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Cover Page Footnote

The authors are grateful to the Cardin Lab and the Yale Animal Resources Center for their support with tasks integral to the success of this research including mice handling, task and equipment design, and programming.

Altering sensory learning by chronic inactivation of VIP interneurons

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ABSTRACT

Vasoactive intestinal polypeptide-expressing interneurons (VIP-INs) play a key role in the regulation of cortical circuits and are implicated in perceptual function and psychiatric disease. However, their role in perceptual augmentation and learning remains understudied. We performed chronic, localized ablation of VIP-INs in the primary visual cortex of adult mice using caspase-induced apoptosis to better understand how VIP-INs contribute to visual perception and the ability to learn a visual detection task. We find that chronic VIP-IN ablation does not affect naïve performance on a full-screen visual contrast detection task. However, mice with suppressed levels of VIP-INs achieved their final expert state more rapidly and exhibited a greater detection advantage during high-arousal compared to control mice. These results suggest VIP-INs have an important role in modulating the learning process of cortical networks in the primary visual cortex.

INTRODUCTION

Sensory processing in the brain is finely controlled by both excitatory and inhibitory networks in the cerebral cortex. The activity of inhibitory GABAergic interneurons (INs) help shape how information is integrated by excitatory neurons in a context- and behavior-specific way. Three major classes of INs have been identified as prominent contributors to inhibition in neocortical circuits: parvalbumin-positive (PV) cells, somatostatin-positive (SST) cells, and vasoactive intestinal polypeptide-positive (VIP) cells (Tremblay et al., 2016). Beyond their significance in cortical function, dysfunctional GABAergic INs have also been correlated with cognitive and neurologic disorders such as epilepsy, schizophrenia, anxiety, and autism (Fishell & Rudy, 2011, Mossner et al., 2020). Insight into the roles of GABAergic INs in the cortex may ultimately help elucidate their contributions to these neurologic disorders.

The connectivity of IN classes has been established through anatomical and functional studies. PV- and SST-INs directly inhibit excitatory pyramidal cells through perisomatic and distal dendritic synapses, respectively (Rudy et al., 2010; Atallah et al., 2012; Cottam et al., 2013; Glickfeld et al., 2013; Kubota et al., 2016, Cone et al., 2019). In contrast, VIP-INs primarily inhibit SST-INs, leading to disinhibition of excitatory cells (Pfeffer et al., 2013; Pi et al., 2013; Fu et al., 2014; Karnani et al., 2016; Garcia-Junco-Clemente et al., 2017; Cone et al., 2019). While advancements have been made in understanding the role of GABAergic INs as a whole on cortical activity, their heterogeneous responses to stimuli within subclasses (Khan et al., 2018) have made their unique contributions to sensory processing difficult to fully characterize.

The visual cortex—where PV-, SST-, and VIP-INs make up 80% of the IN population (Pfeffer et al., 2013)—presents a unique opportunity to better understand the varied inhibitory IN subtypes due to the ability to simultaneously investigate sensory processing, perception, and cognition. By studying animal models engaged in perception tasks, the largely unexplored effect of IN manipulation on sensory perception can be identified. The few existing studies using optogenetic activation or suppression of VIP-INs have demonstrated both increased and decreased activity of the surrounding local network (Ayzenshtat et al., 2016; Cone et al., 2019). These differing results are likely due to vastly different ways of stimulating interneurons, such as differing power and frequency of the optogenetic manipulation. Furthermore, optogenetic manipulation only transiently activates or suppresses activity, a characteristic that makes it difficult to study the long-term effects of IN-specific activation or suppression on perceptual learn-

ing.

Perceptual learning refers to long-lasting changes to an organism's cortical network that improves its ability to respond to its environment by using previously unused information (Gibson and Gibson, 1955; Goldstone, 1998). Improved performance on visual tasks has been attributed to improvements in the existing cortical network's ability to reweight its sensory inputs after task-relevant training (Dosher and Lu, 2017). Chronic disruption of VIP-INs using gene deletion early in development impaired contrast perception and disrupted perceptual learning at low-contrast visual stimuli (Batista-Brito et al., 2017). However, gene deletion early in development may have confounding effects from circuitry compensatory mechanisms. Given the mixed literature on VIP-INs, further research is needed to identify the role of VIP-INs in visual perception and learning.

The chronic local removal of VIP-INs in the primary visual cortex (V1) of adult mice may shed insight on the normal function of VIP-INs in perception and perceptual learning, a difficult challenge to solve using only acute optogenetic approaches. We found that chronic ablation of VIP-INs using selective caspase-induced apoptosis in the adult mouse visual cortex led to faster perceptual learning and improved final steady-state performance during arousal. Our results suggest that task performance using small visual stimuli may be particularly sensitive to these effects.

MATERIALS AND METHODS

Experimental animal model

All animal handling and maintenance was performed in accordance with the regulations set by the Yale University School of Medicine Institutional Animal Care and Use Committee. Transgenic mouse lines were crossed to produce VIP-Cre$^{+/0}$/Ai9$^{+/0}$ reporter animals. Both male and female mice were used.

Caspase injection and headpost surgery

Genetically engineered caspase was used to selectively deliver caspase to molecularly defined VIP-INs in the visual cortex (Yang et al., 2013). Using an aseptic technique, anesthetized adult mice were bilaterally injected with 1 µl of caspase virus (rAAV5/Flex-taCasP3-TEVP, ~10^{12} viral particles) or 0.9% saline in V1 at a depth of 350 µm beneath the pial surface and a rate of 0.060 µl/min. After injection, the skull surface was sanitized and mice were implanted with an adhesive cement (C&B Metabond, Parkell) headpost stabilized by a skull screw (McMaster-Carr) placed in the anterior pole. Two nuts (McMaster-Carr) were placed within the cement headpost to allow for headpost fixing during behavioral experiments. Mice were given 3-5 days following surgery to recover prior to wheel and task training.

Wheel training and visual detection task

Mice were headposted in place with a natural running head angle on top of a circular wheel. Mice were headposted daily for increasing intervals until they exhibited consistent running bouts throughout a 60-minute session (~8-10 days) as measured by a wheel sensor. Mice were also placed on a water-controlled schedule with careful weight monitoring. Once mice stabilized to 83-86% of their starting weight and exhibited consistent running bouts, mice were trained on a GO/NOGO contrast visual detection task (Figure 1A). Mice were first trained to respond by licking to a full-screen shifting vertical grating (contrast = 100%, spatial frequency = 0.05 cycles per degree, temporal frequency = 2 Hz, duration = 1 second) and were rewarded with a 3 µl water droplet upon successful detec-

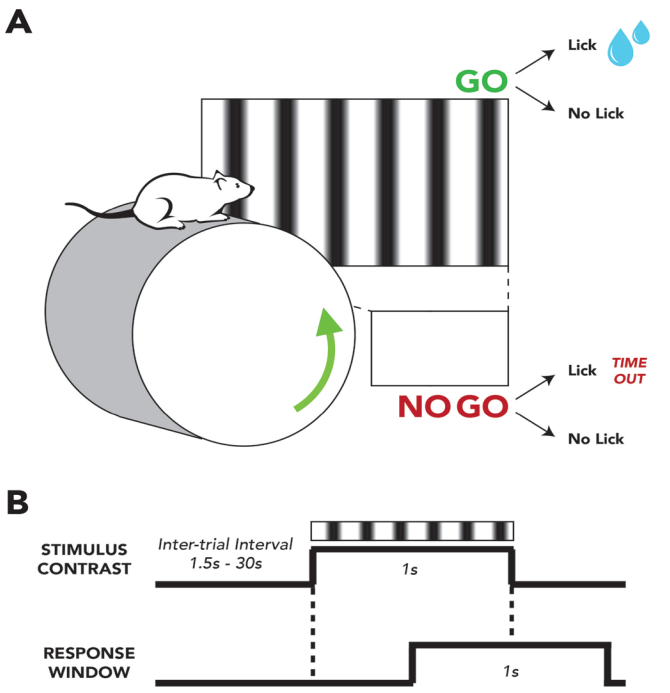

Figure 1. Schematic of visual detection task. *(A) Water-deprived mice were trained to respond by licking upon detection of a full-screen shifting vertical grating stimulus. Detection results in a water delivery reward, while a false hit results in a time out. Mice are head-fixed and allowed to run freely on wheel. Tasks are run for 45 mins/day for 10-15 days. (B) The stimulus begins with the presentation of a grating for 1 second. Mice have 1 second to respond to the visual stimulus following a 0.5 second delay following stimulus onset.*

tion of the grating stimulus within 2 seconds of stimulus presentation (Figure 1B). Incorrect hits were followed by a time out (Figure 1A). Inter-trial intervals were randomly varied using an exponential distribution with a flat hazard rate. Mice were trained until they achieved a correct hit rate of at least 95% and a maximum false alarm rate of 10% (~5-10 days). They were then placed on the visual detection task of interest with a full-screen shifting vertical grating of varying contrasts (0.35%, 0.5%, 0.75%, 1%, 2%, 5%, 10%, 20%, and 100%) for 10-15 days. The visual detection task was based on one used in a previous study (Batista-Brito et al., 2017). Given that surgical recovery and behavioral task training takes approximately 22-35 days in total, all mice used for behavioral experiments began the varying contrast detection task no earlier than 22 days following injection. Training timepoints were chosen to allow for learning and ensure the caspase virus could achieve full ablation (Figure S1).

Behavioral data analysis

All quantitative analysis of perceptual performance data was performed using MATLAB. For each session, we constructed psychometric performance curves using a sigmoid function based on the hit rate (HR) at each contrast. The true hit rate was found by correcting for the false alarm rate (FAR) per session ($HR_{true} = (HR_{observed} - FAR) / (1 - FAR)$). Sessions were removed from the analysis if the median FAR at the two lowest contrasts (0.35% and 0.5%) exceeded 50% or if the median HR at the highest contrast (100%) was below 75%. Additionally, all sessions were required to have at least 50 trials for inclusion. Complete task disengagement at the end of a session was identified and removed, as well as intra-session bouts of task disengagement indicated by 10 subsequent trials of inactivity. Performance was separated by arousal state indicated by quiescence or any duration of locomotion during a visual stimulus trial. The psychometric performance curve per day per mouse was constructed by bootstrapping the trials per session. We used a hierarchical bootstrapping approach (Saravanan, Berman, and Sober, 2019) to produce summary data. To do so, we created 5,000 new datasets by resampling with replacement first at the level of animals followed by trials within a session. We then computed the mean across all trials for each contrast for each resampled data set. The final statistic is computed on this population of resampled means. Resampled hit rates were compared by calculating the probability that resampled hit rates were greater than a specified day (over time comparisons) or greater for caspase mice compared to control mice (between experimental group comparisons). To track perceptual learning, the parameters used to plot the performance curves were also used to analyze the change over time in: 1) the contrast needed to achieve 50% detection (C_{50}), and 2) the change in true hit probability at a given contrast.

Histological analysis

Upon completion of the behavioral task, mice were transcardially perfused with 4% paraformaldehyde (PFA)/phosphate buffered saline (PBS) solution. Brains were removed and fixed in 4% PFA/PBS solution for 24 hours and subsequently stored in PBS. Tissue was sectioned at 40 µm using a vibrating blade microtome, mounted, and visualized by light microscopy. Cell counting was performed manually using a standardized 100 µm x 100 µm grid overlay to determine the average VIP cell density in layers 2/3 of V1 across three consecutive sections. All figures were created using Prism, MATLAB, and Adobe Illustrator.

RESULTS

Caspase-induced apoptosis selectively ablated VIP-INs in V1

We confirmed the efficacy of injecting 1 µl of caspase virus in a subset of the mice used for behavioral experiments (n = 4/8 caspase mice, n = 4/8 control mice) ex-vivo. Cell density in most mice was comparable to values seen during a previous caspase efficacy and time course study (Supplemental Methods, Figure S1) and were not significantly different between the hemispheres of each mouse (student's t-test per mouse, $p > 0.10$; Figure 2A). In general, caspase mice had significantly reduced VIP cell density ($\rho_{avg, caspase} = 16.6$ vs. $_{\rho avg, control} = 235.1$; unpaired student's t-test, $p < 0.001$; Figure 2B). While a histological analysis on the full cohort of behavioral mice could not be conducted due to COVID-19 interruptions, the partial histological dataset shows selective VIP-IN ablation occurred at levels consistent with the findings from the experimental method validation study (Figure S1).

VIP-ablation enhanced the perceptual learning timeline

Generally, all mice demonstrated improved task performance by maintaining detection of high contrasts and learning to respond to low contrasts over time. This trend is indicated by a leftward shift in the psychometric performance curve (Figure 3). Detection of 1% and 10% contrasts was not significantly different between early and

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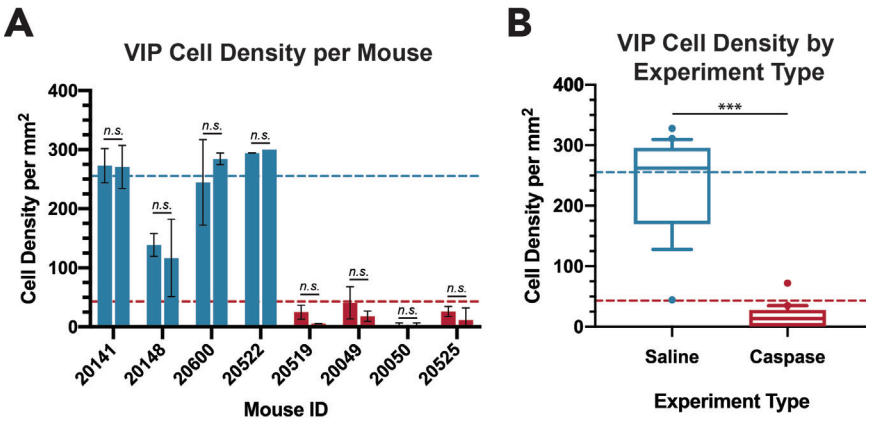

Figure 2. Successful ablation of VIP-INs in mice used for behavioral experiments. *(A) To verify the success of caspase-induced cell death in mice used for behavioral experiments, brain tissue was fixed, sectioned, and imaged. Average VIP cell density (per mm2) were computed within each hemisphere of experimental mice using 2 to 3 subsequent coronal sections of V1. Mice injected with caspase are depicted in red (n = 4) while those injected with saline are depicted in blue (n = 4). Error bars depict the SD in each hemisphere. Unpaired Student's t-tests were used to determine significant differences in cell density between the two hemispheres of each mouse (n.s. = p-value > 0.10). The dashed blue and red lines demarcate the mean VIP cell density expected following 21 days of saline or caspase incubation, respectively. Cell counts for n = 4 caspase mice and n = 4 control mice were not conducted due to COVID-19 interruptions. (B) Box and whiskers plot showing the 10-90th percentile of VIP cell density found in mice used in behavioral experiments (n = 4 caspase, n = 4 control). Cell counts below the 10th percentile and above the 90th percentile are indicated by single dots. The dashed blue and red lines demarcate the mean VIP cell density expected following 21 days of saline or caspase incubation, respectively. Unpaired students' t-tests were used to determine a significant difference in cell density between caspase and control mice (*** = p-value < 0.001).*

late days for controls (day 1 > day 8, p = 0.59 and 0.29, respectively) and caspase mice (day 1 > day 8, p = 0.29 and 0.20, respectively) (Figure 4A). Mice did improve their detection of 2% contrast gratings over time (day 1 > day 8, p = 0.09 (control), <0.001 (caspase); Figure 4A). However, detection of 2% contrast did not exceed detection by chance (50% detection) for either group after day 6. This suggests more significant improvements in perception could have occurred in the 2-5% contrast range.

Perception of stimuli was comparable between groups during the early phase of learning (days 1 and 2). There was no significant difference between controls and caspase-injected mice in early detection of 2% and 5% contrasts (probability of resampled caspase means being greater than or equal to control means was p = 0.6832 and 0.6909, respectively) (Figure 4B). Arousal, as indicated by locomotion, improved detection of stimuli comparably between groups (Figure 5A). During the middle phase of learning (days 4 and 5), caspase mice exhibited increased detection of the 2% contrast grating compared to control mice. A caspase advantage at 2% contrast is seen in 92.36% of all paired hierarchical bootstrapping mean hit rates (Figure 4C). Improved performance during the middle phase of learning was driven by improved detection during times of locomotion (Figure 5B). During the late phase of learning (days 8 and 9), the bootstrapped hit rates of caspase and control mice reflected unity (Figure 4D). Small but insignificant improvements in late performance during locomotion were made by both groups compared to that during the middle phase (Figure 5C). However, late phase caspase mice performance during quiescence significantly decreased compared to that of the middle phase (Figure 5C). Overall, learning appeared to occur faster in caspase mice as indicated by a significant leftward shift (caspase middle vs. early performance, p < 0.01) in the 3-day average psychometric performance curve during locomotion in the middle phase of learning

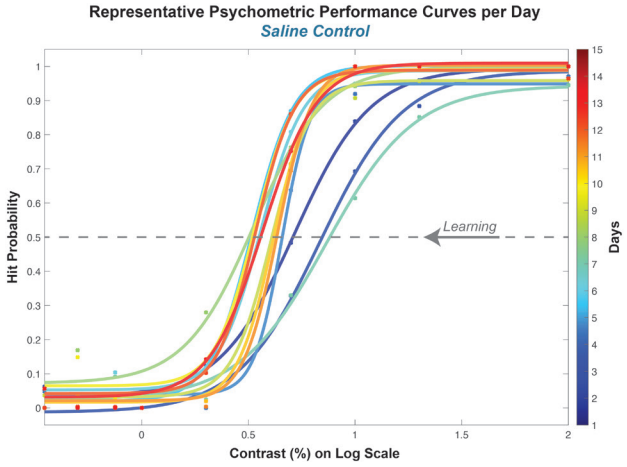

Figure 3. Psychometric performance curves of a single mouse across multiple days. *Mice were run daily on a visual detection task of varying contrasts (0.35%, 0.5%, 0.75%, 1%, 2%, 5%, 10%, 20%, and 100%). Psychometric performance curves were created by bootstrapping the trials per mouse and per day fit to a sigmoid function. Hit rates underwent data cleaning and false alarm correction. Individual hit rates are shown using markers color-coded by the task day. The contrast at which the gray dashed line and the psychometric curve intersect is the contrast at which the mouse detects the stimulus in 50% percent of trials (C_{50}). Movement of the C_{50} to lower values is generally noted within each mouse as an indicator of perceptual learning.*

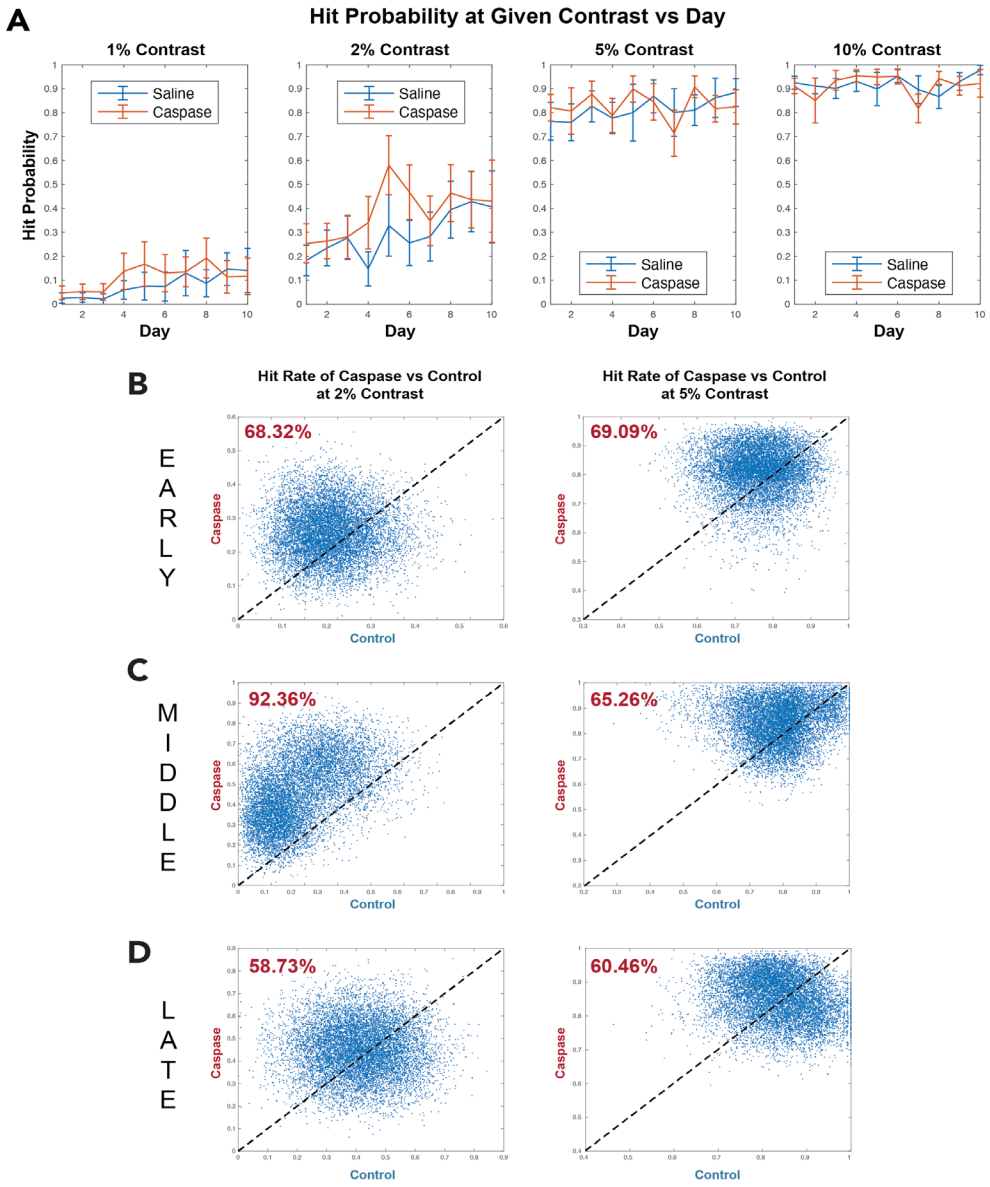

Figure 4. Comparing the perception of low contrast stimuli over time between types of experimental mice. *(A) Hierarchical bootstrapping was conducted by creating 5,000 datasets constructed by resampling at the level of animals followed by trials of a given day. The mean hit rate at each contrast was computed. The mean hit rate at 1, 2, 5, and 10% contrasts is graphed over time per experiment type. Mice injected with caspase and saline are indicated by the red and blue lines, respectively. Error bars indicate the SEM. (B-D) The joint probability distributions of VIP-ablated and control mice for the early (Day 1 and 2), middle (Day 4 and 5), and late (Day 8 and 9) phases of learning were plotted to compare the hit probability at 2% and 5% contrasts. The red percentage value indicates the percentage of paired trials in which VIP-ablated mice performed better than control mice at the given contrast and stage of learning.*

not seen in control mice (Figure 5B). We find that mice with diminished VIP-IN density exhibit an enhanced rate of perceptual learning and improved perception during arousal compared to control mice.

The C_{50} value is an indicator of the lowest contrast at which a mouse is able to detect a stimulus with a greater than chance probability. The C_{50} value is extrapolated from the measured hit rates using the psychometric performance curves. All mice in the caspase and control groups achieved a reduction in their C_{50} during the task (Figure 6A), suggesting improved performance. Some mice exhibited increments in their C_{50} during later days and were not included in the analysis of days thereafter. Given that most mice (n = 4/8 control, n = 6/8 caspase) met exclusion criteria (see Materials and Methods) by day 9, C_{50} analyses were focused on days 1-8. The control group demonstrated moderate C_{50} reductions through day 6 (31.9% reduction achieved), while the caspase group demonstrated C_{50} reductions through day 8 (80.6% reduction achieved) (Figure 6A). We found that of mice that did not exhibit chronic task exhaustion, mice with VIP-ablation showed greater percentage reductions in C_{50} suggesting improved task performance compared to their control counterparts (Figure 6A). Similarly, as a raw change in C_{50} compared to day 1 performance, the caspase group achieved a larger maximum decrease in C_{50} ($\Delta_{caspase}$ = -0.321 vs. $\Delta_{control}$ = -0.200) in a shorter time period ($time_{caspase}$ = 6 days vs. $time_{control}$ = 8 days) compared to the control group (Figure 6B). However, it is difficult to determine the precise timing of when the learned steady-state was achieved given that the sampled group reduced in size during later days due to high false alarm rates (see Materials and Methods). Generally, the data suggest that of mice that do not expe-

rience task exhaustion, caspase mice make faster and larger reductions in C_{50} relative to control mice. This further supports that mice with localized chronic VIP-IN ablation experience enhanced perceptual learning.

VIP-ablation has similar enhancing effects on the performance of a small stimulus task

After completion of the full-screen visual detection task, a small cohort of mice (n = 2 caspase, n = 2 control) were retrained for detection of a smaller circular grating (20° azimuth) in an exploratory experimental extension to test the robustness of our findings to stimulus design (Supplemental Methods, Figure S2). Task performance generally improved among both groups of mice with psychometric curves resembling those of the large stimulus task (Figure S2). Overall, VIP-ablation appears to enhance perception and perceptual learning of a small stimulus task compared to control mice (Figure S2). The enhanced perception of lower contrasts (~5%) is lasting throughout the duration of task learning (Figure S2). Despite the small sample size, this extension demonstrates our findings are likely robust to stimulus size.

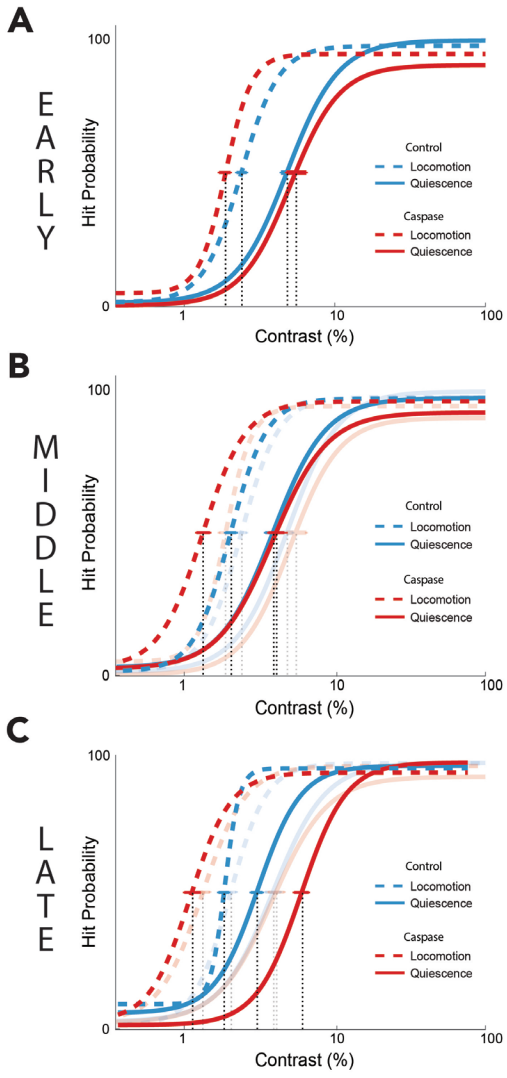

Figure 5. Psychometric performance curves of control and caspase mice over time by arousal state. *The psychometric performance curve fits were averaged across early (days 1-3), middle (days 4-6), and late (days 7-9) phases of learning. States of locomotion and quiescence are represented by the dashed and solid lines, respectively. Mice injected with caspase and saline are indicated by the red and blue lines, respectively. Error bars indicate the C_{50} SEM. (B-C) The dark shaded lines indicate curves for the middle (B) or late (C) phase of learning. Light shaded lines represent performance from the previous learning phase for comparison.*

DISCUSSION

We have shown that localized chronic ablation of VIP-INs through caspase-induced apoptosis does not affect naïve (early) performance on a full-screen visual detection task. However, mice with suppressed levels of VIP-INs achieved their final expert state more rapidly than control mice and exhibited better performance during locomotion. We further explored the effect of localized VIP ablation on the performance of mice on a small stimulus task, and found similar enhancing effects on both perception and learning. These results suggest VIP-INs have an important role in modulating the learning process of cortical networks in the primary visual cortex.

Our approach of chronic ablation in adult mouse V1 allowed us to identify the importance of VIP-INs in perception and learning. Recent literature has focused on optogenetic activation or suppression which only produces a transient effect (Ayzenshtat et al., 2016; Cone et al., 2019). While helpful in elucidating the online role of VIP-INs in perception, optogenetic approaches make studying long-term learning mechanisms difficult. Additionally, chronic suppression or heightened activation are more likely than transient suppression and activation outside of the lab setting.

We found that the chronic ablation of VIP-INs does not affect performance at high contrasts (>10%) during any segment of the learning timeline. Given VIP-IN activity is normally suppressed below baseline in response to high contrast gratings in all directions (Millman et al., 2019), this makes intuitive sense. However, our finding that VIP-ablation resulted in mice improving their detection of low contrast stimuli (2% and 5% contrasts) faster than control mice is in opposition to the existing literature, albeit limited. One study finds that dysregulation of VIP-INs through ErBB4 gene deletion in early develop-

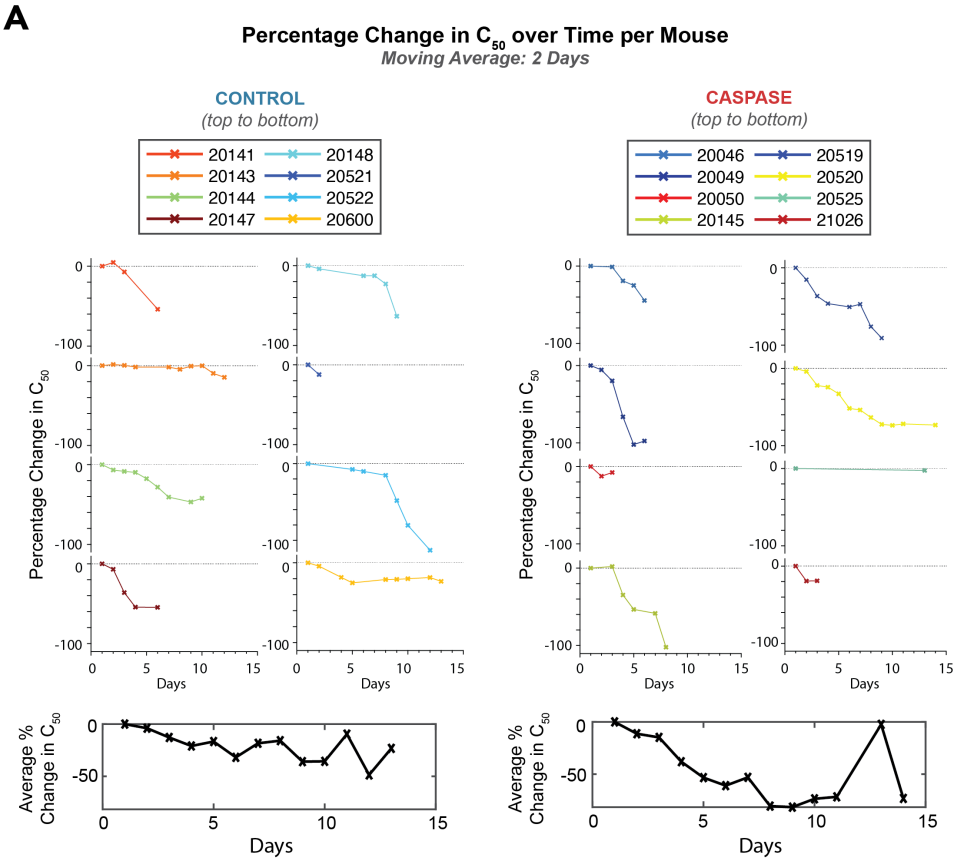

Figure 6. Comparing perceptual learning using C_{50} values as an indicator of performance.
(A) The contrast at which mice detect 50% of trials (C_{50}) is plotted for each individual mouse. The C_{50} value at each day is a 2-day moving average and normalized as a percentage change from the C_{50} on Day 1. Traces for individual mice are separated into section delimited by dashed lines and begin at 0% on Day 1. Individual sessions were removed based on a high false alarm rate at low contrasts or low hit rate at high contrasts (Materials and Methods). Mice that exhibited a C_{50} increase greater than or equal to 5% compared to Day 1 were not included thereafter. The average percentage change in C_{50} over time is plotted by experiment type. (B) The change in C_{50} compared to Day 1 performance is presented in units of log10(% contrast) and averaged using a 2-day moving average by experimental type (caspase in red and control in blue). Mice were removed from a given day based on a high false alarm rate at low contrasts or low hit rate at high contrasts (Materials and Methods). The sample size for caspase mice ($N_{caspase}$) and control mice ($N_{control}$) is indicated in red and blue, respectively.

ment impairs perception at all contrasts under 5% (Batista-Brito et al., 2017). The hit probabilities achieved by the control mice at low contrasts reported in Batista-Brito et al. (2017) (near 100% hit rate for 1-2% contrasts) were much higher than in our experiments (under 50% detection). One explanation for these discrepancies may lie in key differences in their task design, such as the presentation of gratings in multiple directions and the use of a tone to cue the onset of a trial. The converse of our finding, that VIP-IN activation impairs performance on a visual task is also opposed by the literature. One study found that optogenetic activation of VIP-INs improved contrast increment detection (Cone et al., 2019). However, activation and inactivation of the same neuronal class has been found to not produce consistent insights (Phillips and Hasenstaub, 2016). As such, our use of chronic ablation as opposed to transient activation may explain our seemingly conflicting results.

One possible explanation of our results is that chronic VIP-IN ablation shifted the tuning of excitatory pyramidal cells to a spatial frequency aligned with the one used in our behavioral task (0.05 cycles/degree). One study found that optogenetic suppression of VIP-INs resulted

in a stronger network response to stimuli of lower spatial frequencies (Ayzenshtat et al., 2016). If the overall network favored a frequency higher than 0.05 cpd at normal baseline, a shift toward our lower task-specific spatial frequency may explain the improved performance of the caspase mice.

A second explanation relies on the fact that locomotion generally increases neural responses in both broad- and narrow-spiking cells (Niell and Stryker, 2010). More specifically locomotion increases pyramidal cell activity (Niell and Stryker, 2010; Ayaz et al., 2013; Fu et al., 2014, Millman et al., 2019). Consistent with this literature, our findings indicate that locomotion improves performance of a visual contrast detection task at all phases of learning. In general, the group of caspase mice engaged in locomotion more so than the control group according to preliminary data. The increased arousal-state of caspase mice may have resulted in greater pyramidal cell gain even at low contrasts compared to control mice. However, recent studies have found that chronic VIP-IN activity disruption eliminates the visual response gain observed during periods of locomotion (Batista-Brito et al., 2017, Mossner et al., 2020) weakening this explanation.

A final explanation could be that chronic VIP-IN ablation shifted inhibition away from the soma and toward distal dendritic sites. Of all INs, PV-INs provide the largest level of inhibition on pyramidal cells when controlling for cell population, unitary inhibitory postsynaptic charge, and probability of connection to pyramidal cells (Pfeffer et al., 2013). Given that chronic VIP-IN suppression is expected to lift inhibition off of SST-INs (Pfeffer et al., 2013; Pi et al., 2013; Fu et al., 2014; Karnani et al., 2016; Garcia-Junco-Clemente et al., 2017; Cone et al., 2019), more SST-INs would be allowed to inhibit PV-INs. As a result, pyramidal cells may experience less inhibition from PV-INs at the soma and more inhibition through distal dendritic sites from SST-INs. Given that action potentials are determined by the integration of all inhibitory and excitatory postsynaptic potentials at the cell soma, the shift in inhibition along the somatodendritic axis of pyramidal cells may make firing of pyramidal cells more likely. As a result, caspase mice could experience greater response gain to visual stimuli compared to control mice.

In summary, we find that localized ablation of VIP-INs in the primary visual cortex may improve the perceptual learning timeline of a contrast detection task and final steady-state performance during times of locomotion when using both full-screen and small vertical grating stimuli. VIP-IN ablation does not appear to affect performance during naivety. Given that the greatest change in performance occurred in the 1-10% contrast range, future experiments should aim to gain data granularity over that specific range. The clear role of VIP-INs in perception and perceptual learning highlighted in this paper reveals the need for future work to explore the robustness of our findings by altering the parameters of the behavioral task, including stimulus size.

ACKNOWLEDGEMENTS

The authors are grateful to the Cardin Lab and the Yale Animal Resources Center for their support with tasks integral to the success of this research including mice handling, task and equipment design, and programming.

SUPPLAMENTAL MATERIALS

Supplemental Methods, Figure S1, and Figure S2 are available in the online appendix.

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