulus spike rates from wild type (gray) and VGAT-ChR2 (blue) mice. Each circle indicates one neuron. Bottom: modulation index calculated based on the top plot. Above each data point are results from one-sample t-tests to

determine differences from zero within each population, and lines above the data points are results from two-sample t-tests to determine differences between populations. (C) As same as [B] but for anesthetized (green) and awake behaving sessions (red, including both target-aligned and distractor-aligned S1) of VGAT-ChR2 mice. (D) As same as [B] but for awake behaving sessions of VGAT-ChR2 mice in target-aligned S1 (magenta) and distractor-aligned S1 (orange). (E) As same as [B-D] but separated for excitatory (pink) and inhibitory (purple) neurons under different contexts. (F) Big box on the left: modulation indices calculated based on the spike rates in [E]. Small boxes on the right: two-way ANOVA for the modulation indices of anesthesia and awake behaving contexts and neuron types: top: no significant main effect of neuron type; middle: a significant main effect for context; bottom: no significant interaction effect. (G) As same as [F] but for target-aligned S1 and distractor-aligned S1 from awake behaving recording sessions. ANOVA results: top: a significant main effect for neuron type; middle: no significant main effect of context (alignment); bottom: a significant interaction effect.

Discussion:

The major significance of this study is identifying a mechanism by which frontal cortex suppresses behavioral and neuronal responses to distractor stimuli. Within frontal cortex, we focused on a region that is part of the sensorimotor cortical whisker system, termed 'whisker motor cortex' or wMC. Using optogenetic suppression, we demonstrated that wMC robustly contributes to distractor response suppression (Fig 1G, Supplementary Fig 1A,B). From S1 single unit recordings in behaving mice we revealed an asymmetry in stimulus selectivity, in which distractor-aligned S1 neurons respond to both distractor and target stimuli while target-aligned S1 neurons respond selectively to target stimuli (Fig 2, Fig 3G). By combining wMC optogenetic suppression with S1 single unit recordings in behaving mice we demonstrated that wMC contributes to target-aligned S1 stimulus selectivity, such that with wMC suppression S1 neurons more strongly encode distractor stimuli (Fig 2F, Fig 3F). This reduction in distractor gating likely underlies, at least in part, the increase in false alarm rate during wMC suppression (discussed further below). Lastly, we provide strong evidence that wMC modulation of S1 is context-dependent and proactive (present prior to stimulus onset). Thus, in addition to frontal cortex gating distractor stimuli from lower order to higher order processing (vertically) (Fries, 2005), this study emphasizes the importance of frontal cortex gating across receptive fields (horizontally).

For combined behavioral-physiological studies, an important consideration is whether the task-related neuronal signals could be fully or partially accounted for by movement (Zagha et al., 2022). A specific concern for our study is whether the apparent asymmetric stimulus selectivity, and its modulations by wMC, is instead reflecting movement on 'Go' trials in our Go/No-Go task design (which are more prevalent on target than distractor trials in expert mice, Aruljothi et al., 2020). We believe this is unlikely for three reasons. First, differences in selectivity (between target-aligned S1 and distractor-aligned S1, between control trials and wMC suppression trials) are observable by 30 ms post-stimulus onset. This is well before the response time (>200 ms), before the onset of uninstructed whisker movements that are part of the 'Go' motor sequence (>80 ms, Aruljothi et al., 2020, and data not shown), and well before the emergence of significant choice probability in S1, which includes the contributions of 'Go' movements (>165 ms, Zareian et al., 2021). Second, target-aligned S1 neurons during task performance are more sensory selective than S1 neurons under anesthesia, during which movements are largely suppressed. Third, wMC suppression causes a rotation in stimulus selectivity rather than a shift of the population, as would be expected from increases in arousal or movement (Carsen et al., 2019). For these reasons we believe that our reported modulations of stimulus selectivity are truly reflecting sensory processing rather than movement confounds.

A major framework of top-down cortical modulation is the enhancement of aligned (center) sensory responses and the suppression of unaligned (surround) sensory responses (Angelucci et al., 2002; Hupé et al., 1998; Keller et al., 2020; Moore & Armstrong, 2003; Zhang et al., 2014). Data from our study, however, do not support this framework. Notably, wMC suppression had only minor impacts on encoding of aligned stimuli (Fig 2E,H). This was observed for both large and

small amplitude stimuli (Supplemental Fig 2), and therefore is unlikely due to response saturation. Differences between our and previous studies may be due species, modality, or methodology. Our data are more consistent with top-down cortical modulation suppressing sensory processing, specifically for the propagation of distractor stimulus responses into target-aligned cortex (Fritz et al., 2003; Fritz et al., 2010; Moran & Desimone, 1985; Nassi et al., 2013). In some ways our data resemble the work of Moran and Desimone (1985) in non-human primates, which showed contractions of the receptive fields of higher order sensory neurons when target and distractor stimuli were placed simultaneously within their receptive fields (Moran & Desimone, 1985). Such studies motivated the biased competition hypothesis, to explain sensory filtering in the context of multiple stimuli competing for limited cognitive resources (Desimone & Duncan, 1995). Three important differences with our study are that we observed distractor gating and receptive field modulations 1) with the presentation of individual (rather than simultaneous) stimuli, 2) located in different hemifields, and 3) within primary sensory cortex. Nonetheless, future studies are required to determine whether both observations, identified in different species and different behavioral contexts, reflect a common neuronal mechanism.

We speculate as to the mechanisms of receptive field modulation and its impacts on behavioral responses. Our analyses of pre-stimulus modulations were notable for a preferential wMC activation of distractor-aligned S1 inhibitory neurons (Fig 4G). While this increased inhibitory drive did not substantially suppress distractor stimulus encoding in distractor-aligned S1, we hypothesize that these inhibitory neurons may prevent the spread of distractor evoked responses into target-aligned cortex. Additionally, we have considered why ‘spillover’ of distractor responses into target-aligned S1 would impair distractor suppression. In a concurrent study (Zareian et al., 2022), we demonstrate that activation of target-aligned dorsolateral striatum (DLS) is critical for response triggering, for both target and distractor stimuli. Whisker-evoked responses propagate widely and across hemispheres in naïve rodents (Aronoff et al., 2010; Aruljothi et al., 2020; Ferezou et al., 2007). If behavioral response triggering is indeed conditioned on activating target-aligned DLS, then preventing distractor stimulus propagation into the upstream target-aligned S1 would facilitate distractor response suppression.

We note that wMC modulation of S1 is only a partial component of both wMC function and S1 dynamics. wMC suppression not only increased false alarm rates, but also substantially increased premature responses (during the 200 ms post-stimulus lockout window) (Supplementary Fig 1A,B). We do not find strong evidence for increased premature responses being accounted for by activity in S1. The ability to withhold across the lockout window may be due to other wMC projections, such as to the dorsolateral striatum (Mao et al., 2011), subthalamic nucleus (Li et al., 2020), thalamus (Nakajima et al., 2019; Wimmer et al., 2015), and/or brainstem nuclei (Ioffe, 1973). Additionally, we recognize that wMC suppression does not fully equalize target-aligned and distractor-aligned stimulus selectivity (Fig 2F,I and Fig 3F). Thus, we suspect the involvement of additional top-down neuromodulation (Goard & Dan, 2009; Lee & Dan, 2012; Zagha & McCormick, 2014) and/or bottom-up plasticity through training.

When are top-down cortical inputs activated to modulate sensory processing? A widely accepted framework is that stimulus-triggered bottom-up inputs are required to activate higher order regions, which in turn deliver feedback signals (Angelucci et al., 2002; Hupé et al., 1998; Manita et al., 2015; Nassi et al., 2013). In this ‘reactive’ framework, the bottom-up and top-down signals in sensory cortex occur sequentially and are temporally dissociable (Cauller, 1995; Cauller & Kulics, 1988; Kulics, 1982; Kulics et al., 1977; Manita et al., 2015). Additionally, this framework provides little motivation for studying the impacts of top-down regions on pre-stimulus activity. However, we show that wMC robustly modulates S1 before stimulus onset. Importantly, this pre-stimulus modulation is context-dependent, with a stronger drive onto putative inhibitory neurons in distractor-aligned S1. Accordingly, changes in S1 sensory processing during wMC suppression were evident early, during the initial bottom-up sensory phase. These findings are more consistent with a ‘proactive’ framework, in which top-down regions sets the initial conditions for sensory processing according to goal-direction and internal state well before a stimulus arrives (Zagha, 2020).

Methods:
All experimental protocols were approved by the Institutional Animal Care and Use Committee of University of California, Riverside. Both male and female wild-type (C57BL/6) (1 male and 1 female) and transgenic (VGAT-ChR2-YFP) (7 male and 3 female) mice were purchased from Jackson Laboratories and were subsequently housed and bred in an onsite vivarium. The mice were kept in a 12/12 h light/dark cycle, and the experiments were conducted during the light phase. At the beginning of the experiments, all mice were between 1.8 and 4.2 months old (age: 85.7±8.2 days).

Surgery:
Mice were anesthetized using an induction of ketamine (100 mg/kg) and xylazine (10 mg/kg) and maintained under isoflurane (1-2% in O_2) anesthesia. A lightweight metal headpost was attached to the exposed the skull over dorsal cortex, creating an 8 × 8 mm central window. Mice were treated with meloxicam (0.3 mg/kg) and enrofloxacin (5 mg/kg) on the day of the surgery and for two additional days after the surgery. For mice that were used for anesthetized recordings, the recordings were done the same day after the surgery. For mice that were introduced to the behavioral task, water restriction was initiated after recovery from surgery for a minimum of 3 d. For mice prepared for optogenetic experiments, the bone over the bilateral S1 and wMC was thinned under isoflurane anesthesia 2-3 days prior to the optogenetic perturbation. Between recordings, the skull was protected with Kwik-Cast (World Precision Instruments). For further surgergical details, see Aruljothi et al., 2020 and Zareian et al., 2021.

Behavior and whisker stimulation:
MATLAB software and Arduino boards were used to control the behavioral task. Head-fixed mice were situated in the setup during behavioral sessions. Two piezoelectric benders with attached paddles were used: one placed within one whisker field and assigned as the target; the other placed within the opposite whisker field and assigned as distractor. Both paddles targeted the D2/E2-D3/E3 whiskers within their respective whisker fields and the assignments of target and distractor remained consistent for each mouse throughout training and recording. Each whisker stimulus was a single rapid deflection, with a triangular waveform of fixed velocity and variable duration. In each recording session, two stimulus amplitudes were applied: the large amplitude was near the saturation of the psychometric curve and the small amplitude was $1/4^{th}$ of the duration of the large amplitude, within the dynamic psychometric range. The amplitudes were customized for each mouse, in expert mice ranging from 1.4 ms to 11.2 ms duration. In all behavioral sessions, target and distractor amplitudes were equal duration. The number of target vs distractor trials and large amplitude vs. small amplitude trials were approximately balanced and pseudo-randomly presented. Additionally, 30% of non-reward catch trials without whisker stimuli were distributed pseudo-randomly throughout the session.

A 200 ms lockout period (delay) was introduced after stimulus onset and before the response window. Licking during the lockout period was punished by aborting the current trial and resetting the inter-trial interval (6-10.5 s). After the lockout period, there was a 1-s response window. Licking during the response window of a target trial was considered a ‘hit’ and was rewarded with a fluid reward (approximately 5 µl of water) from the central lickport. All other licking was punished with resetting the inter-trial interval. No licking during the response window of distractor trial or catch trial was considered a ‘correct rejection’ or ‘correct withholding’, respectively, and was rewarded with a shortened inter-trial interval (1.4-3.1 s) and subsequent target trial. Behavioral sessions typically lasted for 1 to 2 hours and generated 200-400 trials.

Mouse weights were maintained above 85% of their pre-surgery weights throughout the training and recording sessions. Mice were considered as experts once their discrimination of target and distractor stimuli (discrimination d prime = $Z_{\text{hit rate}} - Z_{\text{false alarm rate}}$, in which Z is the inverse of the normal cumulative distribution function) reached a threshold (discrimination d prime>1) for three consecutive days. For all behavioral-physiological data presented in this study, mice were performing at expert level during data collection. For more training details and learning trajectories, see Aruljothi et al., 2020; for more training setup information, see Zareian et al., 2021.

Electrophysiological recording and whisker receptive field mapping:
All electrophysiological recordings were obtained from 9 VGAT mice and 2 wild type mice. On average, 7 sessions were recorded from each mouse (range 1-18). For electrode implantation, a small craniotomy with durotomy (approximately 0.5 mm in diameter) above the S1 barrel field (from bregma: 2.3-4 mm lateral, 1-2.2 mm posterior) was made under isoflurane anesthesia the same day of recording (used for up to three days of acute recordings). After approximately 30 minutes post-surgery, mice were tested in the behavioral task without electrode implantation to ensure recovery to normal behavior. Upon evidence of normal expert behavior, a silicon probe (Neuronexus A1x16-Poly2-5 mm-50s-177) was advanced into the brain using a Narishige micro-manipulator under stereoscope guidance. This silicon probe design has 16 electrode sites, arranged in two columns and clustered within 375 μm, allowing for tetrode clustering of single units. We positioned the recording sites to target layer 5, from 500 to 1000 um below the pial surface (mid-point of the silicon probe recording sites: 626.0 ± 10.5 μm). Whisker alignment for S1 recordings was verified by two methods (as described in Zareian et al., 2021). First, during electrode implantation we verified correct alignment by hand mapping of several individual whiskers and observing real-time local field potential (LFP) display. Second, post-hoc we plotted the large amplitude stimulus evoked multi-unit spiking activity and only included sessions with robust and fast-rising peaks in the post-stimulus time window (peak response reaching at least 1.4×baseline activity within 50 ms post-stimulus window).

Optogenetic suppression and opto-tagging:
To transiently suppress specific cortical regions, we optogenetically stimulated GABAergic interneurons using VGAT-ChR2-YFP mice (Guo et al., 2014; Zhao et al., 2011). Control studies with identical optical illumination were performed in wild type mice without ChR2 expression. For optogenetic stimulation, LED fiber optic terminals were placed above wMC and/or S1. Optogenetic GABAergic stimulation was used for both suppression studies as well as for opto-tagging of recorded GABAergic interneurons. For both applications, 470 nm blue light was delivered through a 400 μm core diameter optical fiber (Thorlabs). Optogenetic stimulation was delivered using a triangular function, beginning 200-500 ms before whisker stimulus onset, peaking 100-200 ms after stimulus, and decaying for 400-600 ms. This protocol was used to 1) prevent transient onset/offset effects of square pulse illumination and 2) ensure a relative strong and stable suppression for 100 ms pre-stimulus through 100 ms post-stimulus. Maximum intensity at peak stimulation was 18 mW/mm^2 at the fiber tip. For the behavioral sessions without electrophysiological recordings, optical suppression was applied on one third of all trial types, randomly distributed. For the sessions (awake or under anesthesia) with electrophysiological recordings, simultaneous optical suppression and opto-tagging was conducted, in which optical suppression was randomly applied on one third of all trial types and opto-tagging was randomly applied on 7-10% of all trial types.

Barrier and masking methods were used to prevent visual detection of the optical stimulus. Barrier methods consisted of wrapping the headpost and optical fiber in opaque material. Masking consisted of applying a 10 Hz blue light LED stimulation (duty ratio=50%) directly above the subject's eyes on all trials, beginning 180 ms before optical stimulation onset and ending 170 ms after optical stimulation offset. Masking light was given on all trials (irrespective of suppression or stimulus type).

Electrophysiological recording data pre-processing:
Neuralynx software was used for data acquisition and spike sorting. Putative spikes were identified as threshold crossings over 18-40 μV. Spike sorting and clustering was conducted offline by SpikeSort3D software, first through the KlustaKwik function followed by manual inspection of waveform and inter-spike interval distributions. On average, 23 units were identified in each recording session (22.8±5.4). Further data analyses were conducted using MATLAB software (MathWorks). Spike times were binned within 5 ms non-overlapping bins. For more details about spike sorting, see Zareian et al., 2021.

Data analysis:
All data were analyzed using SPSS or custom-written code in MATLAB. ANOVA was conducted in SPSS by univariate general linear model. Standard Error of Mean (SEM) were used throughout the article unless otherwise stated.

Behavioral detection d prime: $d' = Z_{\text{Hit Rate}} - Z_{\text{Spontaneous Licking Rate}}$. Z is the inverse of the normal cumulative distribution function. Response rates of 0 and 1 were adjusted as 0.01 and 0.99 respectively to avoid yielding infinite values.

Neuronal encoding d' across a 100 ms post stimulus window: $d' = \sqrt{2} \times Z_{\text{AU-ROC}}$. AU-ROC is the area under the receiver operating curve (ROC), in which the curve is composed of the spike counts within 100 ms pre-stimulus windows and 100 ms post-stimulus windows. Each window was composed to two 50 ms epochs.

Neuronal encoding d' across 20 ms post stimulus sliding windows: $d' = \sqrt{2} \times Z_{\text{AU-ROC}}$. This calculation is similar to that described above, except the post stimulus window was a single 20 ms window, and was compared to 5 consecutive 20 ms pre-stimulus windows. The post-stimulus 20 ms sliding window was sampled every 5 ms, thereby consisting of 75% overlap, up to 100 ms post-stimulus. To account for the 5x sampling of the pre-stimulus window, we multiplied the post-stimulus histogram by 5 before plotting the ROC. AU-ROC values of 0 and 1 were adjusted as 0.003 and 0.997 to avoid yielding infinite values.

For the linear fitting and the slopes for 95% confidence intervals, we used MATLAB functions to calculate the value of the slopes: the polyfit function was used to calculate the slope for the middle linear fitted line and the polyparci function was used to calculate the 95% confidence intervals. These data were plotted by the fitlm function.

Data inclusion criteria and quality control:
'Task engaged' was defined as a continuous period of at least 10 min with no greater than a 60 s gap of non-licking. For any session with more than one engaged period, only the longest continuous segment is used for further analyses. Sessions without continuous engagement for at least 10 min were excluded from further analysis. 'Task unengaged' epochs always followed periods of task engagement. Unengaged epochs were recorded for approximately 30 min and contained at least 300 trials. We suspect that task disengagement was due to lack of motivation from satiety after receiving sufficient rewards.

For analyses of behavioral outcomes, at least 5 trials of a given type were required to be included in the session analysis. For calculations of spontaneous licking rate, we used the 1s pre-stimulus window of all trial types. These values were similar to the spontaneous licking rates based on catch trials yet included substantially more trials in their calculation.

For recording data indicated as behaving/target/distractor sessions, we analyzed only the 'task engaged' epochs as defined above, so that the behavioral and neuronal data were based on the same trials. In Fig 4 B, 'VGAT' is based on all sessions recorded from VGAT-ChR2 mice, regardless of the engagement status or wakefulness. Similarly, Supplementary Fig 3 is based on all recording sessions.

<u>Principle whisker alignment inclusion criteria:</u>
Out of 78 recording sessions, 14 were unaligned, 64 were aligned, based on criteria described above. Only the aligned sessions are used for neuronal data analyses. wMC suppression sessions with unaligned S1 recordings were included for behavior only analyses, along with wMC suppression sessions without extracellular recordings.

<u>Visual mask-induced noise filtering:</u>
For optogenetic sessions, we applied a 10 Hz mask light above the eyes of mice, which sometimes caused a 10 Hz (onset triggered) or 20 Hz (onset and offset triggered) noise in the neuronal recording data. To minimize the influence of this contamination, we applied a band-pass filters ('designfilt' function of MATLAB, designed based on Butterworth notch filter) to the spike

count time series for single unit or multi unit data, depending on the analyses, before analyzing the data to decrease the frequency components between 9-11 Hz, and 19-21 Hz.

Putative excitatory and putative inhibitory neurons inclusion criteria:
To identify putative excitatory or inhibitory units, we analyzed the time window of the optogenetic light duration (excluding the first and last 100 ms time bins at the start and the end of the triangle waveform) to calculate the averaged trial-by-trial light-on spike rate for each unit (using an equivalent window for light-off control trails). We calculated the difference of averaged rates between light-on trials and light-off trials, and determined significance from two-sample t-tests with a threshold of $p<0.1$. Out of these significantly modulated units, if the average spike rate of light-on trials was larger than that of light-off trials (enhanced), the units were considered as putative inhibitory neurons; if the average spike rate of light-on trials was smaller than that of light-off trials (suppressed), the units were considered as putative excitatory neurons. Any unit with $p>=0.1$ was not categorized and not included in further cell-type analyses.

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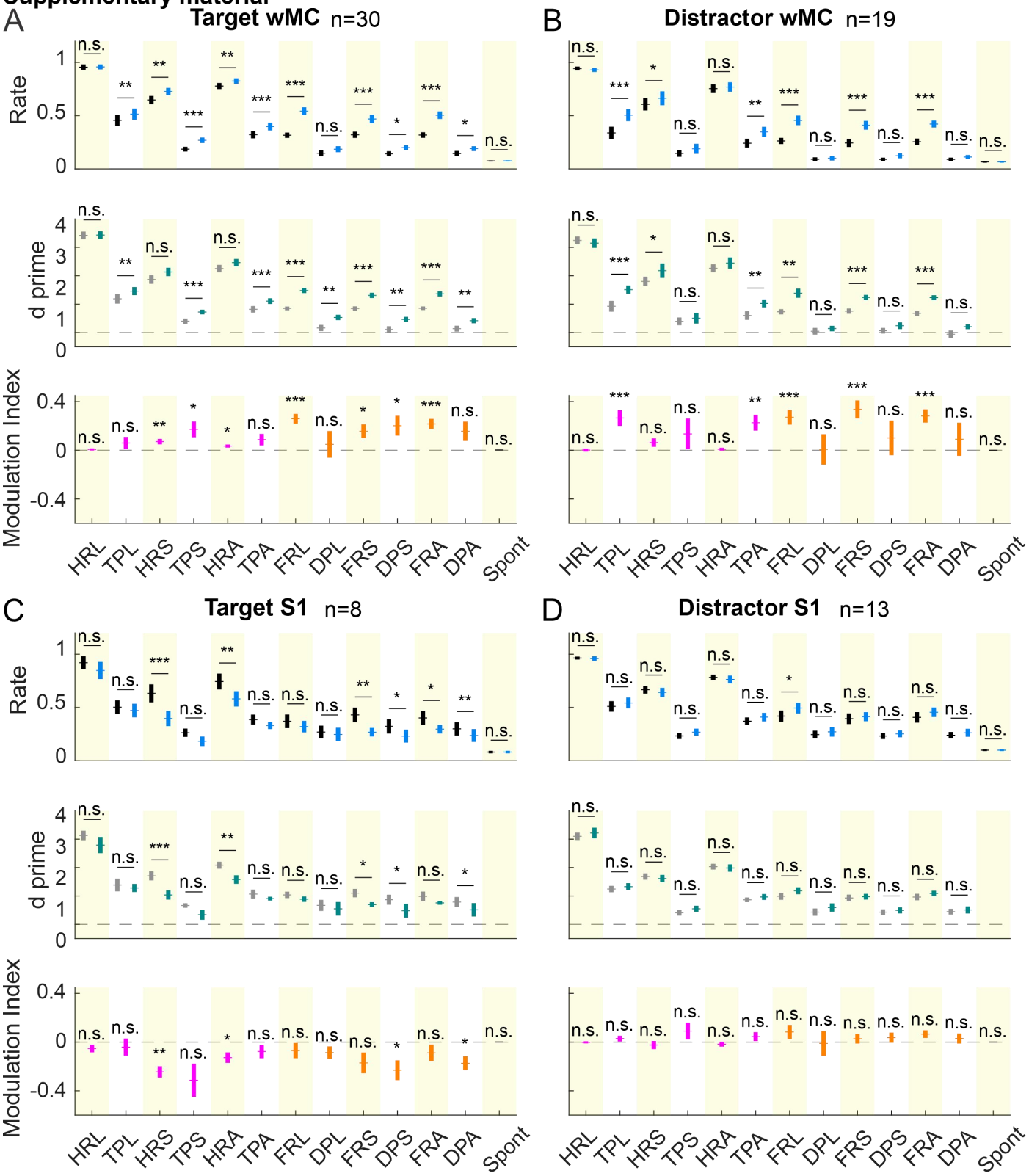
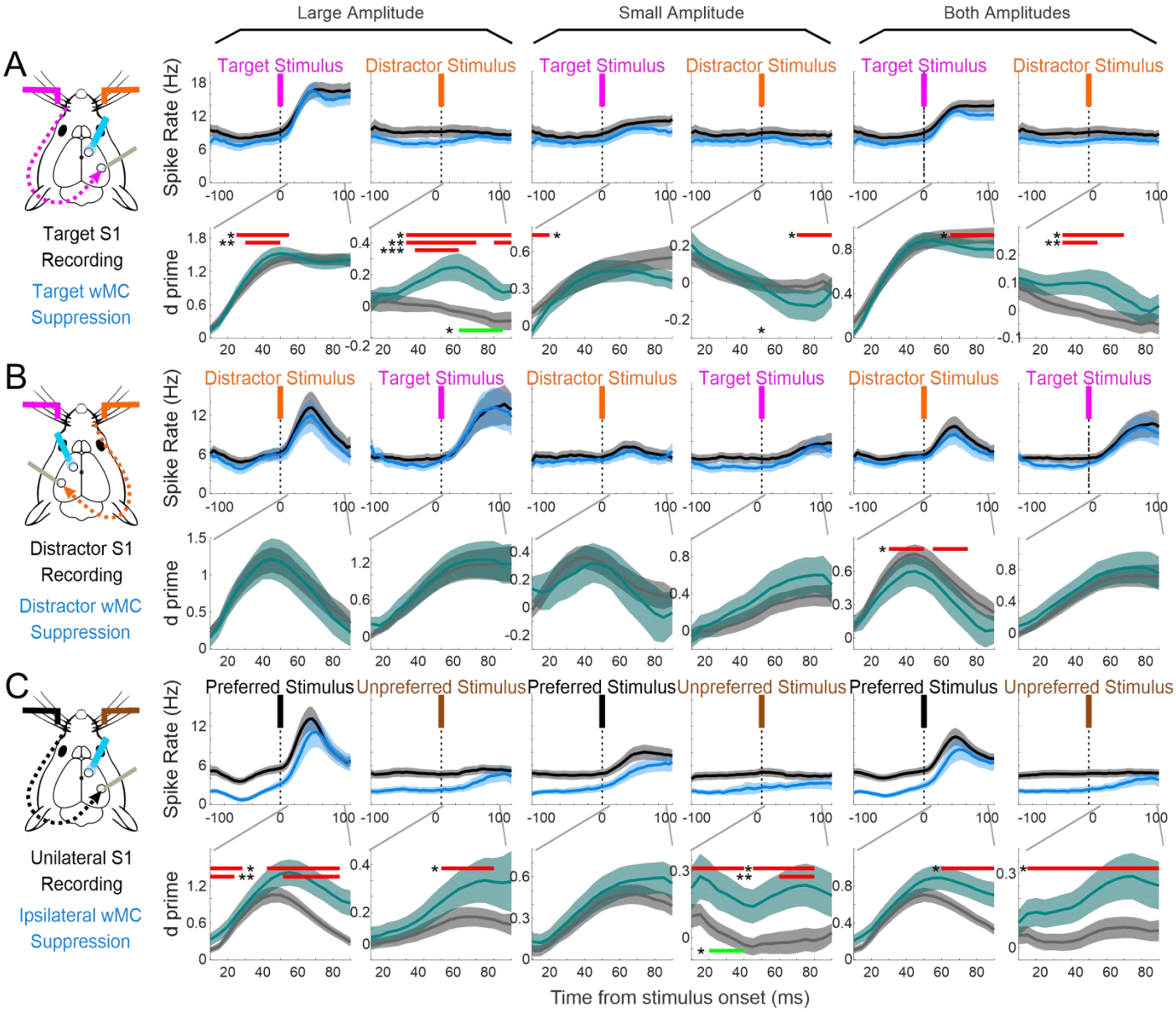
Supplementary material

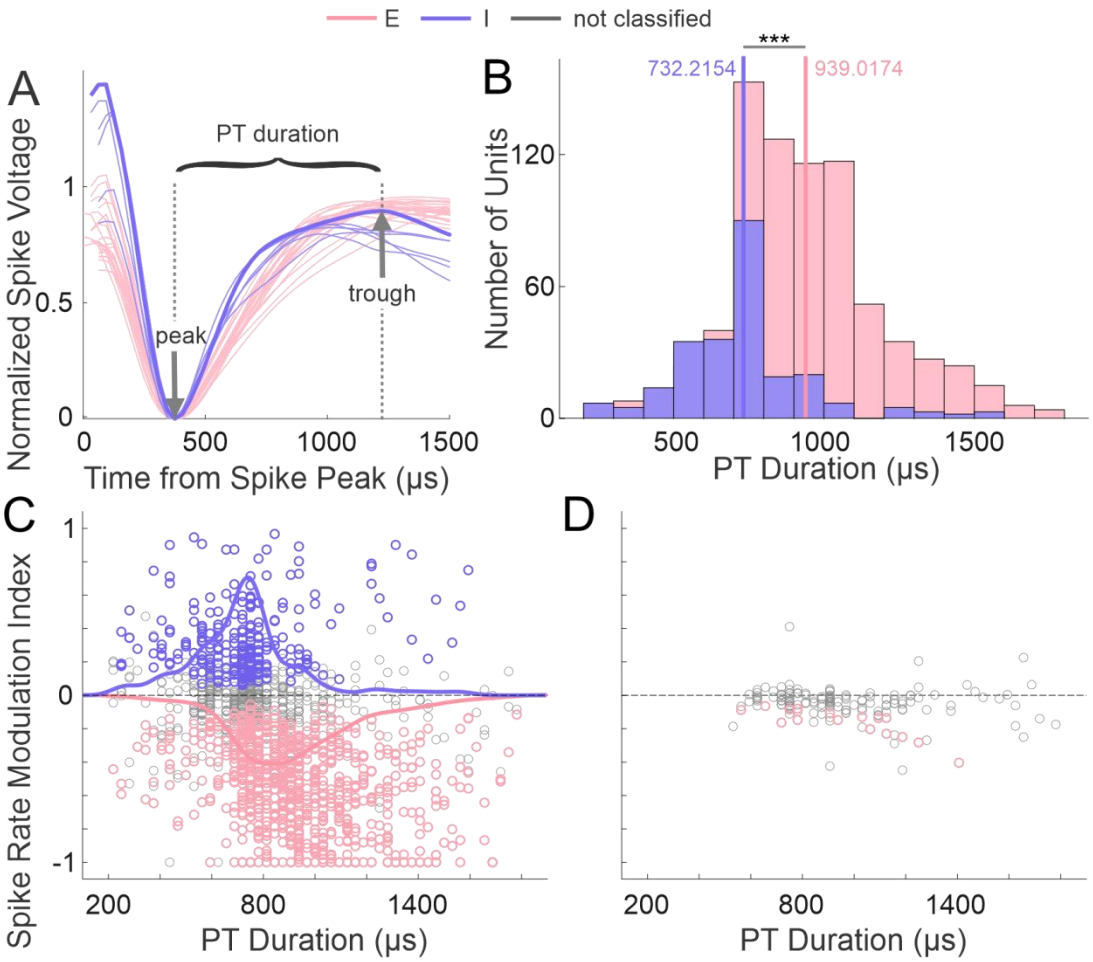


Supplementary Figure 1: Behavioral effects of optogenetically suppressing target-aligned wMC (A), distractor-aligned wMC (B), target-aligned S1 (C), and distractor-aligned S1 (D). HRL: hit rate for large amplitude stimuli; TPL: target premature licking rate for large amplitude stimuli; HRS: hit rate for small amplitude stimuli; TPS: target premature licking rate for small amplitude stimuli; HRA: hit rate for all stimulus amplitudes (large and small); TPA: target premature licking rate for all stimulus amplitudes; FRL: false alarm rate for large amplitude stimuli; DPL: distractor premature licking rate for large amplitude stimuli; FRS: false alarm rate for small amplitude stimuli; DPS: distractor premature licking rate for small amplitude stimuli; FRA: false alarm rate for all stimulus amplitudes; DPA: distractor premature licking rate for all stimulus amplitudes; Spont: spontaneous licking rate. All the yellow shaded areas are applied for separating non-premature rates (shaded) from

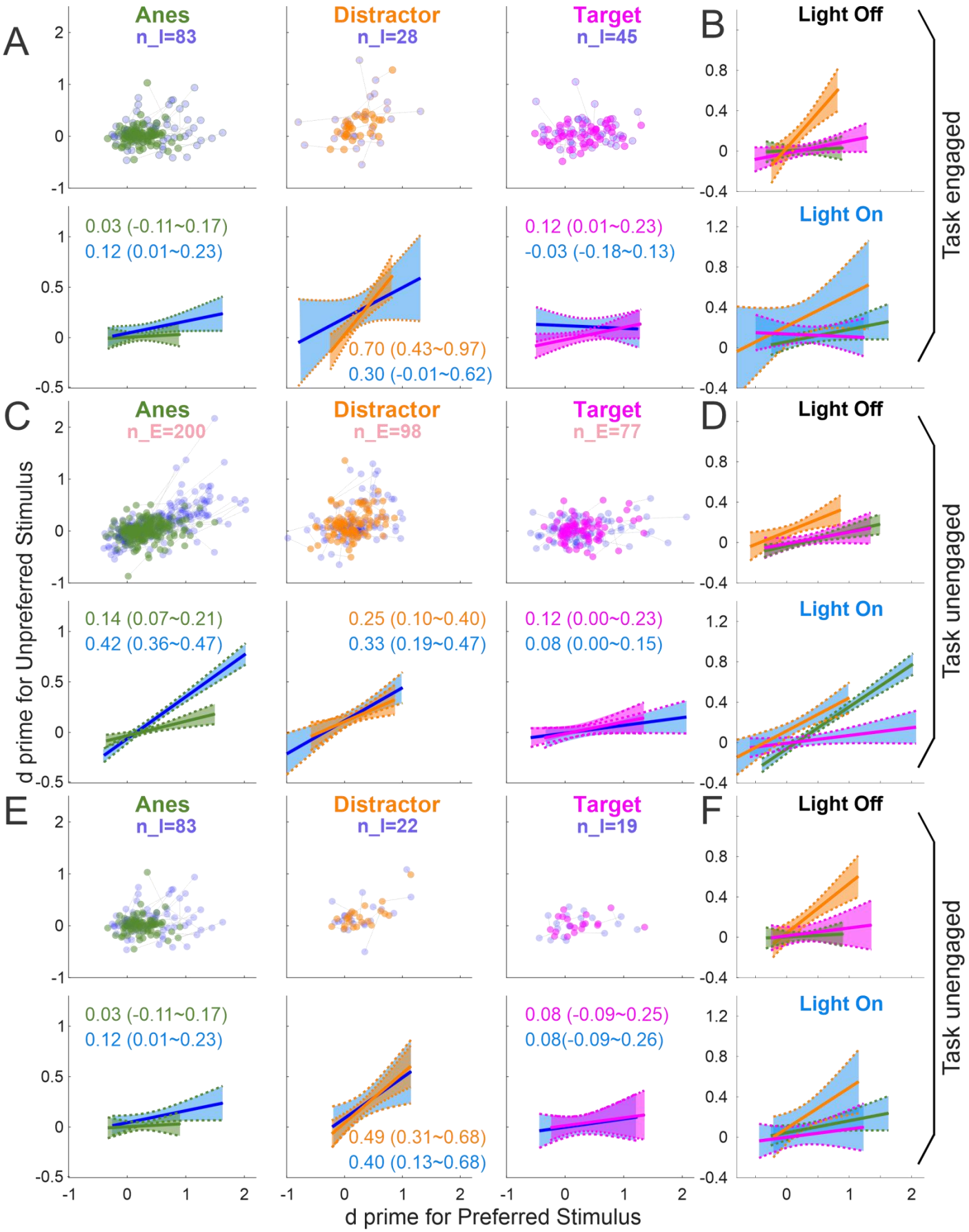
premature rates (not shaded). See Methods, for calculations of response rates (top row), d prime (stimulus response rates normalized by spontaneous response rates, middle row), and modulation index (comparison between control and opto suppression trials, bottom row). As in the rest of the study, p values are indicated as: n.s. (p>=0.05), *(0.01<=p<0.05), **(0.001<=p<0.01), or ***(p<0.001).



Supplementary Figure 2: Neuronal spike rates and d prime of S1 neurons during wMC suppression in response to different stimulus amplitudes (following the same plotting as Fig 2E,F,H,I). (A) Target-aligned S1 recordings and target-aligned wMC suppression. Black traces indicate averaged spike rates across all sessions during light off control trials while blues traces indicate light on wMC suppression trials. Gray traces indicate neuronal d prime across all session from light off control trials while dark green traces indicate light on wMC suppression trials. (B) Same as [A] but for distractor-aligned S1 recordings and distractor-aligned wMC suppression. (C) Same as [A] but for naive mice under anesthesia. In all plots, curves indicate average values ± standard error (shaded). The red bars indicate d prime value pairs that are significantly different (paired t test); green bars indicate d prime values from light off control conditions are significantly lower than zero (one sample t test).



Supplementary Figure 3: Opto-tagging method and verification. Putative excitatory or putative inhibitory neurons are assigned based on significant decreases or increases, respectively, in spike rate during opto-stimulation within the S1 recording site, using p<=0.1 as the significance threshold. (A) Spike widths of putative inhibitory (purple) and excitatory (pink) neurons from one example session. Spike width is calculated as peak-trough (PT) duration. (B) Histogram of putative excitatory and inhibitory neuron counts of different spike widths. Two vertical lines indicate the average spike widths of each population, which are significantly different from each other (two sample t test, $p=1.73\times10^{-28}$). Putative inhibitory neurons have shorter spike widths, as expected, yet there is substantial overlap between these populations. (C) Distribution of spike width versus opto-tagging modulation index from VGAT-ChR2 mice (n=72 recording sessions). Each data point is one unit, and the two curves show the density distributions. Modulation index (MI) is calculated as the change in spike rate during opto-tagging. MI>0 indicates units enhanced by direct light stimulation; MI<0 indicates units suppressed by direct light stimulation. 1613 neurons are recorded, in which 762 neurons (47.24%) are characterized as putative excitatory neurons, 246 neurons (15.25%) are characterized as putative inhibitory neurons, 605 neurons (37.51%) are not significantly modulated by opto-tagging and therefore unassigned. (D) As same as [C] but the units were recorded from control WT mice (n=6 recording sessions). In WT mice, 155 neurons were recorded, in which 16 neurons (10.03%) are significantly modulated by opto-tagging, consistent with an expected false positive rate of 10%.



Supplementary Figure 4: S1 neuronal encoding of preferred and unpreferred stimuli, according to cell type and task engagement. (A) As same as Fig 3 D-F, but for inhibitory neurons recorded: under anesthesia (1st column), in distractor-aligned S1 in awake performing mice (2nd column), and in target-aligned S1 in awake performing mice (3rd column). (B) The overlay of the control (top) and wMC suppression (bottom) linear fits from the second row of [A]. (C, D) As same as Fig 3 [D-

G], but for unengaged awake recording sessions. (E, F) As same as Fig 3 [D-G], but for inhibitory neurons recorded from unengaged awake recording sessions. Anesthetized data is duplicated for ‘engaged’ and ‘unengaged’ categories, and included for reference. Note, for putative excitatory neurons when task unengaged [C], the stimulus selectivity profiles for distractor-aligned (orange) and target-aligned (pink) S1 neurons are not significantly different. Furthermore, for these conditions, wMC suppression (blue) does not change stimulus selectivity. These data are in marked contrast to S1 excitatory neurons during task engagement (Fig 3E,F).