Dear Maria,  
  
  
Thank you for submitting your Article, "Cortical efficient coding dynamics shape behavioral performance.." Please accept my sincere apologies for the considerable delay in returning a decision on your manuscript. It has now been seen by 2 referees, whose comments are below.  
  
While the referees find your work of some interest, I am sorry to say that they have raised serious concerns about the conceptual advance your findings represent over earlier work and the strength of the novel conclusions that can be drawn at this stage. We feel that these reservations are sufficiently important as to preclude publication of this paper or a revision in Nature Neuroscience.  
  
You might want to consider our sister journal [*Nature Communications*](https://www.nature.com/ncomms/about) as a potential venue for the publication of these results. *Nature Communications* publishes high quality and influential research and across the full spectrum of the natural sciences. More information on the journal, the potential benefits of transfer and a link to transfer your paper, can be found at the bottom of this email. Please note that the editorial team at *Nature Communications* will consider your manuscript independently of our suggestion to transfer.  
  
We are sorry we cannot be more positive on this occasion, and we thank you for the opportunity to consider this manuscript. We hope that you will find our referees' comments helpful and that you will soon receive a more encouraging response elsewhere.  
  
  
Sincerely,  
Sachin  
  
Sachin Ranade, PhD  
Senior Editor  
Nature Neuroscience  
ORCID: 0000-0002-5150-5776  
  
  
Referee expertise:  
  
Referee #1:  
  
Referee #2:  
  
Referee #3:  
  
  
Reviewers' Comments:  
  
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.  
  
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.  
  
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.  
  
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.  
  
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.  
  
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.  
  
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.  
  
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.  
- 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.  
- 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.  
- 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.  
  
  
Minor comments:  
  
Abstract. "Furthermore, variability in cortical gain predicted behavioral performance beyond the effect of stimulus-driven gain control" -- this is unclear.  
  
Results. The normative model is not adequately described in the main text.  
  
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.  
  
Line 90. “Adaption”  
  
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.  
  
Line 125. “Kruskall” (spelling)  
  
Line 135. “Mice initially trained”. Missing “were”.  
  
References 14 and 29 are the same.  
  
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?  
  
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.  
  
Fig 1d. Unclear if these are arbitrary LOG units or not.  
  
Fig 1e. Is this mean level on the x-axis? Legend and axis label are unclear.  
  
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.  
  
Fig 3b. What does "rel." stand for?  
  
Fig 3b. It would be good to show per-mouse data for this.  
  
Fig 3b legend. "Behavioral performance the initial training contrast" -- some words missing?  
  
Fig 3c. Again, it would be helpful to see individual-animal psychometric functions to know what is going into the average in 3d.  
  
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.  
  
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.  
  
Fig 5c. Consider changing the color bars, which currently strongly emphasise some very small negative coefficients.  
  
Fig. 5 legend. Last line: “Wilsoxon”. Spelling.  
  
I think Extended Data Fig. 2 is first mentioned near the end of the Results, rather than with the description of Fig. 2.  
  
Extended Data Fig. 4c,d. “-Inf” is unnecessary and not defined: just say background (if necessary, abbreviated as Bkd).  
  
Extended Data Fig. 5b. It’s impossible to make out any structure in the inset 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”.  
  
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.  
  
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.  
  
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.  
  
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?  
  
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.  
  
Minor Comments  
1.Line 393: changes in