**Cortical efficient coding shapes behavioral performance.**

Chris Angeloni1,2, Wiktor Mlynarski3, Aaron M. Williams2,5, Katherine C. Wood2, Linda Garami2, Eugenio Piasini5, Ann Hermundstad4, Maria N. Geffen2,5

1Department of Psychology, University of Pennsylvania, Philadelphia, PA, USA

2Department of Otorhinolaryngology, University of Pennsylvania, Philadelphia, PA, USA

3Institute of Science and Technology Austria, Klosterneuburg, Austria

4Janelia Research Campus, Howard Hughes Medical Institute, Ashburn, VA, USA

5Department of Neuroscience, Department of Neurology, University of Pennsylvania, Philadelphia, PA, USA

**Abstract**

The efficient coding hypothesis postulates that neurons shape their response properties to match their dynamic range to the statistics of incoming signals. However, whether and how such efficient neuronal codes inform behavior has not been previously shown directly. Here, we trained mice to detect a target presented in noise shortly after a change in the noise contrast. The observed changes in behavior followed the predictions of a normative model of efficient cortical sound processing. Target detection and sensitivity improved in low contrast relative to high contrast noise. Furthermore, the time course of target detectability varied depending on contrast, decreasing rapidly after a transition to high contrast, and increasing at a slower rate after a transition to low contrast. The auditory cortex was required for detection of targets in noise and cortical neuronal responses exhibited the predicted patterns of target detectability. The magnitude of gain modulation in cortical neurons predicted individual differences in behavioral performance. Combined, our results demonstrate that efficient neural codes in auditory cortex directly influence perceptual behavior.

**Introduction**

As we navigate the world around us, the statistics of the environment can change dramatically. The efficient coding hypothesis postulates that neurons match their limited dynamic range to the statistics of incoming sensory signals[1]. Thus, through adaptation of their response properties, neurons can preserve their ability to encode information within many types of environments[2–4]. Such neuronal adaptation to the statistics of the environment has been found throughout different sensory modalities and brain regions[5–13]. In the auditory system, neurons exhibit contrast gain control, adapting the gain of their response function to match the contrast (variance) of the incoming sounds[14–18]. Yet it remains unknown whether and how contrast gain control in the auditory system informs behavior, as a direct link between neuronal adaptation and behavior has not been previously established. The goal of our study was to test the hypothesis that the efficient coding in auditory cortex shapes behavioral performance in an auditory task.

The efficient coding hypothesis has been formally implemented through normative models of brain function[3,19–22]. These models allow us to simulate how neural function constrains behavior and to assess whether and how neuronal adaptation shapes sensory representations. There has been previous work demonstrating that efficient codes can explain psychophysical biases[23] and shape the rate of information transmission when stimulus statistics change dynamically [19,21,22]. These studies, which are either theoretical in nature or based in human psychophysics, rely on assumptions of neuronal mechanisms of efficient coding that were not simultaneously measured. As such, there are no studies combining behavioral psychophysics with recordings of brain activity to simultaneously test the neural assumptions and behavioral predictions of these models.

Psychophysical studies suggest that the auditory system exhibits adaptation to acoustic contrast. In humans, target volume discriminability is greater in low contrast than in high, an effect consistent with gain control observed in primary auditory cortex[24]. Similar effects have also been shown in ferrets performing an acoustic localization task, where it was demonstrated that neural responses in the inferior colliculus of anesthetized ferrets changed in a manner consistent with observed perceptual shifts[10]. However, it remains unclear whether the observed behavioral effects are indeed due to changes in gain in auditory neurons, as previous behavioral studies were not performed with simultaneous neural recordings, so a direct relationship between neural gain and perceptual performance has yet to be assessed.

Our goal for the study was to first build a formal framework based on efficient coding to predict behavioral detection of targets given changes in background sound contrast. Next, to directly test the role of efficient coding in auditory behavior, we trained mice to detect targets in variable contrast backgrounds. Mouse behavior followed the model predictions. Simultaneous chronic neural recordings show that the neural code in auditory cortex is not only predictive of individual differences in behavior, but also that variability in neural contrast adaptation is predictive of individual variability in task performance in a contrast-dependent manner. Combined, our results identify a novel relationship between efficient neuronal coding and acoustic behavior, and provide a normative framework that can be used to predict behavioral performance across other behaviors and sensory modalities.

**Diagram

Description automatically generatedFigure 1.**

1. Experimental setup. Head-fixed mice are presented with sounds from an ultrasonic speaker. During behavior, mice receive water rewards through a lick spout. In a subset of mice, tetrodes were implanted in ACtx to record spiking activity.
2. GO/NO-GO task design. *Left:* example NO-GO trials. From top to bottom: spectrogram of an example low-to-high contrast trial (colorbar indicates volume in dB SPL); waveform for sample spectrogram; example spectrogram for a high-to-low contrast trial; waveform for example spectrogram; temporally jittered response window to estimate false alarms over time; schematic lick responses during in the window; timeout delivered after the first lick for 7 seconds. Vertical red dashed line indicates the contrast switch after 3 seconds. Black horizontal scale bar indicates 1s. *Right:* example GO trials. From top to bottom: same as in left panel, except the response window immediately follows target presentation and licks within the target window trigger a ~5uL water reward.
3. Target manipulation example waveforms. *Top:* overlaid trials where target volume differed. Volume is indicated by the amplitude and colorbar, with low volume targets shaded in cyan, and high volume targets shaded in magenta. *Bottom:* overlaid trials where target timing differed. Target timing is indicated in the colorbar, with light magenta targets occurring shortly after the contrast switch, and darker targets occurring at increasing delays. The red vertical dashed line indicates the contrast switch.
4. Normative model of the task. Left inset shows volume distributions for backgrounds (light lines) and targets (dark lines) in low and high contrast. (1) Spike generation process: a 1-dimensional sensory stimulus consisting of a background that transitions between low and high contrast (light lines) with superimposed targets (solid dots) feeds into a model neuron. The response of the model neuron is governed by a sigmoidal function which then generates stochastic spikes through a Poisson process. (2) Based on the observed spiking, a variance estimator integrates spike counts to estimate the current variance of the stimulus. (3) This estimate is then used to adjust the gain of the model neuron to optimize the estimate of stimulus variance at each time step. (4) The average change in gain of the model after each contrast transition. Dashed lines and dots indicate the time taken to reach half of the range of gain values in each contrast.
5. Model psychometric functions. Discriminability between model spike rates in response to the background and targets as a function of contrast and target volume. Light dots indicate model discriminability whereas the solid lines indicate logistic fits to the data (see *Methods*). Dashed lines indicate detection thresholds (defined as from the logistic fit). Arrow indicates target mean of 1.50 which is the volume used to assess time courses in **f**.
6. Model target discrimination as a function of time and contrast. Dashed vertical line indicates the time where the background contrast changes.
7. Model predictions for the effects of contrast on psychometric thresholds, slopes, and adaptation times.

**Results**

*A novel target-in-noise detection task and normative model for task predictions.*

To assess how perceptual performance is impacted by stimulus contrast, we devised a GO/NO-GO task in which head-fixed mice were trained to detect targets embedded in different contrast backgrounds. During each trial, the mouse was first presented with 3s of dynamic random chords (DRCs) of one contrast, after which a switch occurred, either to a higher or lower contrast background. At variable delays after the switch, broad-band target chords were superimposed on the background chords, and mice were trained to lick for a water reward upon hearing the target. Target trials were interleaved with noise-only trials, during which the mouse was trained to withhold licking, but would receive a 7s timeout if licking after the contrast switch (Figure 1a,b). To assess behavioral sensitivity to targets, we parametrically varied target volume in each contrast (Figure 1c, top panel) and to assess behavioral adaptation, we parametrically varied target timing (Figure 1c, bottom panel). This stimulus design allowed us to quantitatively test whether and how adaptation to background contrast affects behavioral performance.

To build an intuition for the effects of contrast gain control on target detection behavior, we developed a normative model of task performance constrained by efficient neural coding. In this model, we simulated a neuron designed to estimate the contrast of the recent stimulus by adjusting the gain of its nonlinearity. A detailed description of the model is provided in the methods, but briefly: 1) at each timestep, a background stimulus which varied in contrast generated stochastic spikes in the model neuron, 2) based on this spiking activity, the variance of the background in a brief window before the current timestep is estimated, 3) the variance estimate error is then fed back to the model neuron and the neuron adjusted the gain of its nonlinearity to improve the estimate (Figure 1d, panels 1-3). Additionally, we simulated target responses by adding targets at different volumes at each timestep after a contrast transition. This allowed us to probe the model neurons sensitivity to targets as it adapted to the background.

Using this framework for efficient coding of stimulus contrast, we examined how discriminable target responses were from background responses as a function of target volume and timing. This model generated three primary hypotheses: 1) When varying the target mean in each contrast, we observed that in low contrast, the model is more sensitive to changes in volume, as indicated by the steeper slope, and has lower detection thresholds compared to high contrast (Figure 1e). 2) When holding target volume fixed and varying target time relative to the change in contrast, target detectability increases after a switch from low to high contrast, but decreases after a switch from high to low contrast (Figure 1f). 3) The time course of gain adaptation in the model is asymmetric: gain changes faster after a switch from low to high contrast than after a switch from high to low contrast (Figure 1d, panel 4). Next, we tested these hypotheses by analyzing mouse performance in an analogous GO/NO-GO task (Figure 1).

*Mouse behavioral detection is modulated by background contrast.*

Mice were initially trained in a simple version of the GO/NO-GO task, where they were required to lick in response a high SNR target presented on go trials, and withhold licking on trials in which only background noise was presented. Mice learned this task reliably, typically reaching criterion performance of 80% correct within 2-3 weeks in either contrast and performed this task for many weeks (Figure 2a). After mice performed above criterion for at least three sessions, they moved on to psychometric testing.

By varying the volume of presented targets, we collected psychometric curves of 21 mice in low and high contrast (Figure 2b). Across all mice (n = 21), we found that targets were easier to detect in low contrast, observing significantly lower detection thresholds in low contrast (*M* = 7.29, *SD =* 1.44) compared to high contrast (*M =* 12.89, *SD =* 1.80; paired t-test: *t(40)* = -11.13, *p* = 8.14e-14, Figure 2c). In a group of mice (n = 4), we presented targets of the same volume in low and high contrast, to ensure that the dynamic range of target volumes was matched across contrasts (Figure 2d). We found significantly lower target thresholds in low contrast (*M* = 5.33, *SD =* 2.46) compared to high contrast (*M =* 12.28, *SD =* 1.31; paired t-test: *t(5)* = -4.38, *p* = 0.007; Figure 2e) and significantly higher psychometric slopes in low contrast (*M* = 0.054, *SD =* 0.007) compared to high contrast (*M =* 0.038, *SD =* 0.002; paired t-test: *t(5)* = 3.86, *p* = 0.012; Figure 2f). These results demonstrate that background contrast has a substantial impact on task performance, and that mice are more sensitive to targets presented in low contrast.

To assess behavioral adaptation to the background contrast, we presented targets at threshold volume at variable delays following the contrast transition. We observed behavioral time-courses consistent with our model: in high contrast, mice initially were able to detect targets with high accuracy which fell off over time, while in low contrast we observed increasing detection rates over time (Figure 2g). We next quantified the speed of behavioral adaptation in each contrast. First, we found that in high contrast, the first significant drop in performance occurred between the first two time points, while in low contrast the first significant increase in performance occurred between the first and third time points (Figure 2g, Table 1). Then, by fitting each mouse’s adaptation time-course with an exponential function and comparing time constants for each contrast, we also found that behavioral adaptation is significantly faster in high contrast (*Mdn* = 0.023) compared to low contrast (*Mdn =* 0.128; Wilcoxon rank-sum test: *rank*  = 547, *Z* = 2.75, *p* = 0.006; Figure 2h).

Chart

Description automatically generated

**Figure 2.**

1. Behavioral performance. Percent correct performance relative to the first session of task exposure. Dots indicate a session, while the traces indicate a running average using a 7 day window. Blue dots and traces indicate sessions in which mice detected targets in low contrast (ie. after high-to-low contrast transitions), while red dots and traces indicate sessions in which mice detected targets in high contrast (ie. after low-to-high contrast transitions).
2. Psychometric functions averaged for n=21 mice in low and high contrast. Error bars indicate SEM over mice at individual target SNRs, while the solid lines are logistic function fits to the average performance per contrast. Colors as in d).
3. Psychometric thresholds per contrast. Each dot represents a mouse, lines connect individual mouse performance on low and high contrast sessions. Bars indicate the average threshold over mice, while error bars in black indicate threshold SEM over mice. Bar colors as in d).
4. Behavioral psychometric functions. Dots with error bars indicate average performance +- SEM over mice as a function of contrast and target volume. Overlaid dark colored lines indicate psychometric fits to the averages, with the black dot indicating the average threshold. Light colored lines indicate the psychometric curves of individual mice. Black horizontal line indicates chance (0.5) performance.
5. Psychometric thresholds per contrast. Each dot represents a mouse, lines indicate where a mice participated in both low and high contrast sessions. Bars indicate the average threshold over mice, while error bars in black indicate threshold SEM over mice.
6. Psychometric slopes per contrast. Presentation as in **e**.
7. Behavioral performance as a function of contrast and target time relative to the switch in contrast. Dots with error bars indicate average performance +- SEM over mice. Solid curves indicate exponential function fits to the average over mice. Black, dashed vertical line indicates the contrast switch. Horizontal lines at the top of the plot indicate significant changes in performance between the first target presentation time and subsequent target presentation times, as assessed by Wilcoxon Sign-rank tests with false discovery rate correction for multiple comparisons.
8. Average time constant of exponential fits in low and high contrast. Presented as in **h**. In all plots, blue indicates when targets were presented in low contrast and red indicates high contrast.

*Auditory cortex is necessary for detection in noise.*

Previous studies have shown that while gain control happens in many areas across the auditory pathway, gain adaptation is strongest in auditory cortex [24,25]. As such, we hypothesized that auditory cortex was likely to be a key brain area supporting the detection of sounds in the presence of background noise, particularly when using background sounds known to modulate neuronal gain. To test this prediction, we inactivated auditory cortex using the GABA agonist muscimol to assess whether it is necessary for task performance. We first validated that muscimol disrupts cortical coding of target sounds by applying muscimol topically to the cortical surface of awake, untrained mice while recording neuronal responses during passive playback of the behavioral stimuli (Supplementary Figure 1a). We first recorded baseline responses to all stimuli, then topically applied muscimol or saline, waited 30 minutes, and recorded stimulus responses again. After muscimol application, there was a marked decrease in neural responses to targets compared to the baseline recordings (Supplementary Figure 1b, top). Notably, in our saline control, we observed little to no change in neural responses after saline application (Supplementary Figure 1b, bottom). We used a 3-way ANOVA to compare the effects of muscimol, contrast, and target volume on target responses in the saline and muscimol recording sessions. We found a significant main effect of muscimol (*F*(1) = 322.65, *p* = 4.88e-67) and volume (*F*(6) = 15.48, *p* = 1.98e-17), but no main effect of contrast (*F*(1) = 0.39, *p* = 0.53), indicating nearly complete suppression of responses to both targets and noise in high and low contrast (Supplementary Figure 1c). These results confirmed that muscimol effectively disrupts the cortical coding of our behavioral stimuli.

To test whether inactivation of auditory cortex affects behavioral performance, we repeated the same experiments in behaving mice, administering muscimol or saline bilaterally through chronically implanted cannulae (Figure 3a). As observed in cortical activity, there was a profound decrease in the rate of responding to both targets (hits) and noise (false alarms) in both contrasts (Figure 3b). We quantified these effects on the psychometric curve using a 3-way ANOVA with cortical intervention (muscimol or saline), contrast, and target volume as factors. We found significant main effects of muscimol (*F*(1,307) = 278.63, *p* = 3.83e-44), contrast (*F*(1,307) = 4.39, *p* = 0.037) and volume (*F*(6,307) = 40.90, *p =* 7.54e-36). Post-hoc tests showed that muscimol application significantly decreased hit rates by 31% (95% CI [28,35]), whereas hit rates were significantly elevated in low contrast by 4.9% (95% CI [2.6,7.6]). Furthermore, we observed significant interactions between target volume and cortical intervention (*F*(6,307) = 14.11, *p* = 4.47e-14), and between target volume and contrast (*F*(6,307) = 2.97, *p* = 7.87e-3), but no significant interaction between contrast and cortical intervention. This pattern of results suggests that muscimol and contrast reshape psychometric performance in a similar manner.

To better quantify the specific effects of muscimol on psychometric performance, we extracted the response rate at maximum volume, false alarm rates, thresholds, and slopes of psychometric functions fit to each session (see Methods). Muscimol significantly reduced every measure of psychometric performance, with the exception of behavioral threshold (Figure 3c, Table 1). From these results, we can conclude that auditory cortex is necessary for performing target in noise detection, regardless of the background contrast.

A potential alternative effect of muscimol is a general loss of function that is not specific to hearing target sounds. To control for this, we devised another task where instead of detecting targets in noise (Figure 3d), mice detected targets in silence (Figure 3e). To ensure equivalency between the two tasks, we took the highest volume trial of the target in noise task (25dB SNR in high contrast; Figure 3d, left panel), and removed the background noise during the target detection period (Figure 3e, left panel). As such, mice detected the exact same targets as in the previous task, but without the flanking noise, allowing us to test whether auditory cortex is specifically required for detection in the presence of noise.

To assess psychometric performance in this new task, we modulated detection difficulty by attenuating the volume of each target. As observed previously, inactivation of auditory cortex hindered detection in high contrast noise (Figure 3d, right panel). However, cortical inactivation had little effect on psychometric performance in silence (Figure 3e, right panel). We quantified these effects on the psychometric curve using a 3-way ANOVA with cortical intervention (muscimol or saline), task (detection in noise or silence), and target volume as factors. We found significant main effects of intervention (*F*(1,181) = 62.83, *p* = 3.62e-13), task (*F*(1,181) = 6.82, *p* = 9.86e-3), and volume (*F*(6,181) = 46.16, *p* = 1.69e-32). Post-hoc tests showed that muscimol significantly reduced hit rates by 21.8% (95% CI [15.2,25.2]), whereas hit rates to targets presented in silence were significantly elevated by 6.7% relative to the noise condition (95% CI [1.7,11.6]). Furthermore, we found significant interactions between cortical intervention and task type (*F*(1,181) = 6.36, *p* = 0.013), intervention and volume (*F*(6,181) = 3.47, *p* = 2.98e-3), and volume and task type (*F*(6,181) = 8.47, *p* = 5.43e-8). Taken together, these results show that while cortical inactivation and the presence or absence of background noise both affect behavioral performance, these effects interact: muscimol has a larger effect on performance when background noise is present.

Diagram

Description automatically generated

**Figure 3.**

1. Setup schematic for chronic muscimol application in behaving mice.
2. Behavioral psychometric functions during muscimol or saline application for n=4 mice. Dark solid lines and filled circles indicate average performance after saline injection. Dark dashed lines and open circles indicate average performance after muscimol injection. Light solid and dashed lines are psychometric curves from individual sessions. Error bars indicate S.E.M. across sessions.
3. Behavioral performance metrics as a function of contrast and pharmacological intervention. Open circles indicate performance in individual sessions. Colored bars indicate average performance across sessions. Bars with low transparency and solid outlines are averages after saline application, while high transparency bars with dashed outlines are averages after muscimol application. Clockwise from the upper left, are plots of the max response rate, false alarm rate, psychometric threshold, and the maximum slope of the psychometric curve.
4. *Left:* Example stimulus spectrogram for the target-in-noise detection task with the corresponding waveform below. The scale line indicates 1 second, and the colorbar indicates the volume for each time-frequency bin. *Right:* psychometric performance for n=2 mice in the target-in-noise task, with target volume on the abscissa and probability of responding on the ordinate. Filled circles and dark solid lines indicate average performance after saline injection and psychometric fits to the average. Red open circles and dark dashed lines indicate average performance after muscimol injection and psychometric fits to the average. Light red solid and dashed lines are psychometric curves from individual sessions. Errorbars indicate S.E.M. across sessions.
5. *Left:* Example stimulus spectrogram for the target-in-silence detection task with the corresponding waveform below. Time scale and volume scale as in **d)**. *Right:* psychometric performance for n=2 mice (same mice as in **d)**) in the target-in-silence task, with target attenuation relative to the highest volume target from the target-in-noise task on the abscissa and probability of responding on the ordinate. Black filled circles and dark solid lines indicate average performance after saline injection and psychometric fits to the average. Open circles and dark dashed lines indicate average performance after muscimol injection and psychometric fits to the average. Light grey solid and dashed lines are psychometric curves from individual sessions. Errorbars indicate S.E.M. across sessions.
6. Behavioral performance metrics as a function of task type (detection in noise or detection in silence) and pharmacological intervention. Formatting and metrics as in **c)**. Dark and light red bars indicate performance in the detection-in-noise task, with application of saline or muscimol. Dark and light grey bars indicate performance in the detection-in-silence task, with application of saline or muscimol.

Previously, we demonstrated interactions between cortical intervention, task and target volume, suggesting that these two manipulations affect the shape of psychometric curves in different ways. As before, we parameterized psychometric performance by fitting each session with a psychometric curve, and extracting the response rate at maximum volume, false alarm rate, response rate at threshold, and psychometric slope. During the target in noise task, we found significant effects of muscimol on the response rates at maximum volume and threshold, a moderate effect on psychometric slope, and no effect on false alarm rate. However, muscimol application had no significant effect on any of these measures in the target in silence task (Figure 3f , Table 1). Taken together, these results demonstrate that cortex is specifically necessary for detection in the presence of noise, and has a much smaller effect on performance during detection in silence.

An additional alternative effect of muscimol is a general loss of the ability to lick. To assess this, we monitored the lick probability of the mice throughout the trial duration, and found that muscimol specifically reduced licking responses during the period where targets were presented (Wilcoxon rank-sum test: *T* = 337, *z* = -4.23, *p* = 2.34e-5; Supplemental Figure 1d, right panel of Supplemental Figure 1e). Mice also tended to lick immediately after the trial onset (Supplemental Figure 1e, left panel), but we found that the lick rates under muscimol and saline conditions were identical during this period (Wilcoxon rank-sum test: *T* = 528, *z* = 0.23, *p* = 0.81). These results suggest that muscimol does not impair the mouse’s ability to lick in general, but results in a specific deficit in licking in response to targets.

Combined, our results demonstrate that the auditory cortex is specifically required for detection in the presence of background noise. Our next goal was to test the relationship between neuronal activity in AC and behavioral performance.

*Population responses to targets track individual behavioral performance.*

To better understand how representations in auditory cortex could give rise to behavior, we chronically recorded from populations of neurons in auditory cortex while mice performed the behavioral task (Figure 4a). In the psychometric task where we varied target volume, many cortical neurons monotonically increased their firing rate with increased target volume (example neuron, Figure 4b; simultaneously recorded populations from two example sessions, Figure 4c).

To leverage our ability to simultaneously record from multiple neurons, we adapted a population vector approach[26] to generate metrics of target from noise discriminability from population activity. To do this, we estimated the coding direction in the high dimensional space of simultaneously recorded neurons by subtracting population vector responses to noise alone from population vector responses to targets. The resulting coding direction vector is the direction in high dimensional space between the average response to noise and targets (Figure 4d, left panel). This vector was trained on all but one trial, and the remaining trials’ population response was projected along this coding direction to generate a single projection value along this coding direction. This was repeated for all trials, and the projection values were averaged for every trial within a 100ms window after target onset. We then grouped these values into trial distributions for each target volume, and compared them to noise trial distributions by estimating a criterion projection value that best predicted whether each was a target or noise trial[27] (example projection value distributions from the recording session in Figure 4C, left panel is shown in Figure 4d, right panel). Using this population decoding method, we then compared the resulting neural performance in the task to behavioral performance.

Using this criterion, we then computed the accuracy of the neural population in discriminating targets from noise at each volume and at each contrast. This allowed us to estimate neurometric functions for direct comparison to the corresponding psychometric functions of each mouse (Figure 4e). On average, neurometric and psychometric functions were qualitatively similar, with neurometric functions exhibiting slightly lower thresholds, and shallower slopes (Figure 4f). We found that behavioral thresholds were highly predictive of the observed neural thresholds across both contrasts (single linear regression: *F*(1,17) = 23.7, *p* < 0.001, *R2* = 0.58; Figure 4g). We also observed a significant relationship between behavioral and neural thresholds in low contrast alone (single linear regression: *F*(1,9) = 6.24, *p* = 0.034, *R2* = 0.34), suggesting that the observed correlation across contrasts is not just due to contrast, but that cortical neurons track behavioral thresholds independently of contrast (Figure 4g). We tested whether neurometric and psychometric thresholds were similarly affected by background contrast using a two-way ANOVA, with thresholds as the dependent variable and threshold measure (psychometric or neurometric) and contrast as independent variables. We found a main effect of contrast (*F*(1) = 29.30, *p* = 5.00e-6), but no main effect of threshold measure (*F*(1) = 0.02, *p* = 0.89) or interaction between measure and contrast (*F*(1) = 0.04, *p* = 0.85), which demonstrates that behavioral and neural thresholds were

Diagram

Description automatically generated**Figure 4.**

1. Experimental setup for chronic ACtx recordings from behaving mice.
2. Example spiking responses to targets and noise in low contrast during behavior. The top portion of the plot is a spike raster ordered by target identity. Colored bars indicate the target volume, grey bars indicate noise only trials. The bottom portion of the plot contains spike rates for each target condition, averaged over trials and smoothed with a 2ms standard deviation Gaussian kernel. *Inset:* Grey solid line indicates the behavioral percent correct for this session. Closed circles and the solid blue line indicate the performance of an ideal observer in discriminating between noise responses and target responses at each volume. Circle colors indicate the presented volume. The dashed horizontal line indicates chance performance (0.5). Error bars are the 95% confidence interval of ideal observer performance as assessed through a bootstrap procedure.
3. Neurograms of populations of simultaneously recorded neurons during a low contrast and high contrast session from the same mouse. Neurons are plotted along the ordinate, while target volume is plotted along the abscissa. Within each plot, shade indicates the neural response to each target, with the average response to noise alone subtracted. White indicates no change in firing rate, blue/red indicate increases in firing rate relative to the noise response, and cyan indicates suppression below the noise response. Asterix indicates the responses of the neuron in panel b).
4. Discriminating targets from noise using population responses. *Left:* schematic of coding direction analysis. In high dimensional neural space, noise trials are represented as a gray point cloud, while target responses are represented as a blue point cloud. The coding direction (CD) is the vector defining the average difference between these two point clouds as indicated by the arrow. *Right:* trial distributions of projections along the coding direction for one session (session CA118-200707, as plotted in **c**). The blue distribution is the average projection value in a 40ms window after presentation of 20 dB SNR targets (indicated by arrow in panel **e**). The gray distribution is the average projection value in the same window during noise only trials. The vertical red line is the criterion which yielded the highest performance in predicting target presence across all trials.
5. Example neurometric and psychometric curves. *Left:* Low contrast curves. Light blue circles and solid lines indicate psychometric performance and a logistic fit, respectively. Dark blue circles and solid lines indicate neurometric performance from the session plotted in the left panel of **c**. The horizontal dashed line indicates chance performance (0.5). The arrow indicates the neural performance computed from the distributions and criterion plotted in **d**. *Right:* High contrast curves from the same mouse for the session plotted in the right panel of **c**.
6. Average psychometric and neurometric functions across mice. Light circles indicate average behavioral performance, dark red and blue circles indicate average neural performance. Light solid curves indicate logistic fits to average behavioral performance, while vertical lines indicate the fit thresholds. Dark solid lines indicate fits and thresholds for the neural data. The dashed vertical line indicates chance performance. Shades of blue and red indicate averages over low and high contrast respectively.
7. Relationship between behavioral and neural thresholds. Each circle represents the average behavioral and neural threshold for each mouse for each contrast (as indicated by the circle fill color). Grey lines and shaded areas indicate the linear regression fit across contrasts, +- the 95% confidence interval. The solid black line indicates unity. Inset text indicates the significance of linear fits between all data points (black), low contrast data points only (blue), or high contrast data points only (red).
8. Relationship between behavioral and neural slopes. Appearance as in **g**).
9. Population decoder performance while varying contrast transition, and target timing relative to the transition (indicated by the dashed vertical black line at 0s). Ticks on the abscissa indicate average target time from the transition in milliseconds. Solid lines and circles indicate the percent correct performance of a target decoder after a switch low contrast (blue) or high contrast (red). Errorbars indicate S.E.M. over sessions. Horizontal lines indicate significant changes in performance between the first target presentation time and subsequent target presentation times, as assessed by Wilcoxon Sign-rank tests with false discovery rate correction for multiple comparisons. The span of the lines indicates the target times being compared, while the color of the lines indicates whether the test was performed within high contrast (red) or low contrast (blue).
10. Adaptation time constants of exponentials fitted to the average neural decoder performance for each mouse in each contrast. Blue and red circles indicate the adaptation time constants from neural populations for each mouse in low and high contrast respectively. Solid black lines indicate time constants from the same mouse.

similarly affected by background contrast. Additionally, we find that across both contrasts there is a significant positive relationship between neurometric and psychometric slopes (single linear regression: *F*(1,17) = 20.4, *p*< 0.001, *R2* = 0.52, Figure 4h), with a significant relationship within high contrast (*F*(1,9) = 7.07, *p* = 0.038, *R2* = 0.46), and a marginally significant relationship in low contrast (single linear regression: *F*(1,9) = 3.93, *p* = 0.079, *R2* = 0.23). We examined whether neurometric and psychometric slopes using a two-way ANOVA, as described above, and found a significant main effect of slope measure (*F*(1) = 5.88, *p* = 0.021) and contrast (*F*(1) = 8.31, *p* = 0.007). Post-hoc testing revealed that psychometric slopes were significantly steeper than neurometric slopes (**DO POST HOC TESTING**). Taken together, these results demonstrate that neurometric and psychometric functions are both affected by contrast in similar ways, and that individual variation in psychometric performance is predicted by population activity in auditory, independently of the effect of contrast.

*Cortical gain tracks individual behavioral performance.*

Our behavioral results and model provide strong evidence that gain control in the auditory system shapes patterns of behavioral performance. To more directly assess the role of gain control in auditory cortex in shaping

behavior, we leveraged the design of our background sounds to estimate the gain of cortical neurons using a generalized-linear-nonlinear model (gLN). Briefly, we estimated the spectrotemporal receptive fields (STRFs) of individual cortical neurons using generalized linear regression and convolved them with the stimulus spectrogram to generate linear predictions of cortical activity (Figure 5a, panels 1-3). We could then compare the linear prediction to the observed firing rate elicited by the background to estimate neural gain control by fitting the nonlinearity of each neuron in high and low contrast (GC model, Figure 5a, panel 4). For comparison, each neuron was fit in a similar fashion using a single, static nonlinearity (static model, Figure 5a, panel 4). This modeling strategy allowed us to estimate cortical gain during different periods in the task, and assess how gain is related to behavioral performance.

Figure 5b-d demonstrates a representative neuron recorded during behavior. Within each session, the background noise was randomly drawn from one of five frozen noise scenes, which allowed us to observe stimulus aligned spike patterns across repeats of each scene (Figure 5b, spike raster). The estimated STRF for this example unit is shown in Figure 5c, along with the nonlinearities estimated for low and high contrast in Figure 5d, and the GC model fit to the data in the bottom of Figure 5b. We first compared the cross-validated performance of a model with a static nonlinearity versus a gain control model, and observed a significant enhancement in the model’s correlation to the observed spikes when modelling gain control (*Mdn:* 0.815), relative to the static model (*Mdn*: 0.645; Wilcoxon sign-rank test (n = 1,535 neurons): *rank* = 64,346, *Z* = -30.23, *p* = 9.26e-201; Figure 5e). After pooling all of the neurons recorded across all mice and sessions, and including only neurons with high reliability in both contrasts (defined as units with noise-to-signal ratio < 100 in low and high contrast, see *Methods*), we observed significantly higher gain in low contrast (*Mdn*: 0.093) than in high contrast (*Mdn*: 0.050; Wilcoxon sign-rank test (n = 1,535 neurons): *rank* = 972,742, *Z* = 22.07, *p* = 6.46e-108; Figure 5f). These results demonstrate that models incorporating gain control are better predictors of cortical activity, and confirm previous reports of robust gain control in ferret and mouse auditory cortex[14,17].

We next assessed whether gain in auditory cortex reliably predicts how well a mouse is able to hear targets in each contrast. To do so, we averaged the gain of target-selective neurons during the target period of the task for each mouse and then compared the target period gain for each mouse to the behavioral thresholds and slopes collected in the psychometric task. We found a significant negative relationship between cortical gain and behavioral threshold across contrasts (single linear regression: *F*(1,12) = 24.2, *p* < 0.001, *R2* = 0.67), suggesting that increased gain yielded greater sensitivity to lower target volumes. However, we didn’t observe this relationship when only including low contrast sessions (*F*(1,7) = 1.42, *p* = 0.27, *R2* = 0.17) or high contrast (*F*(1,3) = 2.02, *p* = 0.25, *R2* = 0.40), so we cannot definitely conclude that contrast-independent fluctuations in gain predict behavioral thresholds (Figure 5f). We conducted the same analysis between gain and psychometric slopes, and found significant positive relationships across contrasts (single linear regression: *F*(1,12) = 12.0, *p* = 0.005, *R2* = 0.50) and within low contrast (*F*(1,7) = 6.96, *p* = 0.034, *R2* = 0.50), suggesting that individual differences in cortical gain influence behavioral sensitivity to changes in volume, independently of contrast gain control.

**Diagram

Description automatically generatedFigure 5.**

1. Schematic of the generalized-linear-nonlinear model. 1) Schematic of a spectrotemporal response function (STRF). 2) Example stimulus spectrogram of low and high contrast. 3) The gray trace is the filter response when convolving the STRF with the spectrogram. The black trace is the observed spike rate during the same stimulus period. 4) Schematized nonlinearities fit separately to low and high contrast periods in a gain control (GC) model, or fit to all data in a static model.
2. Example background-locked responses from a well-tuned cortical unit across the trial duration. The top portion of the plot is a spike raster sorted by the frozen noise pattern (FN1-5) of the background. The bottom portion of the plot is a PSTH of the observed spiking, binned every 25ms (black trace). The colored traces are the GC model predictions in each contrast (red trace uses the red nonlinearity in **d**, blue trace uses the blue nonlinearity in **d**).
3. STRF for this example neuron. STRF values are indicated by the colorbar.
4. Estimated nonlinearities for this example neuron. Points indicate the mean observed firing rate (ordinate), binned according to observed filter prediction values (abscissa). Solid lines indicate exponential function fits to the underlying points. Each line is a fit to the test set in a cross-validation run (see Methods).
5. Correlation coefficients between the observed trial-averaged spike rate and the model prediction for the static model and the gain control model. Each dot is the average correlation across 10 cross-validation folds for each neuron, where black dots are high stimulus locking neurons with low noise ratios (NR < 100) and grey dots are neurons with low stimulus locking (NR > 100). For the remaining figures, only neurons with NR < 100 are included. The solid red line indicates unity. The red “x” indicates the median correlation for each model.
6. Gain control in auditory cortex during the task. Each histogram is the distribution of gain values in high and low contrast across neurons with noise ratios below 100, recorded during behavior. Dashed vertical lines indicate the median of each distributions.
7. Relationship between gain and behavioral threshold. Each circle represents the average gain and behavioral threshold for each mouse for each contrast (as indicated by the circle fill color). Gain values were averaged over target selective neurons. Grey lines and shaded areas indicate the linear regression fit across contrasts, +- the 95% confidence interval.
8. Relationship between gain and behavioral slope. Appearance as in **g**.

**Discussion**

On daily basis, we navigate through many auditory environments, each defined by different statistical properties. The dynamic range, or contrast, of acoustic inputs poses a challenge to the auditory system, which is composed of neurons with limited dynamic range in their response. The efficient coding hypothesis predicts that as acoustic contrast shifts, neurons throughout the auditory pathway adjust their sensitivity, so as to match the dynamic range of their response to that of the stimulus distribution[29]. This process allows auditory neurons to encode volume information within each contrast, despite changes in the dynamic range. Multiple studies have demonstrated that indeed, neurons throughout the auditory pathway exhibit contrast adaptation[14,16,17,25]. Whereas recent work has demonstrated a link between efficient cortical codes and human psychophysical performance [24], whether neuronal contrast adaptation plays a role in auditory perception has not been previously examined simultaneously with behavior. In this study, we directly linked neuronal contrast gain control to auditory behavior through the use of a theoretical model of efficient coding, behavioral psychophysics, and simultaneous manipulation and recordings of cortical activity.

*Summary of results*

The goal of this study was to test the hypothesis that efficient coding at the neuronal level in the auditory cortex shapes auditory behavior. To tackle this complex question, we first developed a normative framework[22] that allowed us to make specific predictions for behavioral performance as expected by contrast gain control. The model predicted that (1) The detection threshold of a target in noise under low contrast should be lower than under high contrast; (2) Upon a shift in the background noise contrast, detection improves upon transition from high to low contrast, but is impaired upon transition from low to high contrast; and (3) The time constant for this change in detection performance is slower for transitions from high to low contrast than from low to high contrast (Figure 1). To test these predictions, we trained mice to detect a target in background noise, as noise contrast shifted from low to high or from high to low. As predicted by the normative model, mice exhibited a lower threshold for detecting targets in low as compared to high background. Over time, we observed a decrease in tone detection after a switch to high contrast, and in increase in tone detection after a switch to low contrast. Behavioral adaptation was faster in high contrast, as compared to low contrast backgrounds, in agreement with our model and previous theoretical models[19] (Figure 2). We furthermore found that AC is necessary specifically for this detection-in-noise task (Figure 3). As predicted by the model, the neurometric threshold for sound detection was greater in high than in low contrast, and we observed that as neurons adapted to transitions in background contrast, the time course of target discriminability adapted similarly to the behavior and model predictions (Figure 4). Additionally, a direct comparison of neurometric and behavioral performance revealed a significant correlation for the thresholds and slopes of the psychometric curves (Figure 4). Finally, we found correlations between cortical gain and behavioral thresholds and slopes (Figure 5), supporting our hypothesis that efficient coding at the neuronal level predicts auditory behavior.

*The role of cortex in behavior.*

The role of auditory cortex in auditory behavior has been subject of debate. A number of prior studies found that auditory cortex was not required for relatively simple behavioral tasks such as frequency discrimination or detection[30,31]. Rather, many studies found that auditory cortex is primarily involved in more complex behaviors, such those requiring temporal expectation[32], localization[33], or discrimination of more complex sounds[34–36]. Consistent with previous findings, we found that AC inactivation selectively impaired the detection of target in noise background, but did not impair detection of targets in the absence of background noise (Figure 3). Furthermore, on subject-by-subject basis, neuronal activity in AC was correlated with behavioral performance of the subject (Figures 4, 5). This set of result establishes that AC is necessary for the detection of targets in complex backgrounds and supports the more general notion that AC is required for more complex auditory tasks, but is not required for simpler tasks.

While the work previously mentioned demonstrates the necessity of auditory cortex in performance of behavior, the brain areas and mechanisms supporting the transformation from stimulus to decision are an active field of study[37,38]. By recording during task performance, we were able to leverage behavioral variability to show that behavioral performance covaried with representations of targets within small neural populations (Figure 4) and cortical gain (Figure 5). There is a large body of literature relating cortical codes to behavioral variability: early studies in the visual system suggested that relatively small numbers of neurons may match or outperform animal behavior in psychophysical tasks[39–41] and that behavioral choice can be predicted from activity in sensory areas[27,41]. These accounts suggest that variability in bottom-up sensory encoding drives the variability in behavioral output, but more recent work suggests that variability in sensory areas is driven by top-down influences[42–45], which are modulated by attention and learning[46–49]. Interestingly, a recent study imaging tens of thousands of neurons in the visual cortex demonstrated that cortical representations have higher acuity than mouse behavioral output, yet did not correlate with behavioral performance, suggesting that perceptual discrimination depends on post-sensory brain regions[50]. Our results suggest that bottom-up adaptation to stimulus statistics shapes behavioral output, as we observed very stereotyped patterns of behavioral adaptation (Figure 2) qualitatively consistent with an efficient encoding model (Figure 1) and patterns of stimulus driven activity in auditory cortex (Figure 4). Indeed, there have been other studies demonstrating that individual differences in sensory-guided behaviors are reflected in cortical activity[51,52], are bidirectionally modulated by cortical manipulation[53,54], and can be predicted from tuning properties in auditory cortex[55,56]. While our results cannot rule out that top-down input is the causal driver of sensory decisions, they do support the notion that the sensory information upon which decisions are made is shaped by neuronal adaptation, which thus affects behavioral outcomes.

*Adaptation in the auditory system.*

Neurons throughout the auditory system adapt to the statistics of the acoustic environment, including the distribution of stimuli over time[57,58] more complex sound patterns[59,60], and even ongoing behavioral and attentional demands[61–66]. Inspired by the latter studies, stimulus

Using these methods, we focused on contrast gain control as a fundamental statistical adaptation that relates to efficient coding[14,17,18,24]. Contrast gain control is present at multiple stages in the auditory system, increasing in magnitude from the inferior colliculus to the auditory thalamus and auditory cortex[24,25] with slower adaptation speeds in auditory cortex than subcortical areas[24]. We found that behavioral detection of targets in backgrounds with changing contrast required the auditory cortex (Figure 3), and leveraged our stimulus to use encoding models to estimate cortical gain during the task, finding that cortical gain was predictive of behavioral performance (Figure 5). Although our study focused on the role of contrast gain control in detection in noise, it is plausible that performance in tasks that rely on simpler statistics might rely on adaptation in sub-cortical areas[11–13]. In general, the combination of carefully designed task stimuli and simultaneously recorded neural activity allowed us to probe gain as a neuronal mechanism underlying behavior, and highlights the utility of encoding models for linking neural codes to behavioral performance[67–70].

*Cellular mechanisms of gain control.*

Whereas this study demonstrates the necessity of auditory cortex for detection in varying-contrast noise, the neuronal mechanisms driving contrast gain adaptation at a cellular level remain unclear. Additionally, while we observed theoretically optimal asymmetric adaptation to changes in contrast, the neural circuits driving these temporal asymmetries are unknown. In the current study, we have likely recorded from a mixed population of excitatory and inhibitory neurons. Different inhibitory neuronal subtypes exhibit specific roles in adaptation[71,72]. Although specific inhibitory neuronal subtypes facilitate divisive or subtractive control of excitatory responses in visual[73,74] and auditory cortex[75,76], the role of these interneurons in contrast gain control has been inconclusive[18]. By combining previously mentioned optogenetic methods with behavioral tasks, future studies may explore and test the specific role of inhibitory neurons in driving changes in neuronal gain during behavior.

*The missing link between efficient coding and behavior.*

Combined, our results develop a framework and provide support for the role of efficient neuronal coding in behavior. The efficient coding hypothesis has emerged as one of the leading principles in computational neuroscience that has shaped our understanding of neuronal coding, architecture and evolution[29,77–80]. Extensive prior research found that human behavior follows principles of efficiency[23,24]. Our work now provides a framework for linking the principles of neuronal coding with behavioral performance. Because of the minimal number of assumptions of the normative model, that operates generally based on the statistics of the inputs and expected statistics of the outputs, we expect that the framework proposed here will be generalized across different sensory modalities and forms of neuronal computation and behavior in future studies of behavior in animal and human models.

**Methods**

*Animals*. All experiments were performed in adult male (n = **xxx**) and female (n = **xxx**) mice (The Jackson Laboratory; age 12-15 weeks; weight 20-30g; **STRAINS**, etc.), housed with, at most, five mice per cage, at 28°C on a 12-h light:dark cycle with food provided ad libitum, and a restricted water schedule (see *Water Restriction*). All experiments were performed during the animals’ dark cycle. All experimental procedures were in accordance with NIH guidelines and approved by the Institutional Animal Care and Use Committee at the University of Pennsylvania.

*Surgery*. Mice were anesthetized under isoflurane (1-3%). Prior to implantation, all mice were administered subcutaneous doses of buprenorphine (Buprenex, 0.05-0.1 mg/kg) for analgesia, dexamethasone (0.2 mg/kg) to reduce brain swelling, and bupivicane (2 mg/kg) for local anesthesia. In mice undergoing electrophysiological experiments, two ground screws attached to ground wires were implanted in the left frontal lobe and right cerebellum, with an additional skull screw implanted over the left cerebellum to provide additional support. A small craniotomy was performed over the target stereotactic coordinates relative to bregma, -2.6mm anterior, -4.3mm lateral. Either custom 16-channel microdrives, 32-, or 64-channel shuttle drives (cite) holding tetrode bundles of polyimide-coated nichrome wires were chronically implanted over auditory cortex, and tetrodes were lowered 800um below the pial surface. The exposed base of the tetrodes were covered with GelFoam (Pfizer) or sterile silicone lubricant and sealed with Kwik-Cast (World Precision Instruments). The plastic body of the microdrive and a custom titanium headplate were secured to the skull using dental cement (C&B Metabond) and acrylic (Lang Dental). Mice undergoing only behavioral experiments were implanted with two skull screws in the cerebellum, and a custom titanium headplate was mounted on the skull as previously described. An antibiotic (Baytril, 5mg/kg) and analgesic (Meloxicam, 5mg/kg) were administered daily (for 3 days) during recovery.

*Water Restriction*. Following surgical recovery (3 days postop), each mouse’s weight was monitored for three days to establish a baseline weight. Over the next seven days, mice were water deprived, beginning with a daily ration of 120uL/g and gradually decreasing their ration to 40-50uL/g. During the task, if mice did not receive their full ration, the remainder of their ration was provided in their home cage. Mouse weight relative to baseline was monitored during all stages of water restriction. Additional health signs were used to determine a health score and subsequent treatment plan if a mouse lost more than 20% of baseline weight, as described by previously published methods[81] and approved by the Institutional Animal Care and Use Committee at the University of Pennsylvania.

*Behavioral Apparatus*. During the Go/NoGo task, the mouse was head-fixed in a custom-built, acoustically isolated chamber. A capacitive touch sensor (AT42QT1010, SparkFun) soldered to a lick spout monitored lick activity. Water rewards were dispensed from a gravity fed reservoir, controlled by a solenoid valve (161T011, Neptune Research) calibrated to deliver approximately 4-5uL of water per reward[82]. Low level task logic, such as lick detection, reward and timeout delivery, and task timing intervals, was directly controlled by an Arduino Uno microprocessor running custom, low-latency software routines. High level task logic, such as trial randomization, stimulus buffering and presentation, and online data collection and analysis were controlled by custom MATLAB (Mathworks) software communicating with the Arduino over a serial port. Digital waveforms were converted to analog signals via a soundcard (Lynx E44, Lynx Studio Technology, Inc.) or a National Instruments card (NI PCIe-6353) and delivered through an ultrasonic transducer (MCPCT-G5100-4139, Multicomp). The transducer was calibrated to have a flat frequency response between 3 kHz and 80 kHz using a 1/4-inch condenser microphone (Brüel & Kjær) positioned at the expected location of the mouse’s ear, as described previously[83,84]. During electrophysiological recording sessions, licks were detected using an optical interrupt sensor (EE-SX771, Omron Automation), to prevent lick-related electrical artifacts introduced by contact with the capacitive sensor.

*Behavioral Timeline*. Each mouse underwent four stages in the behavioral task: 1) water restriction and habituation, 2) behavioral training, 3) psychometric testing, and, 4) offset testing. During the induction of water restriction, mice were simultaneously habituated to head-fixation in the behavioral chambers and receiving water through the lick spout, by providing a water reward for any licks separated by more than 2 s. After the mouse began to receive its entire ration by licking in the booth, behavioral training was initiated (typically 1 week). Each mouse was initially trained and tested in one contrast condition (see *Stimuli*), with the initial training condition counterbalanced across mice. Behavioral performance was monitored during training, and mice were considered trained after completing at least three consecutive sessions with over 80% percent correct (~2-3 weeks). After completing training, behavioral thresholds were measured during at least three sessions in which psychometric stimuli were presented (see *Stimuli*). After estimating the behavioral threshold for each mouse, offset stimulus sets were generated using threshold-level targets. After completion of at least three sessions in the offset task, each mouse was then retrained on the remaining contrast condition. Upon reaching the training criterion of 80% in the new contrast condition, mice were then tested in the psychometric and offset tasks as previously described. For mice in electrophysiological experiments, this sequence of training and testing was continued until the recording site yielded less than three units, or until the mouse stopped performing in the task.

*Stimuli*. All stimuli were created in MATLAB and sampled at 192 kHz or 200 kHz and 32-bit resolution. A set of dynamic random chords (DRCs) were created with different contrasts, similarly to those described in previous studies[14,17,24]. This stimulus was used 1) to measure the spectrotemporal receptive fields of neurons by fitting a linear-nonlinear model, and 2) to modulate the gain of auditory neurons by manipulating stimulus contrast. To construct a DRC, amplitude modulated pure tones were generated at multiple frequencies and then superimposed to create a chord. In some experiments, 34 frequencies were sampled between 4 and ~40kHz in 1/10 octave steps, in the remaining experiments, 33 frequencies were sampled between 4 and 64kHz in 1/8 octave steps. The amplitude envelope of each tone was generated as follows: every 25 ms, amplitudes for each frequency were sampled from a uniform distribution with a mean of 50 dB and a width of ±5 dB in low contrast or ±15 dB in high contrast. Between each 20 ms chord, the amplitude envelope of each frequency band was linearly ramped over 5 ms to the amplitude value for the next chord, such that the total duration of each chord and its ramp was 25 ms. To synthesize the stimuli, amplitude envelopes were multiplied by a sine wave of their respective frequencies, and summed to produce the final waveform.

In all stages of behavioral training and testing, stimuli created for each trial consisted of a DRC background containing a change in contrast, and the presence or lack of a target at a delay after the change in contrast. Each trial was initialized with 3 seconds of DRC noise of one contrast, followed by a switch to the other contrast. Targets consisted of a fixed chord composed of 17 frequencies pseudo-randomly sampled from the frequencies contained in the DRC background, such that the target frequencies were uniformly distributed across the frequency range of the background. To add targets to the background noise, the target amplitude at each target frequency was simply added to a single chord in the amplitude envelope of the background, and ramped as described previously; this procedure ensured that target timing was perfectly aligned to changes in the background noise, removing asynchronous timing cues that could be used by the animal to detect the target. Target amplitudes are described in values of signal-to-noise ratio (SNR) relative to the average level of the background noise (ie. a 50 dB target embedded in 50 dB noise would have an SNR of 0 dB). We note that because the targets only contained power in half of the frequency bands used to construct the noise background, target SNRs were typically above 0 dB. \*\*\*\* INSERT TABLE DESCRIBING ALL DIFFERENT EXPERIMENTAL CONDITIONS \*\*\*\* In all trials, targets were embedded after a change in the background contrast, with a delay and volume dependent on the current training or testing stage (see Behavioral Task).

*Behavioral Task*. We employed a Go/NoGo task to measure mouses’ perceptual ability to detect targets in noise. In this task, each trial consisted of a noise background with a contrast shift, along with the presence or absence of a target after the change in contrast. Mice were trained to lick when they detect a target (hit), or to withhold licking in the absence of a target (correct reject). This behavior was reinforced by providing a 4-5uL water reward when the mouse performed a hit, and by initiating a 7-10s timeout when the mouse licked in the absence of a target (false alarm). Any licks detected during the timeout period resulted in the timeout timer being reset. In a subset of mice, we introduced an additional trial abort period coincident with the first part of the contrast background, before the contrast switch. Any licks detected in this abort period resulted in the trial being reset after a 7-10s timeout, until the mouse withheld from licking during this period. In this task, misses and correct rejects were not rewarded or punished. Trials were separated by a minimum 1.5s inter-trial-interval (ITI). To discourage spontaneous licking, licks were monitored during this period, and if any licks occurred the ITI timer would be reset.

Several of our behavioral tasks varied the timing of the target relative to the contrast shift, which required a method for estimating hit rates and false alarm rates at different times during each trial, and to reward and punish the animal during these times in an unbiased manner. To approach this issue, we considered licks as responses only during a 1 s response window after a target presentation in the trial (eg. if a target was presented 500 ms post-contrast-switch, the response window persisted from 500 to 1500 ms post-contrast-switch). To apply this method to noise-only trials, in which no targets were presented, we considered noise trials as target trials containing infinitely small target amplitudes. For each noise trial, we assigned a response window with equiprobable delay matched to the target conditions, and considered only licks within those “target” response windows. Thus, over the course of a session, we randomly sampled lick probabilities in noise trials during the same temporal windows as those licks considered during target trials. Using this scheme, we treated target and noise trials identically, and estimated hit rates and false alarm rates over time in an unbiased manner.

Each mouse performed three stages in the behavioral task: training, psychometric testing, and offset testing. During the training task, trials consisted of two types, noise trials or target trials presented with equal probability. To facilitate learning, we selected target SNRs at the highest end of the range described previously: in low contrast training sessions, targets were 16 dB SNR, and in high contrast training sessions, targets were 20 dB SNR. To prevent response bias as a function of target timing, we randomly varied the target delay between 250, 500, 750 and 1000ms after the contrast change in each trial. During the psychometric testing task, there were 7 trial types consisting of noise trials and target trials spanning six different SNRs (\*\*\* TABLE\*\*\*). Based on behavioral piloting, we presented high SNR trials with a greater probability, to prevent mice from giving up during the task. In low and high contrast psychometric sessions, the probability of a noise trial was 0.4, the probability of the four lowest target SNRs was 0.05 each, and the probability of the two highest target SNRs was 0.2 each. As in training, target timing was varied randomly between 250, 500, 750 and 1000ms after the contrast change in each trial. After completing at least three sessions of the psychometric task, stimuli were generated for the offset testing task. This task consisted of 15 unique trial types: 3 target volumes (noise trials, threshold target trials, and high SNR target trials), and 5 target delays relative to the contrast change (25, 75, 225, 475, 975 ms delay). Threshold target amplitudes were determined individually for each mouse by estimating target detection thresholds in each contrast condition during psychometric testing sessions, and varied between ~2-12 in low contrast and ~8-16 dB SNR in high contrast. Based on behavioral piloting, noise trials, threshold target trials, and high SNR target trials were presented with probabilities of 0.4, 0.2, and 0.4, respectively. Target delay on each trial was selected with equal probability. In all behavioral stages, trial order was pseudorandomly generated, such that there were no more than three target or noise trials in a row.

***Normative Model***

*Electrophysiological Recordings*. Neural signals were acquired from awake, behaving mice as they performed the psychometric and offset testing tasks described previously. Chronically implanted, 16-, 32-, or 64-channel microdrives[85,86] were connected to one or two 32 channel Intan amplifier headstages. Amplified signals were recorded at 30 kHz using an openEphys acquisition board via an SPI cable, where the signals were digitized. Prior to spike analysis, broadband signals were filtered between 500 and 6000 Hz, offset corrected, and re-referenced to the median across all active channels. The preprocessed data was then sorted using KiloSort[87] or KiloSort2 and the resulting clustering was manually corrected in phy2 according to community-developed guidelines. The resulting units were labelled as single units if they exhibited a clear refractory period and did not need to be split. Splitting assessments were made through manual examination of principle component features for the two best channels of a cluster. If two noticeable clusters in feature space were evident in a unit, the unit was either manually split, or classified as a multiunit.

*Behavioral and Neural Detection Performance.* To calculate performance in target-in-noise detection task we adopted commonly used signal detection theory methods[39,88] to estimate the ability of an ideal observer to discriminate between two sensory distributions: in our case, a distribution for target trials and a distribution for noise trials. When analyzing behavior, we computed the percent correct performance of an ideal observer[89] as a function of the probability of hits and false alarms:

where is the inverse z-transform of a standard normal distribution (normcdf in MATLAB), is the inverse of the normal distribution (norminv in MATLAB), is the hit rate, and is the false alarm rate. For psychophysical performance, hit rates and false alarm rates near 0 and 1 were adjusted using the log-linear rule[90], to reduce biases in performance estimation caused by low numbers of trials.

To calculate neural performance in the same reference frame as the behavior, we employed similar ideal observer techniques. First, neuronal responses (either spike rates or single units, or population projection values), were averaged in a 100ms window post target onset (for noise trials, this window was randomly chosen on each trial to coincide with target presentation times on target trials). Then, using the distributions of responses during target and noise trials, we computed receiver-operating-characteristic curves and took the area under the curve (AUC) as the percent correct of an ideal observer discriminating between the target and noise distributions. To determine whether the AUC value for a given set of trial distributions was significantly different from chance, we performed a bootstrap procedure where we sampled from all the trials with replacement 500 times and recomputed AUC for each sample. If the 95% confidence intervals for this bootstrapped distribution did not include chance (.5), we defined that AUC value as significant. For population analyses which generated single-trial predictions, neural hit and false alarm rates were transformed to percent correct as described above.

To characterize performance, psychometric curves were fit with a logistic function:

where is the x-offset of the function, determined the slope, or sensitivity of the function, determined the guess rate (lower bound), determined the lapse rate (upper bound) and was performance. determined the threshold of this function, defined as the x-value corresponding to the steepest part of the curve. This function was fit to behavioral or neural performance using constrained gradient descent (fmincon in MATLAB) initialized with a 10x10 grid-search of parameters and .

To characterize adaptation time constants, adaptation curves were fit with an exponential function:

where determined the y-offset of the function, was a multiplicative scaling factor, and was the time constant of the exponential in units of . This function was fit to behavioral or neural responses using constrained gradient descent, initialized with a 10x10x10 grid search across all three parameters.

*Population Response Metrics.* On sessions where three or more neurons were simultaneously recorded, we used a coding direction technique[26] to estimate the ability of neural populations to discriminate targets from noise. First, target and noise spike rates for each neuron were averaged in a 100ms window post-target onset. Then, using a leave-one-out procedure, we computed a trial averaged population vector for target trials, , and a separate average population vector for noise trials, . We then estimated the coding direction in high dimensional neural space that best separated the target and noise responses: The held out trial was then projected along this dimension, by taking the population response vector on that trial and projecting it along the estimated coding direction: . This procedure was repeated holding out each trial, and estimating the coding direction from the remaining trials. For psychometric testing sessions, the target responses from the two loudest target volumes were used to estimate coding direction, and in offset testing sessions the target responses from the high SNR target trials were used. After computing projections for every trial, the resulting matrix was normalized between 0 and 1.

*Criterion Classifier*. Based on previously described methods[27], we used a criterion-based decision rule to estimate how a down-stream neuron may read out neural activity during the task. As before, trial distributions of neural responses to targets and noise were created from the average activity in a 100ms window post-target. Then, we sampled 100 criterion values between the minimum and maximum response, and for each criterion estimated the proportion of correct trials under two decision rules: 1) report target present if the response is greater than the criterion, or, 2) report target present if the response is less than the criterion. By assessing these two decision rules, responses that may be suppressed by target presence were treated equally to those in which target presence enhanced the neural response. Finally, we chose the criterion and decision rule that yielded the highest proportion of correct trials, and computed neural hit rates and false alarm rates for each target level, and noise-only. These hit rates and false alarm rates were then transformed to percent correct according the formula above, to ensure equivalency with the behavioral metrics.

*Linear-nonlinear Model*. First, we selected only neurons in the dataset which had reliable stimulus responses (noise ratio < 100). The linear nonlinear model was then composed of two main parts, a spectrotemporal receptive field (STRF) and a set of rectifying nonlinearities. The STRF was fit using gaussian generalized linear regression (glmnet package in MATLAB), with a history window of 300ms (13 stimulus bins) and frequency bins corresponding to the frequencies composing the dynamic random chords (see *Stimuli*). Before fitting the full model, we cross-validated glmnet’s elastic net mixing parameter (cvglmnet in MATLAB) using matched time windows of low and high contrast responses from every trial. Then, using that parameter, we fit the full model using 10-fold cross-validation in the following manner.

For each fold, we selected 90% of the trials for training, leaving the remaining 10% to be held out for testing. Within each trial, we excluded neuronal responses around transitions from silence, or transitions in contrast, to prevent the model from overfitting strong transients in the neural response. Additionally, we excluded neural responses within a 50ms window after target presentations, to prevent overfitting to target responses. Given these exclusion criteria, we calculated the duration of stimulus sampled in the shorter target period for each trial, and, for that trial, sampled the same duration of stimulus within the adaptation period. This procedure ensured that the model was fit to the same amount of high and low contrast stimulation, to avoid overfitting to one condition. Then, a stimulus design matrix was made using these stimulus periods, and the STRF was fit to the neuronal data using lasso-regularized generalized linear regression (glmnet in MATLAB). Based on prior pilot analyses, we found that in reliably responsive neurons, STRFs estimated separately in high and low contrast were nearly identical, so for this analysis we estimated STRFs using both high and low contrast periods (**SUPPLEMENT?**). Using the STRF fit to the training data, we generated a linear prediction of the stimulus by convolving the STRF with the spectrogram of the training stimulus. We then separated the linear predictions into low and high contrast periods. For each contrast period, we generated a histogram of the linear prediction values (50 bins), and for each bin, computed the mean spike rate of the neuron when the linear prediction fell within those bin edges (Figure 5d, scatter points). The resulting set of linear prediction values and average spike rates were fit with an exponential function:

where determined the minimum firing rate, was a multiplicative scaling factor, determined the gain of the exponent, and determined the x-offset, or firing threshold of the neuron. This function was fit to each cell using constrained gradient descent, using a 10x10 grid search for parameters and . These fits were determined for each contrast, and the gain for each contrast for each neuron was estimated using . This entire process was repeated for each cross-validation fold, and the final parameter estimates for the STRF and nonlinearities were taken as the average over the 10 runs.

To determine the relationship between neuronal gain and behavioral performance, we examined our dataset of neurons collected during the psychometric task. First, we selected all of the neurons with significant AUC values to at least two of the six targets to ensure that we were sampling from neurons with information about target volume. Then, across all of these neurons for each mouse, we computed the average neural gain for each contrast. We then compared neural gain for each mouse to corresponding average psychometric thresholds and slopes to assess the relationship between neural gain and behavioral performance.

**Table 1:** Statistical Comparisons.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Comparison** | **Figure** | **Center** | **Spread** | **N** | **Test** | **Statistic** | **p-value** |
| Behavior percent correct, low contrast: time 1 vs. time 2 | 2g | T1: 0.68  T2: 0.70  (median) | n/a | 21 (mice) | Two-tailed Wilcoxon sign-rank test (FDR corrected[91] for multiple comparisons) | Z = -1.93  Rank: 60 | 0.054 |
| Behavior percent correct, low contrast: time 1 vs. time 3 | T1: 0.68  T2: 0.82  (median) | n/a | Z = -4.01  Rank: 0 | 5.96e-5 |
| Behavior percent correct, low contrast: time 1 vs. time 4 | T1: 0.68  T2: 0.87  (median) | n/a | Z = -4.01  Rank: 0 | 5.96e-5 |
| Behavior percent correct, low contrast: time 1 vs. time 5 | T1: 0.68  T2: 0.91  (median) | n/a | Z = -4.01  Rank: 0 | 5.96e-5 |
| Behavior percent correct, high contrast: time 1 vs. time 2 | T1: 0.82  T2: 0.77  (median) | n/a | Z = 2.84  Rank: 181 | 0.005 |
| Behavior percent correct, high contrast: time 1 vs. time 3 | T1: 0.82  T2: 0.77  (median) | n/a | Z = 2.17  Rank: 163 | 0.030 |
| Behavior percent correct, high contrast: time 1 vs. time 4 | T1: 0.82  T2: 0.78  (median) | n/a | Z = 3.36  Rank: 195 | 7.80e-4 |
| Behavior percent correct, high contrast: time 1 vs. time 5 | T1: 0.82  T2: 0.79  (median) | n/a | Z = 1.94  Rank: 157 | 0.052 |
| Percent correct max dB SNR, low contrast: muscimol vs. saline | 3c | Musc.: 0.10  Saline: 0.85  (median) | n/a | 10 musc.. sessions, 10 saline sessions (4 mice) | Two-tailed Wilcoxon rank-sum test | Z = -2.76  Rank: 68 | 0.006 |
| Threshold (dB SNR), low contrast: muscimol vs. saline | Musc.: 14.78  Saline: 9.66  (median) | n/a | Z = 0.72  Rank: 115 | 0.473 |
| FA rate, low contrast: muscimol vs. saline | Musc.: 0.026  Saline: 0.132  (median) | n/a | Z = -2.91  Rank: 66 | 0.004 |
| Max slope (PC/dB), low contrast: muscimol vs. saline | Musc.: 0.026  Saline: 0.072  (median) | n/a | Z: -2.68  Rank: 69 | 0.007 |
| Percent correct max dB SNR, high contrast: muscimol vs. saline | Musc.: 0.06  Saline: 0.80  (median) | n/a | 13 musc.. sessions, 10 saline sessions  (4 mice) | Z = -4.06  Rank: 92 | 4.96e-5 |
| Threshold (dB SNR), high contrast: muscimol vs. saline | Musc.: 16.77  Saline: 18.80  (median) | n/a | Z = -0.35  Rank: 156 | 0.728 |
| FA rate, low contrast: muscimol vs. saline | Musc.: 0.027  Saline: 0.213  (median) | n/a | Z = -3.19  Rank: 107 | 0.001 |
| Max slope (PC/dB), high contrast: muscimol vs. saline | Musc.: 0.012  Saline: 0.058  (median) | n/a | Z = -3.77  Rank: 97 | 1.66e-4 |
| Percent correct max dB SNR, target in high contrast : muscimol vs. saline | 3f | Musc.: 0.07  Saline: 0.82  (median) | n/a | 5 musc. sessions, 5 saline sessions  (2 mice) | Two-tailed Wilcoxon rank-sum test | Z = nan  Rank: 15 | 0.0079 |
| Percent correct at threshold, target in high contrast: muscimol vs. saline | Musc.: 0.03  Saline: 0.53  (median) | n/a | Z = nan  Rank: 17 | 0.032 |
| FA rate, target in high contrast : muscimol vs. saline | Musc.: 0.12  Saline: 0.23  (median) | n/a | Z = nan  Rank: 21 | 0.22 |
| Max slope (PC/dB), target in high contrast : muscimol vs. saline | Musc.: 0.038  Saline: 0.057  (median) | n/a | Z = nan  Rank: 19 | 0.095 |
| Percent correct max dB SNR, target in silence: muscimol vs. saline | Musc.: 0.85  Saline: 0.92  (median) | n/a | 8 musc. sessions, 8 saline sessions  (2 mice) | Z = nan  Rank: 53 | 0.13 |
| Percent correct at threshold, target in silence : muscimol vs. saline | Musc.: 0.11  Saline: 0.22  (median) | n/a | Z = nan  Rank: 55 | 0.195 |
| FA rate, target in silence : muscimol vs. saline | Musc.: 0.029  Saline: 0.041  (median) | n/a | Z = nan  Rank: 60 | 0.44 |
| Max slope (PC/dB), target in silence : muscimol vs. saline | Musc.: 0.028  Saline: 0.031  (median) | n/a | Z = nan  Rank: 63 | 0.645 |
|  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |

**Table 1:** Statistical tests (not included in main text).

Diagram

Description automatically generated

**Supplemental Figure 1.**

1. Setup schematic for acute muscimol recordings in ACtx.
2. Example spike rasters from two different neurons pre- and post-muscimol or saline application. On top of the raster is the timeline for each recording. A baseline recording of all stimuli was performed prior to muscimol application, then all stimuli were recorded again 30 minutes after application. Rasters are sorted by contrast and target volume, with color indicating low or high contrast backgrounds, color shade indicating target volume, and grey indicating noise only trials (-Inf). *Top left panel:* raster of target and noise responses of a representative neuron recorded prior to muscimol application. *Top right panel:* raster of the same neuron 30 minutes after muscimol application. *Insets:* Mean firing rate for each condition. Shade indicates target volume and the scale bar indicates a firing rate of 50Hz. Error bars indicate S.E.M. across trials. *Bottom panels:* Example neuron before and after application of saline. Formatting as in top panels.
3. Firing rate averaged across neurons after drug application in muscimol and saline recording sessions. Filled circles and solid lines are responses after saline was applied while open circles and dashed lines are responses after muscimol was applied. Light shaded open and closed circles that are unconnected by lines are the responses to noise alone. Error bars indicate S.E.M. across neurons.
4. Lick probability over time during muscimol or saline sessions. Dashed vertical lines indicate trial onset (0 s) and the contrast switch (3 s). Green traces are muscimol sessions and black traces are saline sessions. The shading around each trace indicates S.E.M. across sessions.
5. *Left:* comparison of lick probability during the adaptation period. *Right:* comparison of lick probability during the target period. Each circle indicates a session and color is as in **d)**.
6. Cumulative probability of licking throughout the trial, normalized within muscimol or saline conditions to sum to 1. Colors as in **d)**, **e)**. Shading indicates S.E.M. across sessions.

1. Barlow H: **Possible principles underlying the transformations of sensory messages**. *Sens Commun* 1961, **6**:57–58.

2. Brenner N, Bialek W, De Ruyter Van Steveninck R: **Adaptive rescaling maximizes information transmission**. *Neuron* 2000, **26**:695–702.

3. Bharioke A, Chklovskii DB: **Automatic Adaptation to Fast Input Changes in a Time-Invariant Neural Circuit**. *PLoS Comput Biol* 2015, **11**:1004315.

4. Borst A, Theunissen FE: **Information theory and neural coding**. *Nat Neurosci* 1999, **2**:947–957.

5. Maravall M, Petersen RS, Fairhall AL, Arabzadeh E, Diamond ME: **Shifts in Coding Properties and Maintenance of Information Transmission during Adaptation in Barrel Cortex**. *PLoS Biol* 2007, **5**:e19.

6. Baccus SA, Meister M: **Fast and slow contrast adaptation in retinal circuitry**. *Neuron* 2002, **36**:909–919.

7. Gutnisky DA, Dragoi V: **Adaptive coding of visual information in neural populations**. *Nature* 2008, **452**:220–224.

8. Clemens J, Ozeri-Engelhard N, Murthy M: **Fast intensity adaptation enhances the encoding of sound in Drosophila**. *Nat Commun* 2018, **9**:1–15.

9. Clarke SE, Longtin A, Maler L: **Contrast coding in the electrosensory system: Parallels with visual computation**. *Nat Rev Neurosci* 2015, **16**:733–744.

10. Dahmen JC, Keating P, Nodal FR, Schulz AL, King AJ: **Adaptation to Stimulus Statistics in the Perception and Neural Representation of Auditory Space**. *Neuron* 2010, **66**:937–948.

11. Wen B, Wang GI, Dean I, Delgutte B: **Time course of dynamic range adaptation in the auditory nerve**. *J Neurophysiol* 2012, **108**:69–82.

12. Dean I, Harper NS, McAlpine D: **Neural population coding of sound level adapts to stimulus statistics.** *Nat Neurosci* 2005, **8**:1684–1689.

13. Wen B, Wang GI, Dean I, Delgutte B: **Dynamic range adaptation to sound level statistics in the auditory nerve**. *J Neurosci* 2009, **29**:13797–13808.

14. Rabinowitz NC, Willmore BDB, Schnupp JWH, King AJ: **Contrast Gain Control in Auditory Cortex**. *Neuron* 2011, **70**:1178–1191.

15. Rabinowitz NC, Willmore BDB, King AJ, Schnupp JWH: **Constructing Noise-Invariant Representations of Sound in the Auditory Pathway**. *PLoS Biol* 2013, **11**.

16. Willmore BDB, Cooke JE, King AJ: **Hearing in noisy environments: noise invariance and contrast gain control.** *J Physiol* 2014, **592**:3371–3381.

17. Cooke JE, King AJ, Willmore BDB, Schnupp JWH: **Contrast gain control in mouse auditory cortex**. *J Neurophysiol* 2018, **120**:1872–1884.

18. Cooke JE, Kahn MC, Mann EO, King AJ, Schnupp JWH, Willmore BDB: **Contrast gain control occurs independently of both parvalbumin-positive interneuron activity and shunting inhibition in auditory cortex**. *J Neurophysiol* 2020, **123**:1536–1551.

19. DeWeese M, Zador A: **Asymmetric Dynamics in Optimal Variance Adaptation**. *Neural Comput* 1998, **10**:1179–1202.

20. Wen B, Wang GI, Dean I, Delgutte B: **Time course of dynamic range adaptation in the auditory nerve**. *J Neurophysiol* 2012, **108**:69–82.

21. Młynarski W, Hermundstad AM: **Adaptability and efficiency in neural coding**. *bioRxiv* 2019, doi:10.1101/669200.

22. Młynarski WF, Hermundstad AM: **Adaptive coding for dynamic sensory inference**. *Elife* 2018, **7**.

23. Wei X-X, Stocker AA: **A Bayesian observer model constrained by efficient coding can explain “anti-Bayesian” percepts**. *Nat Neurosci* 2015, **18**:1509–1517.

24. Lohse M, Bajo VM, King AJ, Willmore BDB: **Neural circuits underlying auditory contrast gain control and their perceptual implications**. *Nat Commun* 2020, **11**:1–13.

25. Rabinowitz NC, Willmore BDB, King AJ, Schnupp JWH: **Constructing Noise-Invariant Representations of Sound in the Auditory Pathway**. *PLoS Biol* 2013, **11**:e1001710.

26. Li N, Daie K, Svoboda K, Druckmann S: **Robust neuronal dynamics in premotor cortex during motor planning**. *Nature* 2016, **532**:459–464.

27. Christison-Lagay KL, Bennur S, Cohen YE: **Contribution of spiking activity in the primary auditory cortex to detection in noise**. *J Neurophysiol* 2017, **118**:3118–3131.

28. Sahani M, Linden JF: **How Linear are Auditory Cortical Responses?** *Adv Neural Inf Process Syst* 2003, doi:10.1124/dmd.105.005157.concerning.

29. Barlow HB: **Possible Principles Underlying the Transformations of Sensory Messages**. In *Sensory Communication*. . 1961:216–234.

30. Talwar SK, Musial PG, Gerstein GL: **Role of mammalian auditory cortex in the perception of elementary sound properties**. *J Neurophysiol* 2001, **85**:2350–2358.

31. Gimenez TL, Lorenc M, Jaramillo S: **Adaptive categorization of sound frequency does not require the auditory cortex in rats**. *J Neurophysiol* 2015, **114**:1137–1145.

32. Jaramillo S, Zador AM: *Auditory cortex mediates the perceptual effects of acoustic temporal expectation*. 2010.

33. Wood KC, Town SM, Atilgan H, Jones GP, Bizley JK: **Acute inactivation of primary auditory cortex causes a sound localisation deficit in ferrets**. *PLoS One* 2017, **12**.

34. Kato HK, Gillet SN, Isaacson JS: **Flexible Sensory Representations in Auditory Cortex Driven by Behavioral Relevance**. *Neuron* 2015, **88**:1027–1039.

35. Ceballo S, Piwkowska Z, Bourg J: **Targeted Cortical Manipulation of Auditory Perception In Brief**. *Neuron* 2019, **104**:1168-1179.e5.

36. Li Z, Wei JX, Zhang GW, Huang JJ, Zingg B, Wang X, Tao HW, Zhang LI: **Corticostriatal control of defense behavior in mice induced by auditory looming cues**. *Nat Commun* 2021, **12**:1–13.

37. Musall S, Urai AE, Sussillo D, Churchland AK: **Harnessing behavioral diversity to understand neural computations for cognition**. *Curr Opin Neurobiol* 2019, **58**:229–238.

38. Shadlen MN, Kiani R: **Decision making as a window on cognition**. *Neuron* 2013, **80**:791–806.

39. Newsome WT, Britten KH, Movshon JA: **Neuronal correlates of a perceptual decision**. *Nature* 1989, **341**:52–54.

40. Britten KH, Shadlen MN, Newsome WT, Movshon JA: **The analysis of visual motion: A comparison of neuronal and psychophysical performance**. *J Neurosci* 1992, **12**:4745–4765.

41. Shadlen MN, Britten KH, Newsome WT, Movshon JA: **A computational analysis of the relationship between neuronal and behavioral responses to visual motion**. *J Neurosci* 1996, **16**:1486–1510.

42. Nienborg H, Cumming BG: **Decision-related activity in sensory neurons reflects more than a neurons causal effect**. *Nature* 2009, **459**:89–92.

43. Cumming BG, Nienborg H: **Feedforward and feedback sources of choice probability in neural population responses**. *Curr Opin Neurobiol* 2016, **37**:126–132.

44. Tsunada J, Liu ASK, Gold JI, Cohen YE: **Causal contribution of primate auditory cortex to auditory perceptual decision-making**. *Nat Neurosci* 2015, **19**:135–142.

45. Steinmetz NA, Zatka-Haas P, Carandini M, Harris KD: **Distributed coding of choice, action and engagement across the mouse brain**. *Nature* 2019, **576**:266–273.

46. Cohen MR, Newsome WT: **Context-Dependent Changes in Functional Circuitry in Visual Area MT**. *Neuron* 2008, **60**:162–173.

47. Cohen MR, Newsome WT: **Estimates of the contribution of single neurons to perception depend on timescale and noise correlation**. *J Neurosci* 2009, **29**:6635–6648.

48. Ni AM, Ruff DA, Alberts JJ, Symmonds J, Cohen MR: **Learning and attention reveal a general relationship between population activity and behavior**. *Science (80- )* 2018, **359**:463–465.

49. Downer JD, Niwa M, Sutter ML: **Task Engagement Selectively Modulates Neural Correlations in Primary Auditory Cortex**. *J Neurosci* 2015, **35**:7565–7574.

50. Stringer C, Michaelos M, Tsyboulski D, Lindo SE, Pachitariu M: **High-precision coding in visual cortex**. *Cell* 2021, doi:10.1016/j.cell.2021.03.042.

51. Hires SA, Gutnisky DA, Yu J, O’Connor DH, Svoboda K: **Low-noise encoding of active touch by layer 4 in the somatosensory cortex**. *Elife* 2015, **4**.

52. Hobbs JA, Towal RB, Hartmann MJZ: **Spatiotemporal patterns of contact across the rat vibrissal array during exploratory behavior**. *Front Behav Neurosci* 2016, **9**:356.

53. Aizenberg M, Geffen MN: **Bidirectional effects of aversive learning on perceptual acuity are mediated by the sensory cortex**. *Nat Neurosci* 2013, **16**:994–996.

54. Aizenberg M, Mwilambwe-Tshilobo L, Briguglio JJ, Natan RG, Geffen MN: **Bidirectional Regulation of Innate and Learned Behaviors That Rely on Frequency Discrimination by Cortical Inhibitory Neurons**. *PLOS Biol* 2015, **13**:e1002308.

55. Wood KC, Angeloni CF, Oxman K, Clopath C, Geffen MN: **Neuronal activity in sensory cortex predicts the specificity of learning**. *bioRxiv* 2020, doi:10.1101/2020.06.02.128702.

56. Briguglio JJ, Aizenberg M, Balasubramanian V, Geffen MN: **Cortical neural activity predicts sensory acuity under optogenetic manipulation**. *J Neurosci* 2018, **38**:2094–2105.

57. Ulanovsky N, Las L, Nelken I: **Processing of low-probability sounds by cortical neurons**. *Nat Neurosci* 2003, **6**:391–398.

58. Natan RG, Carruthers IM, Mwilambwe-Tshilobo L, Geffen MN: **Gain Control in the Auditory Cortex Evoked by Changing Temporal Correlation of Sounds**. *Cereb Cortex* 2017, **27**:2385–2402.

59. Pennington JR, David S V.: **Complementary effects of adaptation and gain control on sound encoding in primary auditory cortex**. *eNeuro* 2020, **7**:1–17.

60. Espejo ML, Schwartz ZP, David S V.: **Spectral tuning of adaptation supports coding of sensory context in auditory cortex**. *PLoS Comput Biol* 2019, **15**:e1007430.

61. Fritz J, Shamma S, Elhilali M, Klein D: **Rapid task-related plasticity of spectrotemporal receptive fields in primary auditory cortex.** *Nat Neurosci* 2003, **6**:1216–1223.

62. Mesgarani N, Fritz J, Shamma S: **A computational model of rapid task-related plasticity of auditory cortical receptive fields**. *J Comput Neurosci* 2010, **28**:19–27.

63. David S V., Fritz JB, Shamma SA: **Task reward structure shapes rapid receptive field plasticity in auditory cortex**. *Proc Natl Acad Sci U S A* 2012, **109**:2144–2149.

64. Yin P, Fritz JB, Shamma SA: **Rapid spectrotemporal plasticity in primary auditory cortex during behavior.** *J Neurosci* 2014, **34**:4396–408.

65. Niwa M, Johnson JS, O’Connor KN, Sutter ML: **Active Engagement Improves Primary Auditory Cortical Neurons’ Ability to Discriminate Temporal Modulation**. *J Neurosci* 2012, **32**:9323–9334.

66. Fritz JB, Elhilali M, Shamma SA: **Adaptive changes in cortical receptive fields induced by attention to complex sounds.** *J Neurophysiol* 2007, **98**:2337–46.

67. Simoncelli EP, Paninski L, Pillow J, Schwartz O: *Characterization of Neural Responses with Stochastic Stimuli*. MIT Press; 2004.

68. Paninski L, Pillow J, Lewi J: **Statistical models for neural encoding, decoding, and optimal stimulus design**. *Prog Brain Res* 2007, **165**:493–507.

69. Park IM, Meister MLR, Huk AC, Pillow JW: **Encoding and decoding in parietal cortex during sensorimotor decision-making**. *Nat Neurosci* 2014, **17**:1395–1403.

70. Eggermont JJ, Johannesma PIM, Aertsen AMHJ: **Reverse-correlation methods in auditory research**. *Q Rev Biophys* 1983, **16**:341–414.

71. Natan RG, Briguglio JJ, Mwilambwe-Tshilobo L, Jones SI, Aizenberg M, Goldberg EM, Geffen MN: **Complementary control of sensory adaptation by two types of cortical interneurons**. *Elife* 2015, **4**.

72. Natan RG, Rao W, Geffen MN: **Cortical Interneurons Differentially Shape Frequency Tuning following Adaptation**. *Cell Rep* 2017, **21**:878–890.

73. Atallah B V., Bruns W, Carandini M, Scanziani M: **Parvalbumin-Expressing Interneurons Linearly Transform Cortical Responses to Visual Stimuli**. *Neuron* 2012, **73**:159–170.

74. Wilson NR, Runyan CA, Wang FL, Sur M: **Division and subtraction by distinct cortical inhibitory networks in vivo**. *Nature* 2012, **488**:343–348.

75. Seybold B a, Phillips E a K, Schreiner CE, Hasenstaub AR: **Inhibitory Actions Unified by Network Integration**. *Neuron* 2015, **87**:1181–1192.

76. Phillips EAK, Hasenstaub AR: **Asymmetric effects of activating and inactivating cortical interneurons**. *Elife* 2016, **5**:e18383.

77. Attneave F: **Some informational aspects of visual perception**. *Psychol Rev* 1954, **61**:183–193.

78. Simoncelli EP, Olshausen BA: **Natural image statistics and neural representation**. *Annu Rev Neurosci* 2001, **24**:1193–1216.

79. Simoncelli EP: **Vision and the statistics of the visual environment**. *Curr Opin Neurobiol* 2003, **13**:144–149.

80. Młynarski W, Hledík M, Sokolowski TR, Tkačik G: **Statistical analysis and optimality of neural systems**. *Neuron* 2021, **109**:1227-1241.e5.

81. Guo Z V., Hires SA, Li N, O’Connor DH, Komiyama T, Ophir E, Huber D, Bonardi C, Morandell K, Gutnisky D, et al.: **Procedures for behavioral experiments in head-fixed mice**. *PLoS One* 2014, **9**.

82. Isett BR, Feasel SH, Lane MA, Feldman DE: **Slip-Based Coding of Local Shape and Texture in Mouse S1**. *Neuron* 2018, **97**:418-433.e5.

83. Carruthers IM, Natan RG, Geffen MN: **Encoding of ultrasonic vocalizations in the auditory cortex**. *J Neurophysiol* 2013, **109**:1912–1927.

84. Carruthers IM, Laplagne D a., Jaegle A, Briguglio J, Mwilambwe-Tshilobo L, Natan RG, Geffen MN: **Emergence of invariant representation of vocalizations in the auditory cortex.** *J Neurophysiol* 2015, doi:10.1152/jn.00095.2015.

85. Voigts J, Siegle J, Pritchett DL, Moore CI: **The flexDrive: An ultra-light implant for optical control and highly parallel chronic recording of neuronal ensembles in freely moving mice**. *Front Syst Neurosci* 2013, **7**:8.

86. Voigts J, Voigts J, Newman JP, Newman JP, Wilson MA, Wilson MA, Harnett MT, Harnett MT: **An easy-to-assemble, robust, and lightweight drive implant for chronic tetrode recordings in freely moving animals**. *J Neural Eng* 2020, **17**:26044.

87. Pachitariu M, Steinmetz N, Kadir S, Carandini M, Harris K: *Fast and accurate spike sorting of high-channel count probes with KiloSort*. [date unknown].

88. Stanislaw H, Todorov N: *Calculation of signal detection theory measures*. 1999.

89. Rocchi F, Ramachandran R: **Neuronal adaptation to sound statistics in the inferior colliculus of behaving macaques does not reduce the effectiveness of the masking noise**. *J Neurophysiol* 2018, **120**:2819–2833.

90. Hautus MJ: *Corrections for extreme proportions and their biasing effects on estimated values of d’*. 1995.

91. Benjamini Y, Hochberg Y: **Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing**. *J R Stat Soc Ser B* 1995, **57**:289–300.