# Reviewer #1:

**Comments for the Author:**

*This paper reports the results of an investigation into the effects of changing the sound level distribution (contrast) of background sounds on the response gain of auditory cortical neurons and sound detection behaviour in mice, with the aim of establishing the neural substrate for this important form of adaptation to sound statistics. The principal conclusions are that the data obtained are consistent with a normative model of efficient coding and that the cortical responses shape the performance of the animals, implying a direct relationship between the two.  
  
These findings are based on a comprehensive series of well-designed and executed experiments that complement previous work on contrast gain control at different levels of the auditory pathway in mice and ferrets, by incorporating a task that convincingly demonstrates contrast-dependent changes in mouse sound detection behavior and by recording simultaneously from the auditory cortex of these animals. These are important and timely extensions of the previous studies. The GLM procedure used for estimating the dynamics of gain control in auditory cortex is also very nice. However, the claims about efficient coding accounting for contrast gain control and the link between cortical neuronal adaptation and behavior (made at several places in the Introduction and Discussion) are neither directly addressed nor supported by the data. Consequently, the advance provided by this study is relatively limited. While the paper does describe a detailed and valuable dataset, some of the findings are inconsistent and in places the results are very difficult to follow.*  
**Major comments:**  
*1. The GC-GLM used to fit the time course of gain changes is similar to the approach used in previous phenomenological models with exponentially-decaying integration of recent contrast. In terms of predicting neuronal responses, the main advance over those models is to use a GLM rather than an LN model with dynamic gain changes. This is a good advance, which seems sensible and likely to improve predictions. However, the authors need to show that the GC-GLM outperforms the model used in the ferret papers by Rabinowitz and colleagues and in mice by Lohse and colleagues. The current comparison between the GC-GLM and a static LN model or an LN with two gain states is a bit of a straw man because it is almost inevitable that any model that can capture dynamics is going to outperform models that don’t.*

As the reviewer points out, we used a GLM rather than an LN model with exponential decay in order to fit any potential time course of gain adaptation, exponential or otherwise. We agree that comparison of the GC-GLM to the dynamic models mentioned by the reviewer would be a more compelling test of model performance. To address this, we will fit the dynamic model presented in Lohse et al., 2020 to our data to test whether the additional flexibility of the GC-GLM further improves fits to the data.  
  
*2. Similarly, the Poisson GLM has various properties that have been described before (e.g., in Rabinowitz et al., 2011), including that response gain is scaled according to the contrast of the stimuli and that the time courses of cortical gain changes are asymmetric. These are phenomenological observations. It is also well understood that compensation for changes in contrast is likely to be beneficial, resulting in noise-tolerant representations (Rabinowitz et al. 2013) and optimizing discriminability (Lohse et al. 2020). The normative aspects of the GLM predict that changing contrast will alter thresholds and psychometric function slopes and result in asymmetric time constants. While these properties are borne out by the experimental data, validation of the model would be much stronger if the normative model predicted specific time constants, or made other falsifiable predictions, which could then be compared quantitively with the neural responses or behavior. Furthermore, the proposed connection between efficient coding and behavior depends on the normative model, and this connection has not been explained or justified in a convincing way, undermining one of the main conclusions of the study. In other words, this study does not show that contrast gain control in the auditory system conforms to efficient coding substantially more than previous work in this field.*

Our intent for the normative model was to develop an intuition about how contrast gain control in a single neuron could shape the ability of that neuron to decode the presence of targets in noise. The predictions of this model were meant to be qualitatively compared to behavior. The model and the experimental data span a large gap: the model is composed of a single, untuned neuron, while the behavioral output of the animal likely depends on the coordinated activity of populations of tuned neurons with varying degrees of adaptation. It is unknown how gain compensation affects neural representations at a population level, as such, we chose to study how the dynamics of a simplified neuron would optimally adapt to contrast.

That said, this simple model can be used to generate falsifiable predictions for the data: one can consider the relative change in model outputs for each stimulus contrast to more quantitatively assess the model’s relationship to the data (for instance, comparing the ratio of the time constants, thresholds, and slopes in low and high contrast). Reframing the model predictions and experimental findings in this manner may provide a more compelling comparison of the model predictions to the data, and we plan to do this in the next revision.

*3. Extended Data Figure 5 shows that STRF structure is stable across contrast, which is very important for interpreting the effects on response gain. However, this is based on acute recordings. Has a similar analysis been performed for the chronic recordings obtained during task performance, where top-down modulation of cortical tuning properties is likely to occur (as demonstrated by previous studies in a range of species)? Such short-term plasticity in STRFs could be contributing to apparent changes in gain.*

We designed our stimulus to avoid task-related changes in tuning by using broad-band targets rather than the pure tone targets used by Jonathan Fritz and colleagues in previous work. That said, it is important to understand whether the tuning in different epochs of the trial is affected by task-engagement, particularly when interpreting the task-related changes in gain presented in Figure 6. We plan to perform this analysis on our data set in the next revision.  
  
*4. Although different target ranges are used, there doesn’t seem to be a control that matches the mean sound level for the two contrast conditions. Since the mean sound level will vary between the low and high contrast DRC backgrounds, it is possible that the observed effects result (partially or completely) from adaptation to mean level, rather than adaptation to contrast.*

Previous work examining the effect of contrast on discrimination of target volume performed this control and found that contrast-dependent changes in perception were present whether or not they controlled for mean sound level (Lohse et al., 2020). Given these previous findings, we chose not to control for the small increase in sound level during high contrast.  
  
*5. The muscimol experiments were designed to demonstrate whether auditory cortex is required for the mice to perform the sound-in-noise detection task. The behavioral effects of muscimol varied markedly between sessions (Fig. 4), with some cases showing no impairment relative to saline controls. Can these differences be related to the effects of muscimol on cortical activity in individual animals/sessions? It would also be good to see an analysis which shows that the average reduction in P(respond) and threshold is robust across multiple mice. As far as I can tell, there are only 2 mice in each group (muscimol and saline), which is a very small sample size.*

We cannot ascertain with this dataset whether variability in the effect of muscimol was related to variability in the suppression of cortical activity as this cohort of mice were not implanted with recording devices. However, when we recorded from auditory cortex in awake, untrained mice we did observe robust suppression of cortical activity when applying muscimol (Supplemental Figure 4). It is possible that the variability in performance is due to incomplete injections, but this seems unlikely, as the experimenter always monitored the injection tubing to verify that muscimol or saline were injected fully.

In Figure 4b-c, data from 4 mice are plotted, while in Figure 4e-f, data from 2 mice are plotted, as indicated in the figure legend. We will also report the average change in perceptual variables across mice, rather than across sessions, but note that our experimental manipulations and controls are within mouse and were based on previous inactivation studies in rodents with similar numbers of subjects and sessions (Raposo et al., 2014; Ceballo et al., 2019).  
  
*6. While the muscimol experiments are useful in indicating a specific role for auditory cortex in sound-in-noise detection (the target-in-silence condition is an essential and welcome control for this), they do not address the more relevant question of whether auditory cortex is required for contrast gain control. This would require a different approach from the one used. The muscimol experiments do not provide evidence for a direct link between adaptive processing in the cortex and behaviour and therefore their value for this study is limited.*

We agree that the muscimol experiments do not directly address whether auditory cortex is required for contrast gain control. While specifically disrupting gain control in the auditory cortex would be the perfect experiment in this case, the neural mechanisms of gain control are an active line of research and remain poorly understood in the auditory system (Wilmore et al., 2013; Lohse et al., 2020; Cooke et al., 2020).

However, in the context of the current work, we wished to show that cortical activity is required for the behavior. As such, establishing whether cortical activity is required for the task supports the correlations we observed between cortical activity and performance in Figures 5 and 6.  
  
*7. The authors have attempted to address this through a complex series of analyses in Figs. 5 and 6 that explore the relationship between neurometric and psychometric functions. While these reveal a correlation between the neural and behavioral data, and show (in some of the data) that both are affected by contrast, they do not show a direct connection between the two (which would ideally involve demonstrating a causal relationship). The accompanying text is hard to follow and potentially suffers from too many analyses. Furthermore, there are several inconsistencies in the data that reduce the reader’s confidence in the findings.*

We will rewrite this passage of the manuscript to make these analyses easier to follow. Specific suggestions will be addressed as follows.  *The main examples are:  
- Depending on which mice were included (and therefore the range of target levels), the slopes of the neurometric and psychometric functions were (as expected) steeper in the low contrast condition in some cases, whereas the opposite result was found when all the animals were included.*

Indeed, we found that the slope of the psychometric function was affected by two sources of variability: the range of the targets presented and the contrast of the background. We attempted to convey that when keeping the target range matched across the contrast conditions, the psychometric slope was affected by contrast as expected. We will restructure how we present the results in this section to make these distinctions more clear.

*- On lines 292-294, the text states that neurometric slopes "significantly improved psychometric slope predictions” which seems to contradict the “n.s.” on Figure 5h.*

This statement is still true. In Figure 5g and 5h, each asterisk indicates whether a mixed effects model including both the neurometric measure and contrast was a better fit to the data than a model excluding the neurometric measure (grey asterisk) or excluding the contrast (black asterisk). In the case of the slopes, including neurometric slopes significantly improved the model fit, but including the contrast did not. However, as in the behavior, if we include only mice with matched target volumes, psychometric slope was significantly predicted by both neurometric slopes and contrast, as presented in Extended Data Figure 5a.

*- The fact that the psychometric slopes in Fig. 5h (and Extended Data Fig. 3) were not affected by contrast is puzzling and is surely a concern, particularly since the aim of the study was to account for the neural basis of contrast gain control.*

As in the previously presented behavioral data, when presenting the same target volumes in low or high contrast, we did observe significant decreases in psychometric and neurometric slopes (Extended Data Figure 5a).

*- It is stated (on line 356) that a step from low to high contrast reduces behavioral thresholds. I would have expected the opposite to occur (and Fig. 6g suggests that I’m right, so perhaps this is a mistake in the text). Furthermore, it is puzzling that some mice took part in the low contrast sessions, whereas others were tested with high contrast stimuli. This would be more convincing if the contrast was varied within animals to determine whether neurometric and psychometric performance changed in the same way.*

The specific statement on line 356 is a typo and has been corrected in the manuscript.

All mice (with the exception of one mouse, CA122, as noted in the Methods), performed the tasks in both contrasts on separate sessions. Mice were first trained to detect targets in one contrast, then, after testing, were retrained to detect targets in the other contrast. This procedure was counterbalanced, such that half of the mice were first trained in high contrast, while the other half were first trained in low contrast. This training procedure was described in the Methods (*Behavioral timeline*, lines 555-565).

We structured our analysis of the neurometric and psychometric performance on the fact that the same mice were exposed to low and high contrast. To account for potential variability in the effect of contrast within each mouse, the data in Figures 5 and 6 were analyzed with mixed effects linear models. This approach allowed us to specifically model the effect of contrast within each mouse in addition to the relationship between neurometric parameters and psychometric parameters, and had the added benefit of being able to deal with unbalanced samples and repeated measures (for a recent review of the application of these models in neuroscience, see Yu et al., 2021; in Neuron). We attempted to explain this approach in lines 267-271, but will revise the results section to emphasize the fact that we recorded responses during low and high contrast within mice and how our analysis was structured to account for these repeated measures.

**Minor comments:**  
  
*Abstract. "Furthermore, variability in cortical gain predicted behavioral performance beyond the effect of stimulus-driven gain control" -- this is unclear.*

This was intended to report the findings in Figure 6, which demonstrate that contrast and variability in gain independently affected variability in psychometric performance.  
  
*Results. The normative model is not adequately described in the main text.*

We will provide more description in the next draft.  
  
*Throughout, the authors use "volume" (which is usually understood to be a perceptual quantity) instead of "sound level” (preferably expressed in units of dB SPL). This is uninformative and really not appropriate.*

We have corrected the text to use sound level instead of volume, where appropriate.

*Line 90. “Adaption”*

Corrected.  
  
*It is not clear from the main text what is meant by the “gain control index, 𝑤𝑡”. While it is obviously fine to leave a full explanation for the methods, some explanation, including what the units are and what the numbers indicate, is needed in the main text. The sentence in the legend for Fig. 2k “Average time course of the gain estimate 𝑤𝑡 for neurons with gain control (ie. gain control is less than 0, n = 45)” is incomprehensible without this.*

We will provide a better description of the gain control index in the main text. By definition, it is unitless, and describes the multiplicative scaling of the response to the stimulus by the contrast. Specifically, wt = 1 means that there is no scaling, wt = .5 is optimal divisive scaling during high contrast, and wt = 1.5 is optimal multiplicative scaling during low contrast.  
  
*Line 125. “Kruskall” (spelling)*

Corrected.  
  
*Line 135. “Mice initially trained”. Missing “were”.*

Corrected.  
  
*References 14 and 29 are the same.*

Corrected.  
  
*Fig 1b. The position of the scale bar implies that there is something significant about the 1 second period before the contrast switch. Maybe move to a different location in the figure?*

Corrected.  
  
*Fig 1c. "Target time" color bar could be easier to distinguish or just show one (multiple waveforms could be construed as several targets being presented in the same trial). The location of the target time color bar (aligned with the ordinate) is also potentially misleading since this axis refers to amplitude/SNR.*

We will rework this figure to make it more intuitive.  
  
*Fig 1d. Unclear if these are arbitrary LOG units or not.*

These are standard units.  
  
*Fig 1e. Is this mean level on the x-axis? Legend and axis label are unclear.*

Yes, it is the mean target level in the same units as in panel 1d. Corrected.  
  
*Fig. 2d. “PSTH of the example cell is plotted in gray. Predictions from the static-LN model are plotted in gray”. Ok, the first is solid shading and the second a line, but the use of the same color is unnecessarily confusing.*

Corrected.  
  
*Fig 3b. What does "rel." stand for?*

Relative, but we will simply revise the label to “Time (s)”

*Fig 3b. It would be good to show per-mouse data for this.*

We will update the figure to show the learning trajectories of individual mice.  
  
*Fig 3b legend. "Behavioral performance the initial training contrast" -- some words missing?*

Corrected.  
  
*Fig 3c. Again, it would be helpful to see individual-animal psychometric functions to know what is going into the average in 3d.*

This curve is an individual mouse’s average psychometric function, which is what goes into Figure 3d, but we will plot individual sessions as curves instead of dots.  
  
*Fig 4b/e. "Dark" is not a clear descriptor of the average curves – distinct colors would be better. Alternatively, make the individual functions gray and have only the averages in red/blue, so you can refer to "red/blue" curves and "gray" curves. This would also help with the legibility of the figures themselves, which are very busy. Also consider not using dashed lines, which are hard to trace through the plot.*

Great suggestions, we will update the figures accordingly.  
  
*Fig 5b. I think colors in the scale are supposed to match shading of the graphs to the left of Time=0, but they are different. Perhaps also flip the legend from top to bottom, so it matches the order of the trials.*

Corrected.  
  
*Fig 5c. Consider changing the color bars, which currently strongly emphasise some very small negative coefficients.*

Corrected  
  
*Fig. 5 legend. Last line: “Wilsoxon”. Spelling.*

Corrected.  
  
*I think Extended Data Fig. 2 is first mentioned near the end of the Results, rather than with the description of Fig. 2.*

Corrected.  
  
*Extended Data Fig. 4c,d. “-Inf” is unnecessary and not defined: just say background (if necessary, abbreviated as Bkd).*

Corrected.  
  
*Extended Data Fig. 5b. It’s impossible to make out any structure in the inset STRFs.*

We will rescale the STRFs to the same size as the thresholded STRFs.  
  
  
  
Reviewer #2

**Comments for the Author:**

*Angeloni et al present an intriguing study on the role of cortical contrast gain control in auditory task performance. The authors find clear similarities between neurophysiological recordings, behavioral task performance, and statistical models of contrast gain control. The most novel and appealing aspect of this study is the analysis of contrast gain control as it occurs during auditory task performance. This approach is a critical step in clarifying the function of contrast gain control in auditory perception, and sensory processing in general.  
  
A primary criticism is that the authors evidence does not back the strength their claims, i.e., “efficient neural codes in auditory cortex directly influence perceptual behavior.” (lines 26-27). Similarly, the manuscript’s title is too strongly worded. The authors demonstrate that contrast gain control was predictive of task performance, and that their task required auditory cortex, however, direct evidence for a causal role of contrast gain control (i.e., “influence”) in task performance was not shown. That would require, for example, systematically affecting task performance by optogenetic manipulation of the time-course of contrast gain control. It appears that such methods were in place (i.e. Supplementary methods beginning on line 147), but specifically left out of this study.*  
  
**Major Comments:**

*1.“Efficient encoding” vs “contrast gain control”—the authors use the two phrases more-or-less interchangeably, however, this study is primarily about contrast gain control, which is a hypothesized mechanism for efficient coding. In combination with the primary criticism stated above, I suggest the title of the manuscript be changed to, “Cortical Contrast Gain Control Predicts Auditory Task Performance”.*

We will update the text to emphasize the relationship between contrast gain control and efficient coding, and will update the title to more accurately reflect the results presented.

*2.The total number of units and animals included per analysis is not clear, which makes it difficult to understand if the results generalized across mice. In addition, the rationale for the different numbers of units per analysis is not clear.*

We attempted to indicate the numbers of animals, sessions, and units for each analysis in Extended Data Table 1, but will revise the main text to be more clear about the specific number of data points and relevant selection criteria.  
  
*3.The description of stimulus levels throughout the manuscript is too vague, e.g. “volume”. Considering that gain depends on the mean sound level, it is important for the authors to specify the levels of stimulus presentation in the main text and figures.*

We will update the text to use “sound level” where appropriate.  
  
*4.I did not see any figures or text verifying that the recordings were done in auditory cortex. Considering the evidence in the literature that task-related auditory processing is different in primary vs higher-order auditory cortex, particularly for complex sounds, it is important that the authors indicate if recordings were done in A1 vs non-A1.*

Many of the microdrives used in this study had drive arrays with relatively large pitch, spanning ~1mm^2 or greater, as such, these recordings likely included portions of A1 and other auditory fields. To verify whether recordings were performed in A1, we dipped the tetrode arrays in DiI before implantation. We will provide a figure demonstrating recording locations in the revision.

*5. Considering that task-related effects in auditory cortex depend on cortical layer, and the authors used a depth probe, are the authors able to localize their effects to a specific layer, or a distribution of layers?*

In this study we did not use a depth probe during the behavior, but rather used chronically implanted microdrives, as described in the Methods (see *Surgery*, lines 510-516). Due to low implant stability when mounting the drive orthogonally to the surface of auditory cortex, we chose to implant the drives on the dorsal surface of the skull above auditory cortex. We then advanced the tetrodes down to ~800-1000um below the cortical surface until we observed spikes which locked to click trains presented to the mouse.  
  
*6.Some of the authors' critical findings depend on the “gain control index (wt) from the fitted model parameters”, yet an explanation of this parameter is left to supplemental information. I suggest the authors include some text in the results that clarifies how the parameter should be understood.*

We will update the text to better describe this important parameter.  
  
**Minor Comments:**

*1.Line 393: changes in*

Corrected.