The Journal of Physiology

Cochlear synaptopathy impairs suprathreshold tone-in-noise coding in the cochlear nucleus

Adam Hockley, Luis R Cassinotti, Michael M Selesko, Gabriel Corfas, and Susan Shore
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Corresponding author(s): Susan Shore (sushore@umich.edu)

The following individual(s) involved in review of this submission have agreed to reveal their identity: Conny Kopp-Scheinpflug (Referee #2)

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1st Editorial Decision **07-Mar-2023**

Dear Professor Shore,

Re: JP-RP-2023-284452 "Cochlear synaptopathy impairs suprathreshold tone-in-noise coding in the cochlear nucleus" by Adam Hockley, Luis R Cassinotti, Michael M Selesko, Gabriel Corfas, and Susan Shore

Thank you for submitting your manuscript to The Journal of Physiology. It has been assessed by a Reviewing Editor and by 2 expert referees and we are pleased to tell you that it is acceptable for publication following satisfactory revision.

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The referee reports are copied at the end of this email.

Please address all the points raised and incorporate all requested revisions or explain in your Response to Referees why a change has not been made. We hope you will find the comments helpful and that you will be able to return your revised manuscript within 4 weeks. If you require longer than this, please contact journal staff: jp@physoc.org.

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We look forward to receiving your revised submission.

If you have any queries, please reply to this email and we will be pleased to advise.

Yours sincerely,

Richard Carson
Senior Editor
The Journal of Physiology

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-Author photo and profile. First (or joint first) authors are asked to provide a short biography (no more than 100 words for one author or 150 words in total for joint first authors) and a portrait photograph. These should be uploaded and clearly labelled with the revised version of the manuscript. See Information for Authors for further details.

-You must start the Methods section with a paragraph headed Ethical Approval. A detailed explanation of journal policy and regulations on animal experimentation is given in Principles and standards for reporting animal experiments in The Journal of Physiology and Experimental Physiology by David Grundy J Physiol, 593: 2547-2549. doi:10.1113/JP270818.). A checklist outlining these requirements and detailing the information that must be provided in the paper can be found at: https://physoc.onlinelibrary.wiley.com/hub/animal-experiments. Authors should confirm in their Methods section that their experiments were carried out according to the guidelines laid down by their institution's animal welfare committee, and conform to the principles and regulations as described in the Editorial by Grundy (2015). The Methods section must contain details of the anaesthetic regime: anaesthetic used, dose and route of administration and method of killing the experimental animals.

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In summary:

-If n {less than or equal to} 30, all data points must be plotted in the figure in a way that reveals their range and distribution. A bar graph with data points overlaid, a box and whisker plot or a violin plot (preferably with data points included) are acceptable formats.

-If n > 30, then the entire raw dataset must be made available either as supporting information, or hosted on a not-for-profit repository e.g. FigShare, with access details provided in the manuscript.

-'n' clearly defined (e.g. x cells from y slices in z animals) in the Methods. Authors should be mindful of pseudoreplication.

-All relevant 'n' values must be clearly stated in the main text, figures and tables, and the Statistical Summary Document (required upon revision)

-The most appropriate summary statistic (e.g. mean or median and standard deviation) must be used. Standard Error of the Mean (SEM) alone is not permitted.

-Exact p values must be stated. Authors must not use 'greater than' or 'less than'. Exact p values must be stated to three significant figures even when 'no statistical significance' is claimed.

-Statistics Summary Document completed appropriately upon revision

-Please include an Abstract Figure file, as well as the figure legend text within the main article file. The Abstract Figure is a piece of artwork designed to give readers an immediate understanding of the research and should summarise the main conclusions. If possible, the image should be easily 'readable' from left to right or top to bottom. It should show the physiological relevance of the manuscript so readers can assess the importance and content of its findings. Abstract Figures should not merely recapitulate other figures in the manuscript. Please try to keep the diagram as simple as possible and without superfluous information that may distract from the main conclusion(s). Abstract Figures must be provided by authors no later than the revised manuscript stage and should be uploaded as a separate file during online submission labelled as File Type 'Abstract Figure'. Please ensure that you include the figure legend in the main article file. All Abstract Figures should be created using BioRender. Authors should use The Journal's premium BioRender account to export high-resolution images. Details on how to use and access the premium account are included as part of this email.

EDITOR COMMENTS

Reviewing Editor:

Thank you for submitting your manuscript entitled " Cochlear synaptopathy impairs suprathreshold tone-in-noise coding in the cochlear nucleus" to the Journal of Physiology.

Your manuscript has been seen by two reviewers who both find your work highly interesting, but also raise some important points that need to be addressed. We would like to consider your response to these concerns in the form of a revised manuscript before we make a final decision on publication.

We therefore invite you to revise and resubmit your manuscript, taking into account all the points raised. Please highlight all changes in the manuscript text file and provide a response to the reviewers'comments. As alerted by the reviewers, the MS requires a revised discussion and improved readability of the figures (please, also note a typo in the Fig. 1D: MyoVIIa).

Senior Editor:

Please ensure that the basis upon which error bars have been calculated is indicated in all relevant figure legends. It should be noted that the statistical policy of the Journal requires that standard deviations, rather than standard errors, be represented.

REFEREE COMMENTS

Referee #1:

This is an interesting and timely manuscript detailing the response properties of neurons in the cochlear nucleus, the obligatory feedforward pathway in the by sending auditory system following exposure to noise designed to elicit subthreshold changes in hearing function sometimes referred to as hidden hearing loss. The manuscript makes a critical link between auditory nerve recordings and more central levels of the nervous system recently reported for neurons in the midbrain of animals exposed to subthreshold damaging noise. Three specific publications are highly relevant to the current manuscript and should be cited, not just generally, but discussed with specific reference to the main findings of the current manuscript not only because they are highly relevant, complementary, and supportive, but also because the current hypothesis addresses, and possibly answers, outstanding questions raised by those reports. These questions are highly relevant to the

mechanisms underlying listening problems in hidden hearing loss/following synaptopathy, and the current manuscript addresses some of these directly. These studies are:-

Hesse LL, Bakay W, Ong HC, Anderson L, Ashmore J, McAlpine D, Linden J, Schaette R. Non-Monotonic Relation between Noise Exposure Severity and Neuronal Hyperactivity in the Auditory Midbrain. Front Neurol. 2016 Aug 25;7:133. doi: 10.3389/fneur.2016.00133. PMID: 27625631; PMCID: PMC5004570.

Monaghan JJM, Garcia-Lazaro JA, McAlpine D, Schaette R. Hidden Hearing Loss Impacts the Neural Representation of Speech in Background Noise. Curr Biol. 2020 Dec 7;30(23):4710-4721.e4. doi: 10.1016/j.cub.2020.09.046. Epub 2020 Oct 8. PMID: 33035490; PMCID: PMC7728162.

Bakay WMH, Anderson LA, Garcia-Lazaro JA, McAlpine D, Schaette R. Hidden hearing loss selectively impairs neural adaptation to loud sound environments. Nat Commun. 2018 Oct 16;9(1):4298. doi: 10.1038/s41467-018-06777-y. PMID: 30327471; PMCID: PMC6191434.

importantly these studies demonstrate including using speech in noise and more complex distributions of sounds, that suprathreshold neural encoding is impaired in hidden hearing loss in a way that is not obvious and straightforward from the relatively simple stimulus paradigms that are often employed in single-neuron physiology. They therefore support the current manuscripts findings and the current manuscript provides an important link between the relatively simple and in some cases nonspecific physiological recordings made in animals exposed to sub threshold levels of damaging noise and the less standard assessment paradigms employed by several recent studies such as Monaghan et al and Bakay et al.

I have no contention with the data presented or how they were captured and the noise exposure and general methodology for quantifying synaptopathy and neural responses in sham and exposed animals rigorous and well justified. However, I believe the manuscript does itself a disservice by not placing these important findings in the context of several, although still limited, number of studies that have explored directly the impact of synaptopathy/hidden hearing loss on neural responses in the central nervous system.

The key section in the results of this current manuscript is entitled Cochlear nucleus TIN thresholds do not increase after synaptopathy. The current data demonstrates some level of hyper-excitability in neurons of the cochlear nucleus, that extends to thresholds in animals subject to prior exposure to loud sounds designed to elicit hidden hearing loss. the fact that threshold shifts but right intensity functions in background noise are smaller, at least at some intensities of noise and some neuron types, in exposed compared to non-exposed animals is consistent with the findings of all of these studies in the midbrain nucleus of the inferior colliculus. It suggests that hidden hearing loss manifests as hyper excitability. Importantly as in the study of bakay et al, and Monaghan et al, the effect of prior over-exposure on thresholds is intensity dependent, being greater at lower versus higher levels of contemporary background noise. This should be stated and discussed because it suggests that the site of action of elevated sensitivity or excitability is either within the cochlear nucleus or if arises from feedback from higher brain centres manifests within the cochlear nucleus. Indeed, given that thresholds are better/lower for the hidden hearing loss group and that this concords with previous findings in the midbrain this section might actually entitled cochlear nucleus TIN thresholds reduced after synaptopathy. By the way the aforementioned studies demonstrate these particulars not with the same exact stimulus parameters but definitely in the same general framework of elevated or hyper excitability. The fact that the greatest difference occured at BS above the noise exposure spectrum is also consistent with the findings of Monaghan and also accords with the well-established half octave shift in cochlear damage by noise. Again as suggested by Monaghan et al, synaptopathy to follow the general rules of noise damage in permanent hearing loss with respect to where basilar membrane excursion, rather than velocity (near CF), is maximum. whilst likely not accounting for all of the midbrain effects, and bearing in mind the difference in the stimulus paradigms, this concordance in terms of not only not elevated thresholds but improved, lower thresholds in hidden hearing loss animals is an important finding.

Another important finding in the current manuscript and this time counter 2 the aforementioned studies is the reduction in suprathreshold firing rates in hidden hearing loss animals in background noise. here compared to Monaghan et al, and Bakay, super threshold firing rates are reduced in the cochlear nucleus. Again this hints at potential sites and mechanisms for changes in neural function. If cochlear nucleus firing rates are reduced following synaptopathy, it suggests that elevated firing rates including in background noise in the midbrain arise from local changes in neural gain i.e. local increases in neural gain in the inferior colliculus. Again, this is an important finding of the current manuscript, but also demonstrates the need to compare the current data and discuss the current findings, with those of previous studies exploring neural responses in the auditory midbrain and hidden hearing loss. I find some of the discussion around the potential changes in suprathreshold firing rates slightly obscure. The sheer multitude of feedforward and feedback circuits in the lower brainstem may reduce maintain or increase buying rates depending on the level of damage to the auditory nerve fibres in hidden hearing loss, animal specific differences, or other factors that relate to the type of stimulus under investigation. these issues should be alluded to in the discussion particularly from lines 425 to 433.

A strength of the current study, less amenable to recordings made in the midbrain, is the ability to distinguish between different cell types and their responses to noise exposure. Interesting Lee these subtle differences lie in a small cell cap type-cells, putatively playing some role either in speech encoding (contentious) or in modulating neural gain. Some discussion on this topic would be appropriate, though only in the sense of acknowledging the remaining work to be undertaken in exploring importance of the different cell types in encoding suprathreshold acoustic information.

Referee #2:

Hockley and co-authors set out to test the hypothesis that noise trauma-induced cochlear synaptopathy could impair coding of suprathreshold tones to a greater degree because synaptopathic noise exposure affects primarily auditory nerve fibers with high-thresholds and low spontaneous rates. In humans, such synaptopathy is often described as hidden hearing loss because following a noise insult, synapses contacting the inner hair cells in the cochlea die, but auditory thresholds as usually measured in an audiogram remain unchanged. Nevertheless, humans with hidden hearing loss suffer from auditory processing deficits such as tone-in-noise or speech-in-noise discrimination as they grow older. Different animal models have been used to explore the neural basis of this phenomenon, but these came to different if not opposing results; either showing increased thresholds or no change in thresholds in behavioral tone in noise tests. Therefore the manuscript presented here is timely and important as it sheds light on those previous discrepancies.

In this study, the authors performed unilateral noise exposure to anesthetized guinea pigs. The initial temporal threshold shift following the noise exposure was measured by ABR recordings. After 4 weeks, the animals underwent neural recordings in the cochlear nucleus, another round of ABR recordings and then histological analysis of the synapse loss in the cochlea.

The main finding of the manuscript is that tone in noise thresholds of single cochlear nucleus neurons are not increased by synaptopathy, siding with previous studies that show no impairment of tone in noise coding in animals with synaptopathy. However, the present manuscript also shows that single cochlear nucleus neurons in animals with synaptopathy rather show that suprathreshold tone in noise thresholds are impaired. As opposed to behavioural testing the authors could take advantage of dissecting the targets of different auditory nerve fibers and show that it is the small cells of the DCN that are most effected by synaptopathy.

Major points

The data seem convincing but their presentation is not to the usual high standard of the Shore lab. The manuscript needs a major make over. There is hardly any description in the text or figure legends of what you did and why and what the figures show. There are no number, no n-numbers, no standard deviations etc. Someone who does not already know what you are doing will have no chance in understanding the important message that is hidden in this manuscript. Especially when addressing the readers of the Journal of Physiology you should keep in mind that only a part of them are neuroscientists and only a minority know about the auditory system.

Along the same lines - the figures need work. They should visualize your findings and help the reader to better understand the data described in the text - so far neither is possible. Remember that some reader will only flick through the figures and if they are not comprehensible, your paper may not get read at all. I have outlined a few suggestions below.

To me the manuscript seems backwards in order. Why don't you think about re-structuring and starting with your strength?

1. Noise exposure causes synapse loss (fig.1) especially in the low SR/high threshold ANFs.

2. Small cells in the DCN are the only cells that receive exclusive input from low SR/high threshold ANFs target - therefore these should be studied!!

3. In the past, vast recordings of small cells were not possible.

4. Due to technical advancement you now recorded hundreds of small cells.

5. Show the two groups (but think about what I say below about the PSTHs) and their deficit in suprathreshold TIN.

6. Then you can show the other chopper and PL cells to explain why behavioral result could go either way when not tested at suprathreshold values....

At least think about this suggestion!!

My other major concern is the rationale of exposing only one ear and then not using the other ear as an internal control for histology and physiology? I just don't understand.

Minor points

Was the fact that noise exposure was done under Ketamine-anesthesia considered? (Pilati/Hamann 2012) showed that neuronal activity in the DCN was altered after noise exposure and that this change was mediated by modulation of Kv3 channels. One way to modulate these channels is via NO-NMDA dependent mechanisms. Anesthetizing animals with an NMDA antagonist may prevent such modulation. Do you have any experience in your lab or from other labs to test if the outcome of the exposure would be different? Please discuss.

I think high threshold ANFs are known to express calbindin or calretinin?? You probably know - can you please put that information in you introduction. This might help in the future to track their targets.

Line 161: Please define BF as opposed to CF to avoid confusion.

Line 168: You state the time point of the final ABR - is that also the day for the for the Neuronexus recording e.g. neural recordings - final ABR - cochlear collection? Please clarify.

Figure 1B: please state to what ABR wave 1 was normalized to. Since you exposed only the left ear - did you also measure the ABR in response to the right ear? Is wave 1 of the right ear what you normalized to? It would be very nice to show in the paper that there are no (?) differences to wave 1 when the right ear is stimulated.

Figure 1C,D: I could not find any details to the histological results. Please add rationale for the cochlear staining you used, how many HC were analyzed in how many animals. Was a within animal comparison made in addition to the sham animals?

Line 249/250: Again - why was no within animal comparison made. Or else, if you do not plan on that, why only expose one ear? Please explain rationale.

Figure 2: For a more complete picture, please provide a typical waveform for each of the 3 different cell types. Same applies later on to the two types of small cells.

Line 264: Please state what you mean by RF stimuli. Are these tone-level combinations anywhere within the receptive field?

Figure 3: The 60dB background noise seem to generate a background firing rate around 50Hz. This is probably in the range of spontaneous activity (if the animals would not be under ketamine anesthesia - would that mean that in awake animals the tone in noise thresholds are always elevated? Again - recording in the right CN would shed light...; please add the data or at least discuss.) This may also be a difference between the small cells and the other two types as they receive additional inputs from high spont fibers.

Figure 3B-D: The chosen figure design is not at all intuitive and is lacks helpful description... no axis labels on the inset and no mention about meaning of that yellow triangle. Please improve!

Line 269 onward: I cannot find any actual numbers for the thresholds of ABRs, single units in control and sham and also in control and sham plus noise. When you state that SCs from noise exposed animals had significantly lower TIN threshold shifts compared to sham animals - is that because the thresholds may be different in the NE animals and then not shift even higher? Could you please provide the numbers for mean threshold, maximum firing rates, spontaneous rates for the different cell types in the text, so that the reader gets the full picture of the results? JP will ask for a data table anyway - so you may as well get the numbers ready.

Figure 4: That is a nice analysis!

Line 316: "Synaptopathy induced by noise exposure was not entirely consistent across animals" one more reason to provide more detail to the histological analysis (see my comment above).

Figure 6: Please also indicate in A that this data is from a small cell.

Figure 6B-D: Shouldn't the y-axis have a unit? If it is the mean reduction in firing rates - Hz??

Figure 7A: Small cells mainly receive inputs from high-threshold / low-spontaneous fibers. That seem to be reflected in the majority of the RLFs. However, there are quite a few RLFs with lower thresholds and an earlier rise to maximum firing rate. Are these part of one of the two shown clusters? How do you define SCs? By high threshold/low spont?

Figure 7B: Please fix the legend box, it is not completely readable as it is.

Figure 7C: Are these grand average PSTHs over all the SC cells in the respective clusters? If so, the SC2 PSTH looks very strange. It almost seems like two populations based on first spike latencies with one group starting the PSTH around 15ms and the other even before 5ms... this is just eyeballing from the figure, but I suggest you really need to look into that. Did you use a ramp for your tone bursts (which you should)? If so how long? Please add those details to the methods.

Line 408: "Initial attempts to titrate our sound exposure level used a lower exposure intensity of 99 dB SPL that resulted in a synapse loss that recovered between 2- and 4-weeks post-exposure, alongside a full recovery of ABR wave 1 amplitudes to baseline levels (data not shown)." THIS would be most interesting to show!! Why have you decided not to show this? It would strengthen your paradigm and also underline the importance of parameter space for future studies. Think about including this in the revised manuscript.

Discussion: When you compare your work with the other studies on synaptopathy and ABRs - please also report whether or not the studies used anesthesia during sound exposure and if so then which. There are accumulating reports that this plays an important role in the outcome of the sound exposure.

Line 435: With SCs receiving exclusive high threshold/low spont input - could it be that they are targeted especially as result of a local stress response like a noise trauma? SCs show a strong expression of CRHR2, a receptor for stress peptides that are suggested to form a local auditory stress axis (Basappa 2012, Pagella 2021). Your present data that sound induced synaptopathy targets exclusively SCs does add a major new piece to this puzzle.

END OF COMMENTS

Confidential Review **25-Jan-2023**

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We look forward to receiving your revised submission.

If you have any queries, please reply to this email and we will be pleased to advise.

Yours sincerely,

Richard Carson
Senior Editor
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REQUIRED ITEMS

-Include a Key Points list in the article itself, before the Abstract.

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-Exact p values must be stated. Authors must not use 'greater than' or 'less than'. Exact p values must be stated to three significant figures even when 'no statistical significance' is claimed.

-Statistics Summary Document completed appropriately upon revision

-Please include an Abstract Figure file, as well as the figure legend text within the main article file. The Abstract Figure is a piece of artwork designed to give readers an immediate understanding of the research and should summarise the main conclusions. If possible, the image should be easily 'readable' from left to right or top to bottom. It should show the physiological relevance of the manuscript so readers can assess the importance and content of its findings. Abstract Figures should not merely recapitulate other figures in the manuscript. Please try to keep the diagram as simple as possible and without superfluous information that may distract from the main conclusion(s). Abstract Figures must be provided by authors no later than the revised manuscript stage and should be uploaded as a separate file during online submission labelled as File Type 'Abstract Figure'. Please ensure that you include the figure legend in the main article file. All Abstract Figures should be created using BioRender. Authors should use The Journal's premium BioRender account to export high-resolution images. Details on how to use and access the premium account are included as part of this email.

EDITOR COMMENTS

Reviewing Editor:

Thank you for submitting your manuscript entitled " Cochlear synaptopathy impairs suprathreshold tone-in-noise coding in the cochlear nucleus" to the Journal of Physiology.

Your manuscript has been seen by two reviewers who both find your work highly interesting, but also raise some important points that need to be addressed. We would like to consider your response to these concerns in the form of a revised manuscript before we make a final decision on publication.

We therefore invite you to revise and resubmit your manuscript, taking into account all the points raised. Please highlight all changes in the manuscript text file and provide a response to the reviewers'comments. As alerted by the reviewers, the MS requires a revised discussion and improved readability of the figures (please, also note a typo in the Fig. 1D: MyoVIIa).

Senior Editor:

Please ensure that the basis upon which error bars have been calculated is indicated in all relevant figure legends. It should be noted that the statistical policy of the Journal requires that standard deviations, rather than standard errors, be represented.
All error bars are SD, and this information has now been added to each figure legend.

REFEREE COMMENTS

Referee #1:

This is an interesting and timely manuscript detailing the response properties of neurons in the cochlear nucleus, the obligatory feedforward pathway in the by sending auditory system following exposure to noise designed to elicit subthreshold changes in hearing function sometimes referred to as hidden hearing loss. The manuscript makes a critical link between auditory nerve recordings and more central levels of the nervous system recently reported for neurons in the midbrain of animals exposed to subthreshold damaging noise. Three specific publications are highly relevant to the current manuscript and should be cited, not just generally, but discussed with specific reference to the main findings of the current manuscript not only because they are highly relevant, complementary, and supportive, but also because the current hypothesis addresses, and possibly answers, outstanding questions raised by those reports. These questions are highly relevant to the mechanisms underlying listening problems in hidden hearing loss/following synaptopathy, and the current manuscript addresses some of these directly. These studies are:-

Hesse LL, Bakay W, Ong HC, Anderson L, Ashmore J, McAlpine D, Linden J, Schaette R. Non-Monotonic Relation between Noise Exposure Severity and Neuronal Hyperactivity in the Auditory Midbrain. Front Neurol. 2016 Aug 25;7:133. doi: 10.3389/fneur.2016.00133. PMID: 27625631; PMCID: PMC5004570.

Monaghan JJM, Garcia-Lazaro JA, McAlpine D, Schaette R. Hidden Hearing Loss Impacts the Neural Representation of Speech in Background Noise. Curr Biol. 2020 Dec 7;30(23):4710-4721.e4. doi: 10.1016/j.cub.2020.09.046. Epub 2020 Oct 8. PMID: 33035490; PMCID: PMC7728162.

Bakay WMH, Anderson LA, Garcia-Lazaro JA, McAlpine D, Schaette R. Hidden hearing loss selectively impairs neural adaptation to loud sound environments. Nat Commun. 2018 Oct 16;9(1):4298. doi: 10.1038/s41467-018-06777-y. PMID: 30327471; PMCID: PMC6191434.

importantly these studies demonstrate including using speech in noise and more complex distributions of sounds, that suprathreshold neural encoding is impaired in hidden hearing loss in a way that is not obvious and straightforward from the relatively simple stimulus paradigms that are often employed in single-neuron physiology. They therefore support the current manuscripts findings and the current manuscript provides an important link between the relatively simple and in some cases nonspecific physiological recordings made in animals exposed to sub threshold levels of damaging noise and the less standard assessment paradigms employed by several recent studies such as Monaghan et al and Bakay et al.

I have no contention with the data presented or how they were captured and the noise exposure and general methodology for quantifying synaptopathy and neural responses in sham and exposed animals rigorous and well justified. However, I believe the manuscript does itself a disservice by not placing these important findings in the context of several, although still limited, number of studies that have explored directly the impact of synaptopathy/hidden hearing loss on neural responses in the central nervous system.

The key section in the results of this current manuscript is entitled Cochlear nucleus TIN thresholds do not increase after synaptopathy. The current data demonstrates some level of hyper-excitability in neurons of the cochlear nucleus, that extends to thresholds in animals

subject to prior exposure to loud sounds designed to elicit hidden hearing loss. the fact that threshold shifts but right intensity functions in background noise are smaller, at least at some intensities of noise and some neuron types, in exposed compared to non-exposed animals is consistent with the findings of all of these studies in the midbrain nucleus of the inferior colliculus. It suggests that hidden hearing loss manifests as hyper excitability. Importantly as in the study of bakay et al, and Monaghan et al, the effect of prior over-exposure on thresholds is intensity dependent, being greater at lower versus higher levels of contemporary background noise. This should be stated and discussed because it suggests that the site of action of elevated sensitivity or excitability is either within the cochlear nucleus or if arises from feedback from higher brain centres manifests within the cochlear nucleus. Indeed, given that thresholds are better/lower for the hidden hearing loss group and that this concords with previous findings in the midbrain this section might actually entitled cochlear nucleus TIN thresholds reduced after synaptopathy. By the way the aforementioned studies demonstrate these particulars not with the same exact stimulus parameters but definitely in the same general framework of elevated or hyper excitability. The fact that the greatest difference occured at BS above the noise exposure spectrum is also consistent with the findings of Monaghan and also accords with the well-established half octave shift in cochlear damage by noise. Again as suggested by Monaghan et al, synaptopathy to follow the general rules of noise damage in permanent hearing loss with respect to where basilar membrane excursion, rather than velocity (near CF), is maximum. whilst likely not accounting for all of the midbrain effects, and bearing in mind the difference in the stimulus paradigms, this concordance in terms of not only not elevated thresholds but improved, lower thresholds in hidden hearing loss animals is an important finding.

Hyperexcitability in quiet threshold

While we do see some increased spontaneous rates in quiet at the level of the cochlear nucleus in bushy cells and stellate cells in animals with synaptopathy, we see much greater increases in spontaneous rates in quiet in the dorsal CN (DCN) (eg, Wu et al 2018). Since the DCN and stellate cells are the major inputs to the IC, they would be expected to influence spontaneous rates in quiet in the IC. In the current study mean rate-level functions are not altered (fig 2) and single-unit thresholds are largely not changed (only increased in Ch Fig S1, and this does not correlate with synaptopathy Fig 6). However, the IC would be influenced only by stellate cells and fusiform cells as small cells and bushy cells do not project to the IC.

Hyperexcitability in TIN thresholds

We do see lower threshold shifts in noise in animals with synaptopathy (fig 4), but the thresholds in both background sound levels do not correlate with synaptopathy (Fig 6). Furthermore, the TIN threshold shifts do not correlate with synaptopathy (Fig 7). While the

trend for lower threshold shifts in animals with synaptopathy (fig 7) would support hyperexcitability, this appears to be due to a combination of the trend for increased thresholds and reduced TIN thresholds (Fig 6), so is not clear evidence of any hyperexcitability. However, the IC could be influenced by suprathreshold coding in the DCN, which has not yet been explored.

Another important finding in the current manuscript and this time counter 2 the aforementioned studies is the reduction in suprathreshold firing rates in hidden hearing loss animals in background noise. here compared to Monaghan et al, and Bakay, super threshold firing rates are reduced in the cochlear nucleus. Again this hints at potential sites and mechanisms for changes in neural function. If cochlear nucleus firing rates are reduced following synaptopathy, it suggests that elevated firing rates including in background noise in the midbrain arise from local changes in neural gain i.e. local increases in neural gain in the inferior colliculus. Again, this is an important finding of the current manuscript, but also demonstrates the need to compare the current data and discuss the current findings, with those of previous studies exploring neural responses in the auditory midbrain and hidden hearing loss. I find some of the discussion around the potential changes in suprathreshold firing rates slightly obscure. The sheer multitude of feedforward and feedback circuits in the lower brainstem may reduce maintain or increase buying rates depending on the level of damage to the auditory nerve fibres in hidden hearing loss, animal specific differences, or other factors that relate to the type of stimulus under investigation. these issues should be alluded to in the discussion particularly from lines 425 to 433.

In suprathreshold TIN data we see reduced spike rates in increasing background sound, evidence of a lack of hyper-excitability, we agree that in combination with the Monaghan study this implies that mechanisms producing increased activity within the IC occur upstream form the ventral cochlear nucleus, either in the IC or in other centers that project to the IC, including the dorsal cochlear nucleus. This has been added to the discussion.

A strength of the current study, less amenable to recordings made in the midbrain, is the ability to distinguish between different cell types and their responses to noise exposure. Interesting Lee these subtle differences lie in a small cell cap type-cells, putatively playing some role either in speech encoding (contentious) or in modulating neural gain. Some discussion on this topic would be appropriate, though only in the sense of acknowledging the remaining work to be undertaken in exploring importance of the different cell types in encoding suprathreshold acoustic information.

Referee #2:

Hockley and co-authors set out to test the hypothesis that noise trauma-induced cochlear synaptopathy could impair coding of suprathreshold tones to a greater degree because synaptopathic noise exposure affects primarily auditory nerve fibers with high-thresholds and low spontaneous rates. In humans, such synaptopathy is often described as hidden hearing loss because following a noise insult, synapses contacting the inner hair cells in the cochlea die, but auditory thresholds as usually measured in an audiogram remain unchanged. Nevertheless, humans with hidden hearing loss suffer from auditory processing deficits such as tone-in-noise or speech-in-noise discrimination as they grow older. Different animal models have been used to explore the neural basis of this phenomenon, but these came to different if not opposing results; either showing increased thresholds or no change in thresholds in behavioral tone in noise tests. Therefore the manuscript presented here is timely and important as it sheds light on those previous discrepancies.

In this study, the authors performed unilateral noise exposure to anesthetized guinea pigs. The initial temporal threshold shift following the noise exposure was measured by ABR recordings. After 4 weeks, the animals underwent neural recordings in the cochlear nucleus, another round of ABR recordings and then histological analysis of the synapse loss in the cochlea.

The main finding of the manuscript is that tone in noise thresholds of single cochlear nucleus neurons are not increased by synaptopathy, siding with previous studies that show no impairment of tone in noise coding in animals with synaptopathy. However, the present manuscript also shows that single cochlear nucleus neurons in animals with synaptopathy rather show that suprathreshold tone in noise thresholds are impaired. As opposed to behavioural testing the authors could take advantage of dissecting the targets of different auditory nerve fibers and show that it is the small cells of the DCN that are most effected by synaptopathy.

Major points

The data seem convincing but their presentation is not to the usual high standard of the Shore lab. The manuscript needs a major make over. There is hardly any description in the text or figure legends of what you did and why and what the figures show. There are no

number, no n-numbers, no standard deviations etc. Someone who does not already know what you are doing will have no chance in understanding the important message that is hidden in this manuscript. Especially when addressing the readers of the Journal of Physiology you should keep in mind that only a part of them are neuroscientists and only a minority know about the auditory system.

Along the same lines - the figures need work. They should visualize your findings and help the reader to better understand the data described in the text - so far neither is possible. Remember that some reader will only flick through the figures and if they are not comprehensible, your paper may not get read at all. I have outlined a few suggestions below.

Thank you for the feedback on data presentation and more detailed points below. We have updated the figures and manuscript, by adding in more description of comparisons and statistics, as discussed further for each point below.

To me the manuscript seems backwards in order. Why don't you think about re-structuring and starting with your strength?

1. Noise exposure causes synapse loss (fig.1) especially in the low SR/high threshold ANFs.

2. Small cells in the DCN are the only cells that receive exclusive input from low SR/high threshold ANFs target - therefore these should be studied!!

3. In the past, vast recordings of small cells were not possible.

4. Due to technical advancement you now recorded hundreds of small cells.

5. Show the two groups (but think about what I say below about the PSTHs) and their deficit in suprathreshold TIN.

6. Then you can show the other chopper and PL cells to explain why behavioral result could go either way when not tested at suprathreshold values....

At least think about this suggestion!!
Thanks for this suggestion, the paper has now been re-ordered to lead with suprathreshold data and then follow with the threshold changes. One figure has also been separated to two parts to increase clarity.

My other major concern is the rationale of exposing only one ear and then not using the other ear as an internal control for histology and physiology? I just don't understand.
There are contralateral effects of noise exposure, such as efferent upregulation in the cochlea, and VGLUT1 & VGLUT2 expression changes in the CN (Heeringa et al 2018). These changes mean that changes the contralateral cochlear nucleus would also be affected by a unilateral exposure, thus not serving as a normal control.

Minor points

Was the fact that noise exposure was done under Ketamine-anesthesia considered? (Pilati/Hamann 2012) showed that neuronal activity in the DCN was altered after noise exposure and that this change was mediated by modulation of Kv3 channels. One way to modulate these channels is via NO-NMDA dependent mechanisms. Anesthetizing animals with an NMDA antagonist may prevent such modulation. Do you have any experience in your lab or from other labs to test if the outcome of the exposure would be different? Please discuss.
We are not recording from neurons of the DCN, which are more affected by anaesthesia than other areas of the cochlear nucleus (Evans & Nelson 1973). While we do not have direct data to compare noise exposure under different anaesthesia or awake, the effects within the VCN and SCC are likely to be minimal.

I think high threshold ANFs are known to express calbindin or calretinin?? You probably know - can you please put that information in you introduction. This might help in the future to track their targets.
Added at line 80

Line 161: Please define BF as opposed to CF to avoid confusion.
BF changed to CF throughout.

Line 168: You state the time point of the final ABR - is that also the day for the for the Neuronexus recording e.g. neural recordings - final ABR - cochlear collection? Please clarify.
Clarified at line 147

Figure 1B: please state to what ABR wave 1 was normalized to. Since you exposed only the left ear - did you also measure the ABR in response to the right ear? Is wave 1 of the right ear what you normalized to? It would be very nice to show in the paper that there are no (?) differences to wave 1 when the right ear is stimulated.

ABR P1 amplitudes were normalized to the 12 kHz frequency, the highest averaged amplitude at baseline, therefore, the averaged ABR P1 amplitude at 12kHz was considered 100%. We did not use the right ear of the exposed animals as controls, instead we decided to test the sham (unexposed) animals. In both groups the internal control is the baseline.
We also analysed the ABR P1 amplitude shifts where values were normalized to their respective baseline (zero) for each frequency, which produced the same final physiological results.

Figure 1C,D: I could not find any details to the histological results. Please add rationale for the cochlear staining you used, how many HC were analyzed in how many animals. Was a within animal comparison made in addition to the sham animals?
The description in Method (Lines 210-215) explains the staining process, the antibodies used, how images were taken and quantified, also how many HCs per image were counted. We counted Ctbp2 (ribbon synapses marker, red) and GluR2 (post synaptic marker, green) puncta in 3 adjacent images per tested frequency, with 8-10 IHCs (MyoVIIa, blue) in each one. Sham ears n=8; exposed ears n=10. Further detail has been added to the legend of Fig 1. No comparison within animal were made due to contralateral effect discussed above.

Line 249/250: Again - why was no within animal comparison made. Or else, if you do not plan on that, why only expose one ear? Please explain rationale.
Rationale explained above

Figure 2: For a more complete picture, please provide a typical waveform for each of the 3 different cell types. Same applies later on to the two types of small cells.
Unlike *in vitro* experiments, spike waveforms from *in vivo* experiments are not useful for defining any characteristics of the cells, due to different waveforms depending on the spatial location of the electrode site relative to the cell body. This is especially true when using multi-channel probes, as used here, therefore, we do not see it relevant to include these data on a figure from extracellular recordings. Spike waveforms when using high-impedance tungsten microelectrodes to record extracellular activity are greater and slightly more useful but still not to the same level as *in vitro* spike waveforms.

Line 264: Please state what you mean by RF stimuli. Are these tone-level combinations anywhere within the receptive field?
RF stimuli were defined at line 176, this has now been clarified in the text at line 300.

Figure 3: The 60dB background noise seem to generate a background firing rate around 50Hz. This is probably in the range of spontaneous activity (if the animals would not be under ketamine anesthesia - would that mean that in awake animals the tone in noise thresholds are always elevated? Again - recording in the right CN would shed light...; please add the data or at least discuss.) This may also be a difference between the small cells and

the other two types as they receive additional inputs from high spont fibers.
1) There are limited data on spontaneous rates in the unanesthetised cochlear nucleus, and papers that do exist show spont rates slightly only higher than during the Ket/Xyl anesthesia used here, generally with spont rates of 10-20Hz (Rhode & Kettner 1987, Evans & Nelson 1973, May & Sachs 1992).

2) Bilateral changes in the cochlea and cochlear nucleus occur following noise exposure. Cochlear efferent changes are discussed above. In addition, contralateral VGLUT1 & VGLUT2 expression is altered (Heeringa et al 2018), reflecting altered inputs and activity and renders the contralateral cochlear nucleus not useful as a control. Therefore, in this study we focused on using a sham-exposed control group.

Figure 3B-D: The chosen figure design is not at all intuitive and is lacks helpful description... no axis labels on the inset and no mention about meaning of that yellow triangle. Please improve!
Axis of the inset is identical to that of the main figure. This should be clearer on the new version.

Line 269 onward: I cannot find any actual numbers for the thresholds of ABRs, single units in control and sham and also in control and sham plus noise.
When you state that SCs from noise exposed animals had significantly lower TIN threshold shifts compared to sham animals - is that because the thresholds may be different in the NE animals and then not shift even higher? Could you please provide the numbers for mean threshold, maximum firing rates, spontaneous rates for the different cell types in the text, so that the reader gets the full picture of the results? JP will ask for a data table anyway - so you may as well get the numbers ready.
Single unit thresholds of SC and PLs are not altered by synaptopathy, but Chs show a significant increase in threshold. This information has been added at line 267. Therefore, the TIN threshold shifts appear to be due to changes ot the noise condition as opposed to the no background sound condition. Mean thresholds and SFRs have been added to the text at line at line 267. Statistics of mean ABR and ABR P1 have been added ot the text at lines 237 & 243.
Maximum firing rates are not used or discussed in this paper so we do not see their inclusion to be necessary.

Figure 4: That is a nice analysis!
Thanks! ☺

Line 316: "Synaptopathy induced by noise exposure was not entirely consistent across animals" one more reason to provide more detail to the histological analysis (see my comment above).
More detail added, as replied to above

Figure 6: Please also indicate in A that this data is from a small cell.
Added

Figure 6B-D: Shouldn't the y-axis have a unit? If it is the mean reduction in firing rates - Hz??
Yes, Hz unit added, thanks!

Figure 7A: Small cells mainly receive inputs from high-threshold / low-spontaneous fibers. That seem to be reflected in the majority of the RLFs. However, there are quite a few RLFs with lower thresholds and an earlier rise to maximum firing rate. Are these part of one of the two shown clusters? How do you define SCs? By high threshold/low spont?
Units were typed by their peristimulus time histograms to tone and BBN, RFs and RLFs. With further typing using a machine learning model described previously (Hockley et al., 2022). This resulted in the 5 categories of units, but not one single measure of high threshold/low spont being used to determine cell type.

Figure 7B: Please fix the legend box, it is not completely readable as it is.
Fixed

Figure 7C: Are these grand average PSTHs over all the SC cells in the respective clusters? If so, the SC2 PSTH looks very strange. It almost seems like two populations based on first spike latencies with one group starting the PSTH around 15ms and the other even before 5ms... this is just eyeballing from the figure, but I suggest you really need to look into that. Did you use a ramp for your tone bursts (which you should)? If so how long? Please add those details to the methods.
Cosine ramp of 5 ms, added to text at line 177.
The double-peak seen in the mean PSTH is the result of the unusual shape of some small cell PSTHs. It is not a result of two different populations, but seen in single-unit PSTHs, such as the example in fig 2. Similar unusual PSTH shapes have previously been reported in small cells by Ghoshal & Kim 1997.

Line 408: "Initial attempts to titrate our sound exposure level used a lower exposure intensity of 99 dB SPL that resulted in a synapse loss that recovered between 2- and 4-

weeks post-exposure, alongside a full recovery of ABR wave 1 amplitudes to baseline levels (data not shown)." THIS would be most interesting to show!! Why have you decided not to show this? It would strengthen your paradigm and also underline the importance of parameter space for future studies. Think about including this in the revised manuscript.
We have chosen to omit this data due to the low number of animals used in our preliminary titration experiments using different noise exposure levels. It is also outside the scope of this manuscript, and synapse recovery in the guinea pig has been shown previously by multiple groups.

Discussion: When you compare your work with the other studies on synaptopathy and ABRs - please also report whether or not the studies used anesthesia during sound exposure and if so then which. There are accumulating reports that this plays an important role in the outcome of the sound exposure.
Discussion added at line 427

Line 435: With SCs receiving exclusive high threshold/low spont input - could it be that they are targeted especially as result of a local stress response like a noise trauma? SCs show a strong expression of CRHR2, a receptor for stress peptides that are suggested to form a local auditory stress axis (Basappa 2012, Pagella 2021). Your present data that sound induced synaptopathy targets exclusively SCs does add a major new piece to this puzzle.
Discussion of this potential mechanism has been added at line 457.

Dear Professor Shore,

Re: JP-RP-2023-284452R1 "Cochlear synaptopathy impairs suprathreshold tone-in-noise coding in the cochlear nucleus" by Adam Hockley, Luis R Cassinotti, Michael M Selesko, Gabriel Corfas, and Susan Shore

Thank you for submitting your revised Research Article to The Journal of Physiology. It has been assessed by the original Reviewing Editor and Referees and has been well received. Some final revisions have been requested.

Please advise your co-authors of this decision as soon as possible.

The referee reports are copied at the end of this email.

Please address all the points raised and incorporate all requested revisions or explain in your Response to Referees why a change has not been made. We hope you will find the comments helpful and that you will be able to return your revised manuscript within 4 weeks. If you require longer than this, please contact journal staff: jp@physoc.org.

Your revised manuscript should be submitted online using the link in your Author Tasks: Link Not Available. This link is accessible via your account as Corresponding Author; it is not available to your co-authors. If this presents a problem, please contact journal staff (jp@physoc.org). Image files from the previous version are retained on the system. Please ensure you replace or remove any files that are being revised.

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REVISION CHECKLIST:

Check that your Methods section conforms to journal policy: https://jp.msubmit.net/cgi-bin/main.plex?form_type=display_requirements#methods.

Check that data presented conforms to the statistics policy: https://jp.msubmit.net/cgi-bin/main.plex?form_type=display_requirements#statistics.

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Please upload two versions of your manuscript text: one with all relevant changes highlighted and one clean version with no changes tracked. The manuscript file should include all tables and figure legends, but each figure/graph should be uploaded as separate, high-resolution files.

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We look forward to receiving your revised submission.

If you have any queries, please reply to this email and we will be pleased to advise.

Yours sincerely,

Richard Carson
Senior Editor
The Journal of Physiology

REQUIRED ITEMS FOR REVISION

-You must start the Methods section with a paragraph headed Ethical Approval. A detailed explanation of journal policy and regulations on animal experimentation is given in Principles and standards for reporting animal experiments in The Journal of Physiology and Experimental Physiology by David Grundy J Physiol, 593: 2547-2549. doi:10.1113/JP270818.). A checklist outlining these requirements and detailing the information that must be provided in the paper can be found at: https://physoc.onlinelibrary.wiley.com/hub/animal-experiments. Authors should confirm in their Methods section that their experiments were carried out according to the guidelines laid down by their institution's animal welfare committee, and conform to the principles and regulations as described in the Editorial by Grundy (2015). The Methods section must contain details of the anaesthetic regime: anaesthetic used, dose and route of administration and method of killing the experimental animals.

-Papers must comply with the Statistics Policy https://jp.msubmit.net/cgi-bin/main.plex?form_type=display_requirements#statistics

In summary:

-If n {less than or equal to} 30, all data points must be plotted in the figure in a way that reveals their range and distribution. A bar graph with data points overlaid, a box and whisker plot or a violin plot (preferably with data points included) are acceptable formats.

-If n > 30, then the entire raw dataset must be made available either as supporting information, or hosted on a not-for-profit repository e.g. FigShare, with access details provided in the manuscript.

-'n' clearly defined (e.g. x cells from y slices in z animals) in the Methods. Authors should be mindful of pseudoreplication.

-All relevant 'n' values must be clearly stated in the main text, figures and tables, and the Statistical Summary Document (required upon revision)

-The most appropriate summary statistic (e.g. mean or median and standard deviation) must be used. Standard Error of the Mean (SEM) alone is not permitted.

-Exact p values must be stated. Authors must not use 'greater than' or 'less than'. Exact p values must be stated to three significant figures even when 'no statistical significance' is claimed.

-Statistics Summary Document completed appropriately upon revision

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EDITOR COMMENTS

Reviewing Editor:

Thank you for the revised version of the MS " Cochlear synaptopathy impairs suprathreshold tone-in-noise coding in the cochlear nucleus" and the replies to the reviewers.

Both reviewers were very pleased with the revised version of the MS. There are however still a few minor points that should be addressed: Please, take into consideration the additional, new comments by the first reviewer. Furthermore, figure 8 (previously Fig. 7) does not seem to have been uploaded during the revision process. Please upload the updated figure in accordance with the previous request of the reviewer 2 (t.i. with fixed figure legend in the panel B). Finally, I assume the x-axes in the Fig. 4 should also state CF rather than BF(?). Please, correct as appropriate.

Please upload a new complete version of the MS including all figures as well as the responses to the new comments by the reviewer 1.

REFEREE COMMENTS

Referee #1:

I am largely happy with this revision (and also appreciate the restructuring as per other reviewer, which makes for a very nice narrative). A few minor comments:

In the reply to my comments; "However, the IC would be influenced only by stellate cells and fusiform cells as small cells and bushy cells do not project to the IC."

I question the validity of this statement. Ultimately cell types that indirectly project to the IC (bushy cells via brainstem nuclei) potentially impact the IC; there is no requirement that any influence of synaptopathy on IC neurons via CN neurons be a direct one. Further, small cells do project to the thalamus, bypassing IC directly, but potentially altering neural sensitivity at a system level, and potentially via efferent influences.

Lines 287-290

I do agree with the general sense of changes in the IC, or DCN pathways, perhaps being the source of elevated gain, activity in the system, but urge some caution regarding definitive statements and comparisons. These data suggest that suprathreshold tone-in-noise responses were unaffected by the addition of noise in PL and Chopper neurons, but those of small cells were affected. First, I posit the explanation that the noise level used here was not sufficient to demonstrate this change. Bakay et al (2018) demonstrated that threshold changes (lower, or better, thresholds) in IC neurons were evident only at higher levels of background noise (using an adaptive paradigm) than 40 and 60 dB. This would argue for the effect being driven by some change to LS/HT fibres (though other explanations, including gain changes are possible). Are 40 and 60 dB sufficient here to make the case? This explanation also makes sense from the likely relative proportion of LS/HT fibres projecting to the three cell types, with small cells receiving the highest proportion of LS/HT fibres. Of course, the major difference may be methodological, since Bakay et al used an ongoing stimulus paradigm and measured adaptive thresholds.

Referee #2:

I thank the authors for their thorough revision. All my initial questions were answered. It is surely an interesting piece of work that will further our understanding of the role of small cells in adaptations to noise exposure and hidden hearing loss.

END OF COMMENTS

1st Confidential Review **13-Apr-2023**

Referee #1:

I am largely happy with this revision (and also appreciate the restructuring as per other reviewer, which makes for a very nice narrative). A few minor comments:

In the reply to my comments; "However, the IC would be influenced only by stellate cells and fusiform cells as small cells and bushy cells do not project to the IC."

I question the validity of this statement. Ultimately cell types that indirectly project to the IC (bushy cells via brainstem nuclei) potentially impact the IC; there is no requirement that any influence of synaptopathy on IC neurons via CN neurons be a direct one. Further, small cells do project to the thalamus, bypassing IC directly, but potentially altering neural sensitivity at a system level, and potentially via efferent influences.

We have specified only direct connections in this regard in the discussion.

Lines 287-290

I do agree with the general sense of changes in the IC, or DCN pathways, perhaps being the source of elevated gain, activity in the system, but urge some caution regarding definitive statements and comparisons. These data suggest that suprathreshold tone-in-noise responses were unaffected by the addition of noise in PL and Chopper neurons, but those of small cells were affected. First, I posit the explanation that the noise level used here was not sufficient to demonstrate this change. Bakay et al (2018) demonstrated that threshold changes (lower, or better, thresholds) in IC neurons were evident only at higher levels of background noise (using an adaptive paradigm) than 40 and 60 dB. This would argue for the effect being driven by some change to LS/HT fibres (though other explanations, including gain changes are possible). Are 40 and 60 dB sufficient here to make the case? This explanation also makes sense from the likely relative proportion of LS/HT fibres projecting to the three cell types, with small cells receiving the highest proportion of LS/HT fibres. Of course, the major difference may be methodological, since Bakay et al used an ongoing stimulus paradigm and measured adaptive thresholds.

We have added a sentence saying that the noise levels might not have been sufficient to mimic the human results but leave the rest the same.

Referee #2:

I thank the authors for their thorough revision. All my initial questions were answered. It is surely an interesting piece of work that will further our understanding of the role of small cells in adaptations to noise exposure and hidden hearing loss.

Dear Dr Shore,

Re: JP-RP-2023-284452R2 "Cochlear synaptopathy impairs suprathreshold tone-in-noise coding in the cochlear nucleus" by Adam Hockley, Luis R Cassinotti, Michael M Selesko, Gabriel Corfas, and Susan Shore

We are pleased to tell you that your paper has been accepted for publication in The Journal of Physiology.

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Yours sincerely,

Richard Carson
Senior Editor
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EDITOR COMMENTS

Reviewing Editor:

It is my great pleasure to inform you that your manuscript entitled "Cochlear synaptopathy impairs suprathreshold tone-in-noise coding in the cochlear nucleus" has been accepted for publication in the J Physiol. Your MS will now be sent to the Production Editors and should soon be ready for proofing.

We look forward to your future submission to the J Physiol.
