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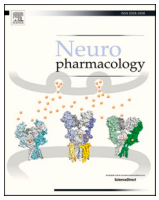

Repetitive stress decreases norepinephrine's dynamic range in the auditory cortex

Ekaterina Kaganovski [a,b], Jennifer Resnik [a,b,*]

[a] Department of Life Sciences, Ben-Gurion University of the Negev, Beer Sheva, 84105, Israel
[b] Zelman Center for Brain Science Research, Ben-Gurion University of the Negev, Beer Sheva, 84105, Israel

A B S T R A C T

Norepinephrine (NE) is a key neuromodulator in the brain with a wide range of functions. It regulates arousal, attention, and the brain's response to stress, enhancing alertness and prioritizing relevant stimuli. In the auditory domain, NE modulates neural processing and plasticity in the auditory cortex by adjusting excitatory-inhibitory balance, tuning curves, and signal-to-noise ratio. However, stress adds a layer of complexity to NE's cortical influence. Although acute stress can transiently boost locus coeruleus's activity and NE release, the effect of repeated stress on NE dynamics in the auditory cortex remains unclear. Using chronic two-photon imaging of the genetically encoded NE sensor GRAB_NE1m in head-fixed mice, we show that repetitive stress strongly attenuates NE responses to high-intensity sounds in the auditory cortex, with continued decline as the stressor becomes chronic. Additionally, repetitive stress disrupts normal habituation within each session: mice no longer exhibit the typical decrease in NE activation following repeated presentations of a loud stimulus. Our findings demonstrate that repetitive stress narrows the dynamic range and adaptability of the noradrenergic system in the auditory cortex, markedly reducing NE responses to intense sounds and eliminating the expected within-session habituation. By demonstrating that prolonged stress compromises NE dynamics in the auditory cortex, our results provide mechanistic insights into how repetitive stress could degrade auditory processing and potentially exacerbate hypervigilance or anxiety-like states.

1. Introduction

Norepinephrine (NE) is a crucial neuromodulator that orchestrates arousal, attention, and stress responses in the brain. It boosts alertness and improves perceptual accuracy (Gelbard-Sagiv et al., 2018; Ghosh and Maunsell, 2024; McBurney-Lin et al., 2019). Its broad influence is mediated by the noradrenergic projections from the locus coeruleus, which innervate sensory cortices, including the auditory cortex (Berridge and Waterhouse, 2003; McBurney-Lin et al., 2019; Morris et al., 2020; Salgado et al., 2011b, 2012). Under normal, non-stressed conditions, NE modulates stimulus processing in the auditory cortex by decreasing spontaneous and auditory-evoked firing, narrowing receptive fields, or improving the overall signal-to-noise ratio (Devilbiss and Waterhouse, 2000; Foote et al., 1975; Gaucher and Edeline, 2015; Lee et al., 2018; Manunta and Edeline, 2004; Martins and Froemke, 2015; Salgado et al., 2011b, 2012), thereby supporting processes like selective attention, learning, and rapid stimulus discrimination.

Stress adds another layer of complexity to NE's neuromodulatory influence on cortical activity. Stress—particularly repetitive stress—can broadly activate LC and significantly alter noradrenergic function throughout the brain (Borodovitsyna et al., 2018; Pavcovich et al., 1990; Privitera et al., 2024). Previous evidence indicates that prolonged exposure to stress can lead to changes in NE levels and dynamics including in sensory regions (Abercrombie and Jacobs, 1987; Keim and Sigg, 1976; Kvetňanský et al., 2008; Pavcovich et al., 1990; Pérez-Valenzuela et al., 2016; Stone and McCarty, 1983). Because normal NE function in the auditory cortex reduces spontaneous firing and enhances sound-evoked responses (Foote et al., 1975; Gaucher and Edeline, 2015; Lee et al., 2018; Manunta and Edeline, 1997; Salgado et al., 2011b, 2012), we reasoned that if NE release were compromised by repetitive stress, spontaneous activity would rise while stimulus-driven responses would diminish. Indeed, in earlier work, we observed an increase in baseline activity and a decrease in stimulus-driven activity in the auditory cortex under repetitive stress (Bisharat et al., 2025), prompting us to hypothesize that decreased NE in the auditory cortex might underlie this enhanced baseline state. In support of this notion, others have reported lower NE per milligram of auditory cortex tissue, as measured by high-performance liquid chromatography (HPLC)-electrochemical detection following twenty-one consecutive days of restraint stress (Pérez-Valenzuela et al., 2016).

These findings raise a critical question: Does repetitive stress change NE dynamics in the auditory cortex in vivo? To investigate this, we used chronic in vivo imaging to track NE dynamics in the auditory cortex of mice subjected to daily mild stress. By monitoring baseline NE activity

* Corresponding author. Department of Life Sciences, Ben-Gurion University of the Negev, Beer Sheva, 84105, Israel.
E-mail address: resnikj@bgu.ac.il (J. Resnik).

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and stimulus-evoked NE responses over multiple days, we reveal that repetitive stress progressively narrows the dynamic range and adaptability of the noradrenergic system in the auditory cortex, resulting in persistently diminished NE activity and disrupted sensory gating.

2. Results

To test the effect of repetitive stress on NE activity in the primary auditory cortex (ACtx), we performed chronic two-photon imaging in awake, head-fixed mice (Bisharat et al., 2025; Kazanovich et al., 2024; Sapir et al., 2025). These mice expressed the genetically encoded NE sensor GRAB_NE1m (Feng et al., 2019) non-selectively in layer 2/3 of the ACtx (Fig. 1a left, N = 4 mice), enabling us to track in vivo changes in NE dynamics (Feng et al., 2019).

2.1. NE activity in the auditory cortex reflects stimulus salience and stressfulness

As an initial step, we presented noise at varying intensities to assess NE responses (i.e., changes in fluorescence corresponding to elevated levels of extracellular norepinephrine when NE binds to the sensor). Specifically, we tested whether a potentially stressful high-intensity noise (90 dB SPL) would elicit a stronger stress response and greater NE activity compared to a low-intensity noise (30 dB SPL), which is unlikely to induce a stress response. To examine the changes in NE transients, we segmented the field-of-view into anatomically identified regions-of-interest (ROIs) centered on putative cells (Glaeser-Khan et al., 2024; Kagiampaki et al., 2023; Kubitschke et al., 2022; Patriarchi et al., 2018) (Fig. 1). As expected, NE activity increased significantly in response to 90 dB SPL noise but was nearly unchanged at 30 dB SPL (Fig. 1a right and Fig. 1b left and right; paired *t*-test, $p = 2.1 \times 10^{-52}$, n: stress = 566, baseline = 427 ROIs).

Before examining the effects of repetitive stress on these NE responses, we confirmed that GRAB_NE1m specifically measured NE dynamics rather than indirect sound-evoked activity. To do so, we first imaged NE responses to a stressor from a different sensory modality—an air puff to the back of the mouse (Fig. 1c, N = 3 mice). As expected, the air puff, being a stressful stimulus, induced a robust fluorescence change, demonstrating strong NE activation in the ACtx during stress without direct auditory input (Fig. 1c). To further validate this, we injected GCaMP6s into a new group of mice to measure neuronal activity in the ACtx under the same conditions (Fig. 1d, N = 3 mice). As anticipated, air puffs elicited minimal changes in neural activity in the ACtx, supporting that NE responses detected with GRAB_NE1m were not due to indirect sensory activation. Together, these experiments confirm that the observed changes in fluorescence reflect changes in stress-induced NE activity and not auditory responses.

2.2. Repetitive stress attenuates NE responses to high-intensity sounds

Next, to investigate how repetitive stress affects NE dynamics in the ACtx, we performed two-photon imaging of NE dynamics in the ACtx under both baseline and repetitive stress conditions. During baseline, mice were imaged and presented with sound stimulus every other day for eight days (on days 1, 3, 5, and 7). For the repetitive stress condition, mice underwent daily 30-min restraint in a 50 mL tube for seven days, a protocol previously shown to induce mild repetitive stress without habituation (Bisharat et al., 2025). Imaging sessions occurred after the restraint on days 9, 11, 13, and 15 (Fig. 2a).

During both baseline and stress conditions, mice were exposed to randomly presented white noise stimuli at five intensities (30–90 dB SPL in 15-dB steps, Fig. 2b; N = 4 mice, n: stress = 566, baseline = 427 ROIs). This stimulus range allowed us to assess whether repetitive stress shifts the NE response curve, potentially reflecting changes in sensory gating.

As expected, baseline recordings showed a strong NE response to 90- and 75-dB noise, a moderate increase at 60 and 45 dB, and minimal changes at 30 dB (Fig. 2b & c, grey). During repetitive stress, NE activity in the ACtx was significantly reduced (Fig. 2c, blue, 2-way ANOVA: condition F = 302, $p = 7.9 \times 10^{-66}$; sound intensity F = 314, $p = 6.2 \times 10^{-241}$; interaction F = 110, $p = 5.3 \times 10^{-90}$ and Supp. Fig. 1). Sounds that initially evoked strong NE responses during baseline elicited much weaker responses during stress, indicating an overall attenuation of NE dynamics (Fig. 2c, post hoc: 90 dB baseline vs. stress, $p = 1.9 \times 10^{-111}$; 75 dB baseline vs. stress, $p = 3.4 \times 10^{-41}$; 60 dB baseline vs. stress, p = 0.044; 45 baseline vs. stress p = 1 and 30 baseline vs. stress dB, p = 1; all Bonferroni-corrected). This was not the case in the control group, which followed the same procedures but without experiencing daily restraint stress (Supp. Fig. 2a, N = 2 mice, n: first week = 232, second week = 265 ROIs). This group exhibited minimal change in noise-evoked NE activity when comparing the first and second week of imaging (Supp Fig. 2b-c, 2-way ANOVA: condition: F = 2.4, p = 0.12; sound intensity: F = 255, $p = 5.5 \times 10^{-176}$; interaction: F = 0.52, p = 0.7).

Despite the stress-induced reduction in NE activity, 90 dB noise continued to evoke a NE response under repetitive stress (Fig. 2c and Supp. Fig. 1b), albeit significantly weaker than at baseline (post hoc: 30 vs 90 baseline $p = 1.9 \times 10^{-200}$, 30 vs 90 stress $p = 1.5 \times 10^{-20}$; Bonferroni-corrected). This effect persisted when controlling for the FOV segmentation (Supp Fig. 3a-c, 2-way ANOVA: condition: F = 21.5, $p = 1 \times 10^{-05}$; sound intensity: F = 14, $p = 3.3 \times 10^{-09}$; interaction: F = 5.1, $p = 6.4 \times 10^{-04}$).

We further examined how NE activity differed between non-stressful and stressful sound intensities by analyzing the intensity-dependent gain—calculated as the slope of the response curve—and the change in NE response between 30- and 90-dB SPL white noise. Repetitive stress led to a significant reduction in gain (Fig. 2d, *t*-test $p = 2.7 \times 10^{-6}$), indicating that NE responses in the ACtx became less sensitive to changes in sound intensity. We also observed a marked decrease in the response difference between 30- and 90-dB SPL white noise (Fig. 2e right, *t*-test $p = 1.6 \times 10^{-37}$), accompanied by a narrower distribution (Fig. 2e left, KS-test $p = 3 \times 10^{-47}$ and Supp. Fig. 3d). Together, these results suggest that repetitive stress blunts NE responses in the ACtx, with the most pronounced effects at high sound levels.

2.3. Repetitive stress leads to an early and progressive reduction in NE activity

To examine the dynamics of NE suppression during repetitive stress, we analyzed the data on a day-by-day basis. We observed a marked reduction in NE activity as early as the first day of stress (first day of stress = day 9, Fig. 3a and -way ANOVA sound intensity-condition interaction F = 108.1 $p = 2.3 \times 10^{-88}$, day-condition interaction F = 2.9 p = 0.03). This suppression was particularly pronounced in response to a 90 dB noise, a high-intensity, stressful sound (Fig. 3b bottom, 1-way ANOVA baseline vs stress F = 25.1 $p = 9.4 \times 10^{-32}$).

We further analyzed how stress progression influenced NE dynamics by calculating the gain per ROI and imaging session. To quantify how NE responsiveness scaled with increasing stimulus intensity over repeated stress exposure, we fitted a linear function to each ROI's day-by-day NE response across noise intensities (Fig. 3c). The slope of this fit serves as a measure of how strongly NE's response scales with changes in stimulus intensity per ROI and session.

When we compared the gain between baseline and repetitive stress days, we found a significant decline in NE activity starting from our first imaging session during repetitive stress (Figs. 3d and 2-way Anova condition F = 207 $p = 9 \times 10^{-72}$, condition × day interaction F = 2.5 p = 0.04, and when controlling for the FOV segmentation - Supp. Fig. 3e). Within the stress period, days 9–15, NE activity showed a gradual decline in gain as stress progressed (1-way Anova F = 4.5 p = 0.004, and post hoc day 9 vs days 13 and 15 p = 0.006 and p = 0.02 Bonferroni corrected for multiple comparisons). These results suggest that NE activity undergoes a sharp initial reduction at the onset of repetitive stress, followed by a continued but more gradual decline as stress becomes

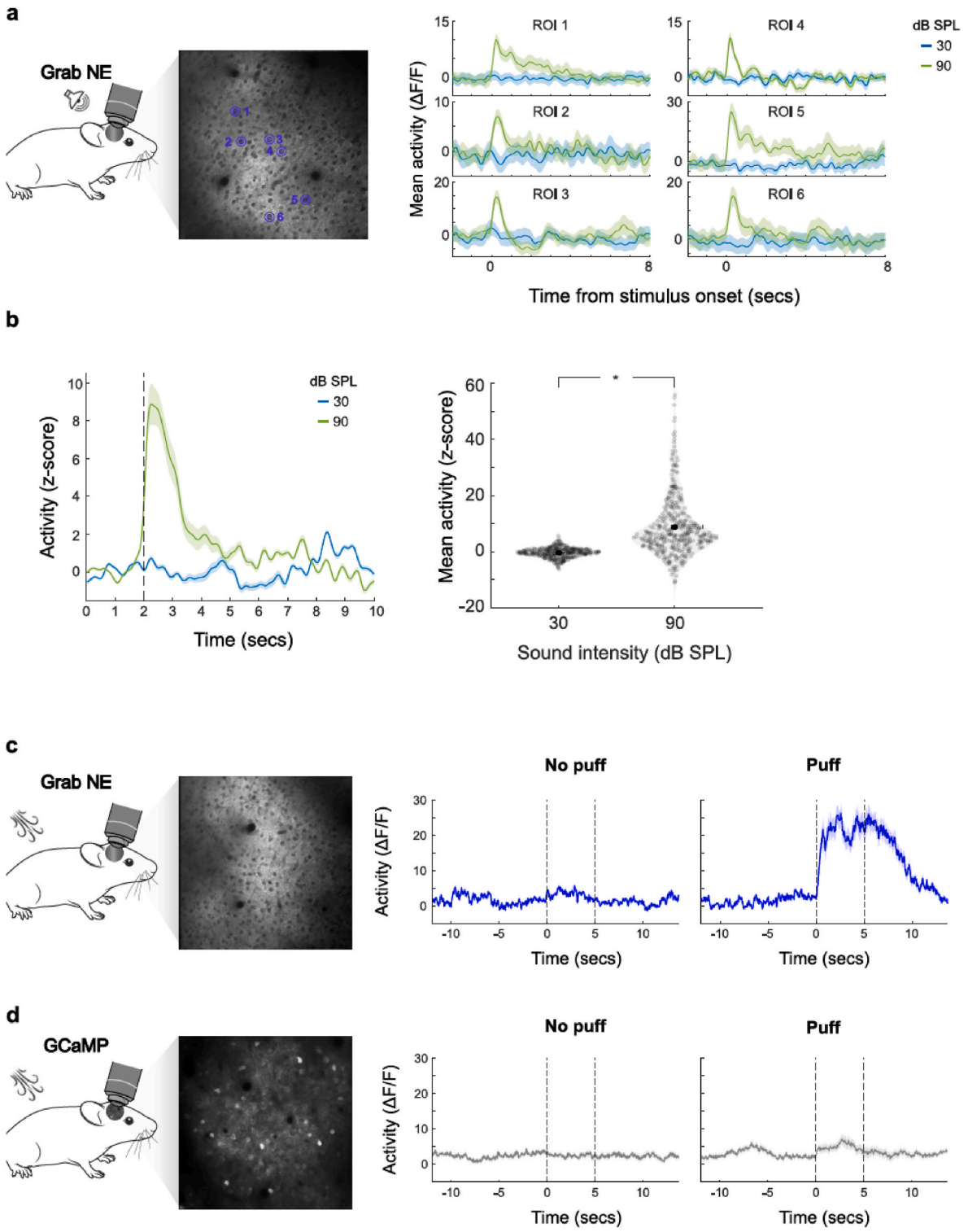

Fig. 1. NE activity in the auditory cortex reflects stimulus salience and stressfulness

(a) Left: Experimental schematics and a representative imaging plane from a GRAB_NE1m-injected mouse. Right: example of NE dynamics in response to 30 and 90 dB SPL white noise for 6 ROIs marked in blue on the left. The fluorescence signal of the GRAB_NE1m sensor reflects the local concentration of extracellular NE and its binding to the sensor.

(b) Left: Changes in normalized NE activity in response to a loud (90 dB SPL, green) vs. soft (30 dB SPL, blue) noise (N = 4 mice, n: 427 ROIs). Right: Increased NE activity in response to a 90 dB SPL noise compared to a 30 dB SPL noise (paired *t*-test, $p = 2.1 \times 10^{-52}$). Data represent mean ± SEM of NE activity per ROI.

(c) Experimental schematics and another example of an imaging plane from a GRAB_NE1m-injected mouse. Increased NE activity following an air puff to the back (N = 3 mice). Data represent mean ± SEM of NE activity per ROI.

(d) Experimental schematics and a representative imaging plane from a GCaMP6s-injected mouse. No significant change in neural activity, modeled by calcium dynamics, following an air puff to the back (N = 3 mice). Data represent mean ± SEM of GCaMP6 activity per ROI. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

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2.4. Repetitive stress reduces sensitivity to sound intensity changes and impairs adaptation to repeating high-intensity sounds

To assess the stability of the NE response over time, we quantified changes in NE activity gain, as the transformation between the mean NE activity growth measured during the first two imaging sessions (mean baseline) to the NE activity growth measured on any given day (Fig. 4a left). Under baseline conditions (and in the control group, Supp. Fig. 2d), NE activity gain remained nearly constant; however, during repetitive stress, the gain decreased well below baseline levels (Fig. 4a right, *t*-test $p = 3.2 \times 10^{-06}$). This suggests that repetitive stress markedly attenuates NE dynamics in the ACtx across days.

Thus far, our results demonstrate that repetitive stress attenuates NE activity across days. We next asked whether repetitive stress similarly affects NE responses within a single session. Specifically, we tested whether NE responses differed between the first and last presentations of a high-intensity sound, assessing potential habituation effects. Under baseline conditions, repeated exposure to a sound is expected to become less salient or stressful (Latimer et al., 2019; Plappert and Pilz, 2005; Yarden et al., 2022; Yarden and Nelken, 2017), leading to habituation

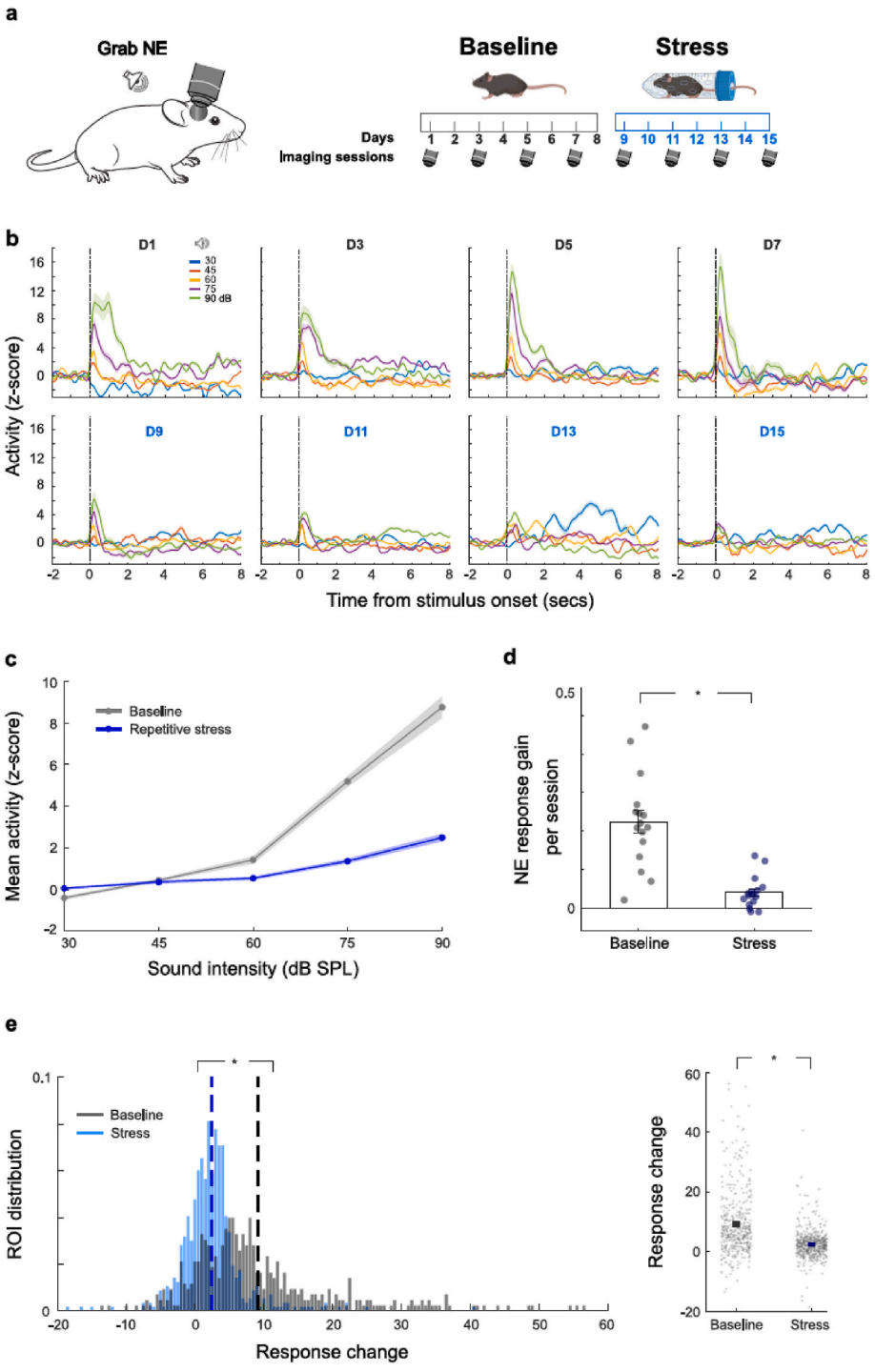

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Fig. 2. Repetitive stress attenuates NE responses to high-intensity sounds
(a) Experiment schematics. We performed two-photon imaging of NE dynamics in the ACtx under baseline and repetitive stress conditions. During baseline, mice were imaged every other day in days 1, 3, 5, 7. Under stress, mice underwent daily 30-min restraint for seven days. Imaging was performed right after restraint on days 9, 11, 13, and 15.
(b) Mean z-scored NE activity across ROIs in response to 30-, 45-, 60-, 75-, and 90-dB SPL white noise in the different imaging days (N = 4 mice, n: stress = 566, baseline = 427 ROIs). Activity was normalized (z-scored) to the 2 s preceding sound onset. Top: Under baseline conditions, NE activity showed a robust response to 90- and 75-dB SPL, a moderate increase at 60- and 45-dB SPL, and minimal activation at 30-dB SPL. Bottom: Following repetitive stress, NE responses were substantially diminished across all sound levels. Data represent mean ± SEM.
(c) Mean normalized NE activity (z-scored) across ROIs during baseline and repetitive stress recordings. NE activity in the ACtx was significantly reduced during stress (2-way ANOVA: condition: $F = 302$, $p = 7.9 \times 10^{-66}$; sound intensity: $F = 314$, $p = 6.2 \times 10^{-241}$; interaction: $F = 110$, $p = 5.3 \times 10^{-90}$). Data represent mean ± SEM.
(d) Intensity-dependent gain, quantified as the slope of the response curve per ROI. Each dot represents the mean slope per session across noise levels under baseline (grey) and repetitive stress (blue) conditions. The gain was significantly reduced during stress (unpaired *t*-test, $p = 2.7 \times 10^{-6}$). Data are presented as mean ± SEM.
(e) Right: response change, defined as the difference in NE activity between 90- and 30-dB SPL noise presentations per ROI. Under repetitive stress, the difference in NE responses to high versus low-intensity noise, as well as the variance, was significantly reduced (*t*-test, $p = 1.6 \times 10^{-37}$, two-sample F-test $p = 2.8 \times 10^{-77}$). Left: Additionally, the distribution of responses became more uniform and less variable (KS-test, $p = 3 \times 10^{-47}$), indicating a loss of intensity-dependent modulation. Dotted lines indicate the mean for each condition. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

and a progressive decline in NE release. If stress alters sensory gating, we hypothesized that NE responses would change differently across the session, either through exaggerated habituation (greater reduction) or impaired habituation (no reduction), reflecting altered engagement of NE signaling.

To test this, we compare NE activity in the first and last 90 dB trial within each session under baseline and stress conditions (Fig. 4b). Under baseline conditions, NE responses to 90 dB noise significantly decreased over the session (Fig. 4b left grey, 2-way Anova, condition $F = 111$ $p = 2.1 \times 10^{-25}$, trial time $F = 66.8$ $p = 5.1 \times 10^{-16}$, interaction $F = 39$ $p = 4.2 \times 10^{-10}$ post hoc $p = 1.8$ x e-20 and when controlling for the FOV segmentation - Supp. Fig. 3f), consistent with normal habituation. In contrast, during stress, NE activity was already reduced at session onset (post hoc $p = 7.9 \times 10^{-31}$) and did not change significantly across trials (post hoc $p = 0.88$), suggesting both a diminished initial response and a lack of within-session habituation.

To further quantify this effect, we calculated the difference in NE activity between the first and last 90 dB trials. During baseline, NE responses predominantly decreased from the first to the last trial, as reflected by a distribution of differences skewed below zero (Fig. 4c, grey), consistent with normal habituation. Under stress, this decline was markedly reduced; response differences clustered around zero (Fig. 4c, blue; *t*-test, $p = 2.2 \times 10^{-11}$; KS test, $p = 5.7 \times 10^{-11}$), indicating impaired habituation. This was not the case in the control group, where the NE responses predominantly decreased from the first to the last trial in both the first and second week of imaging (Supp. Fig. 2e, *t*-test, $p = 0.68$; KS test, $p = 0.93$).

Together, these findings show that repetitive stress diminishes NE activity both across days and within sessions, particularly in response to high-intensity sounds. Under stress, the sound appears less salient from the outset, and NE responses fail to habituate, likely because the already low initial activity leaves little room for further reduction. This flattening of the NE dynamic range—lowering baseline activity and limiting modulation over repetitions—may impair sensory gating, reducing the system's capacity to signal changes in stimulus salience or novelty.

3. Discussion

Our results demonstrate that repetitive restraint stress markedly blunts noradrenergic responses in the auditory cortex, unveiling a key mechanism by which repeated stress could disrupt sensory processing and perception. By chronically imaging GRAB_NE1m signals *in-vivo* across mild repetitive stress, we found that NE release in response to high-intensity sounds was significantly attenuated after just one day of stress, and the response continued to decline over the following sessions. Moreover, stress disrupted the typical within-session decline in NE responses, such that mice no longer exhibited the gradual reduction in NE activation in response to repeated presentations of a loud stimulus, observed during baseline sessions or in the non-stressed control group. Together, these findings suggest that repetitive stress not only reduces the overall amplitude of NE release but may narrow its dynamic range and flexibility in response to salient stimuli.

NE plays a major role in regulating activity in primary sensory cortices [1,2,3]. Under normal, non-stressed conditions, NE helps suppress background firing and improves the signal-to-noise ratio, thereby supporting processes like selective attention, learning, and rapid stimulus discrimination [3,4,5]. These effects arise from multiple mechanisms, including the layer-specific modulation of inhibitory interneurons (Salgado et al., 2011a, 2011b, 2012) or differentially affecting spontaneous and stimulus-driven activity (Foote et al., 1975; Gaucher and Edeline, 2015; Manunta and Edeline, 1997). By reducing spontaneous firing while preserving (and even enhancing) responses to auditory stimuli, NE appears to facilitate the detection of relevant signals over background activity (Foote et al., 1975; Ikeda et al., 2015; Lee et al., 2018). Early observations proposed that NE modulation of GABA release underlies this improvement in sensory discrimination (Foote et al., 1975), potentially lowering the threshold for cortical activation and promoting a state of alertness conducive to learning and attentional processes. While some of the observations were dose-dependent (Devilbiss and Waterhouse, 2000), there is an agreement that the prominent physiological function of central noradrenergic pathways is the enhancement of the efficacy of both excitatory and inhibitory synaptic transmission within target neuronal circuits (Berridge and Waterhouse, 2003).

Our data extends these findings by showing that repetitive stress undermines this finely tuned noradrenergic control in the auditory cortex. While biochemical measurements have shown reduced NE in the auditory cortex following prolonged stress (Pérez-Valenzuela et al., 2016), our chronic imaging approach offers direct functional evidence that *in-vivo* NE dynamics are compromised under these conditions. Thus, while acute stress might transiently increase LC activity and boost NE release (Abercrombie and Jacobs, 1987; Hermans et al., 2014; Privitera et al., 2024; Qi and Gao, 2020), repeated or prolonged stress appears to shift the system toward a less adaptable, lower-gain mode —a transition supported by electrophysiological and molecular evidence of altered LC firing and NE synthesis following prolonged stress exposure (Curtis et al., 1995; George et al., 2013; Isingrini et al., 2016; Reyes et al., 2015).

Mechanistically, the attenuated NE response could result from several factors, including reduced excitability or altered plasticity in locus coeruleus (LC) neurons projecting to the auditory cortex, changes in NE diffusion dynamics, or an increase in NE clearance via enhanced reuptake or degradation that cannot be differentiated with our approach. Future studies could leverage pharmacological interventions or genetic targeting of LC neurons to distinguish whether stress

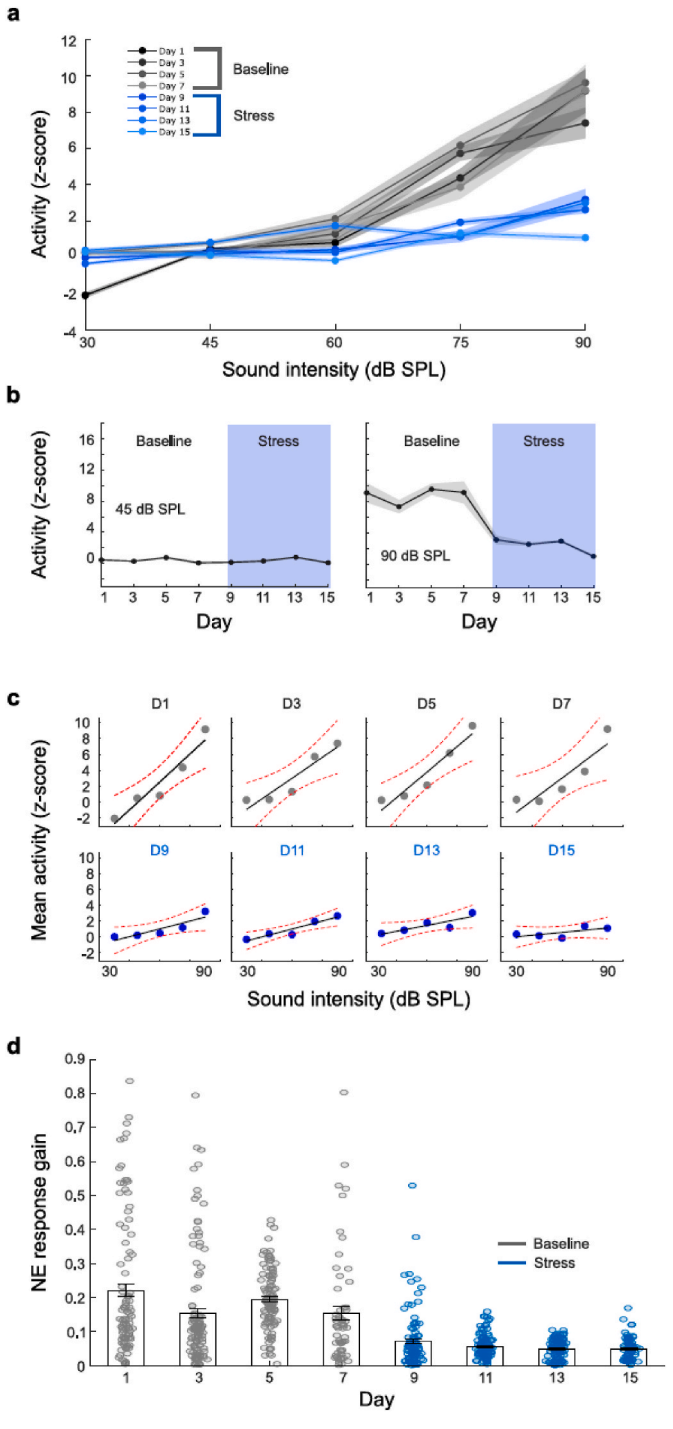

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Fig. 3. Repetitive stress leads to an early and progressive reduction in NE activity

(a) Mean z-scored NE activity across all ROIs in response to different noise levels during baseline (grey) and stress (blue) days. NE activity declines significantly during repetitive stress (3-way ANOVA sound intensity-condition interaction $F = 108.1$ $p = 2.3 \times 10^{-88}$, day-condition interaction $F = 2.9$ $p = 0.03$). Data represent mean ± SEM across ROIs.

(b) Mean NE z-scored activity during baseline and repetitive stress (blue background) in response to 45 and 90 dB SPL noise. There was a significant decrease in NE activity in response to a high-intensity 90 dB SPL noise (1-way ANOVA: baseline vs. stress, $F = 25.1$, $p = 9.4 \times 10^{-32}$). Data represent mean ± SEM across ROIs.

(c) Scatterplots show the mean NE response across ROIs for all sound intensities on the specified day. The dotted lines represent the 95 % confidence interval of the fit. Baseline-top grey and Stress – bottom blue.

(d) NE response gain calculated as the slope of the linear fit of the mean NE response for all sound intensities per ROI. NE response gain is significantly reduced during repetitive stress (2-way ANOVA: condition, $F = 207$, $p = 9 \times 10^{-72}$; condition × day interaction, $F = 2.5$, $p = 0.04$). Within the stress period (blue), the response slope gradually declines as stress progresses (1-way ANOVA: $F = 4.5$, $p = 0.004$; post hoc: day 1 vs. days 3 and 4, $p = 0.006$ and $p = 0.02$, Bonferroni-corrected). Data represent mean ± SEM across ROIs. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

primarily impairs NE release, alters diffusion or clearance kinetics, or affects target engagement. Another possibility is that the reduction of NE activity during sound presentation reflects an increase in tonic NE. While our data and prior biochemical studies suggest a decrease in tonic NE in the auditory cortex (Pérez-Valenzuela et al., 2016) and other sensory areas (Keim and Sigg, 1976), we cannot exclude the possibility that altered tonic NE levels—either locally or across regions— also contribute to the reduced dynamic range observed.

Stress can induce structural and functional changes at multiple circuit levels, including synaptic changes in local inhibitory networks (Berridge and Waterhouse, 2003; Salgado et al., 2012). Since NE normally refines inhibitory drive to sculpt sensory representations, chronically low NE levels may favor heightened baseline activity and inadequate recruitment during sound-evoked responses—consistent with our earlier observations of increased spontaneous firing in chronically stressed mice (Bisharat et al., 2025). Moreover, the pronounced reduction in response variance we observed might reflect a "flattening" of the NE system's dynamic range, with stressed mice remaining in a uniform, downregulated state that cannot scale their response to salient stimuli as effectively. Our within-session analyses further suggest that this already reduced initial NE activity may leave insufficient dynamic range for further decline, effectively preventing normal habituation processes from occurring. In this sense, the failure to adapt within sessions may not reflect impaired plasticity per se but rather a floor effect imposed by chronically low NE signaling.

Reduced NE levels in the auditory cortex point to a possible region-specific downregulation, although one might expect similarly diminished NE in other sensory areas under prolonged stress. This contrasts with the overall increase in NE release observed in subcortical regions like the amygdala (McCall et al., 2017). One possibility is that the LC-NE system under repetitive stress shifts priority to subcortical "survival" circuits at the cost of fine-grained sensory cortex modulation. This interpretation aligns with recent proposals of a modular organization of LC outputs (Chandler et al., 2019), where distinct LC projections exert region-specific control over target structures. In practical terms, stressed individuals might experience less precise auditory perception, while threat-related sensory signals (like a sudden noise) still trigger exaggerated subcortical responses (due to high NE in the amygdala), leading to impaired discrimination or filtering in cortex, accompanied by hyper-reactivity in threat detection pathways.

Functionally, these dampened NE responses may significantly affect how animals process sensory signals under prolonged stress. If NE

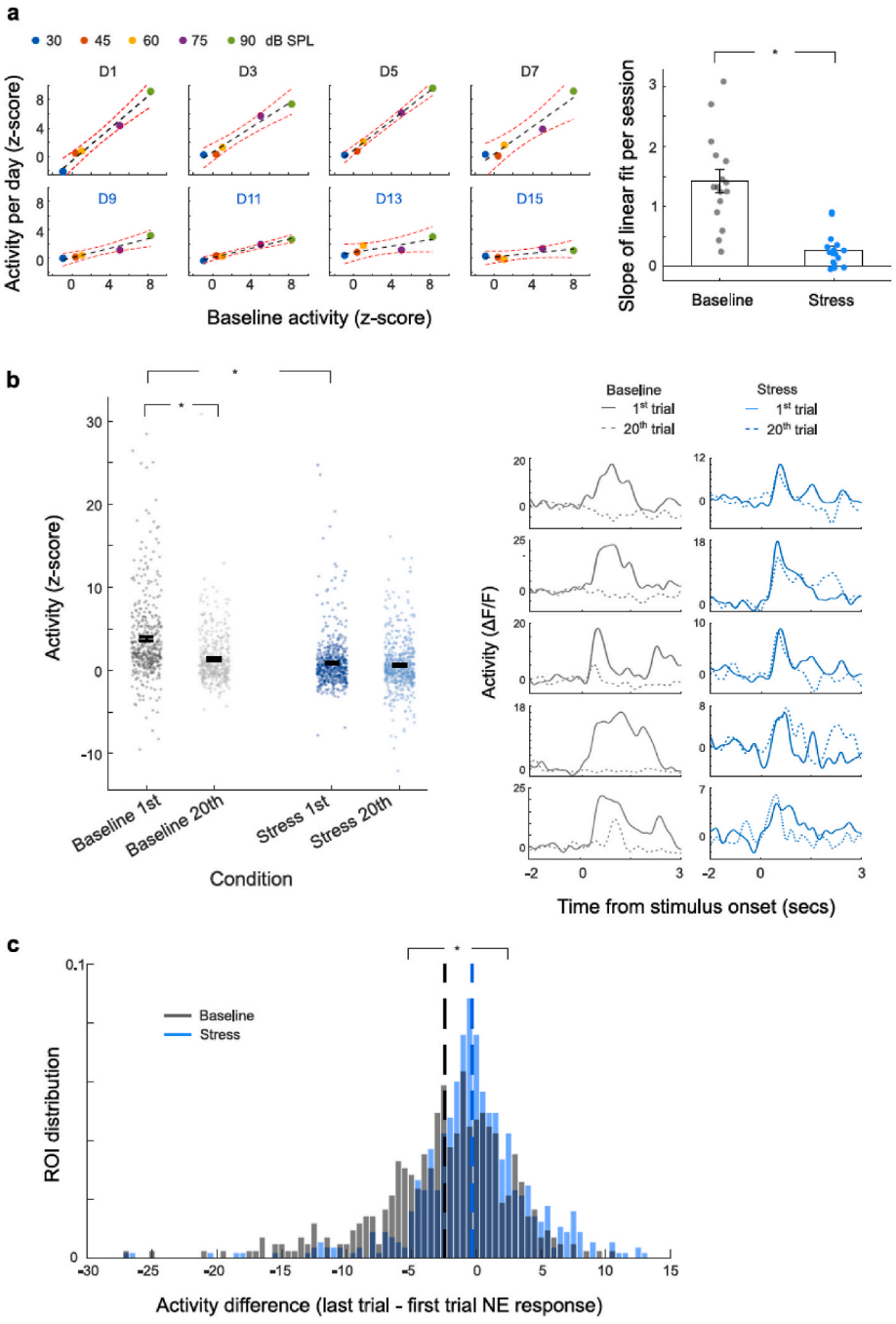

Fig. 4. Repetitive stress reduces sensitivity to sound intensity changes and impairs adaptation to repeating high-intensity sounds

(a) Left: Scatterplots show the mean NE response at each sound level during baseline (first two imaging sessions, x-axis) compared to the response on a given day (y-axis). Right: The slope (m) of the linear fit quantifies daily changes in response gain: $m = 1$ indicates a stable gain relative to baseline, $m < 1$ reflects a divisive flattening of the response function, and $m > 1$ suggests a multiplicative enhancement. Shaded areas represent the 95 % confidence interval of the fit. Under baseline conditions, NE gain remained stable, whereas, during repetitive stress, gain decreased significantly (*t*-test, $p = 3.2 \times 10^{-6}$, data represent mean ± SEM.).

(b) Examples of the NE response in the first (solid line) and last (dotted line) presentation of a 90 dB SPL noise for different ROIs (right). NE responses were overall lower under stress than baseline (left), and NE responses changed across trials (first vs. last) in baseline but not in stress (2-way Anova condition; $F = 111$ $p = 2.1 \times 10^{-25}$ trial time: $F = 66.8$ $p = 5.1 \times 10^{-16}$; interaction $F = 39$ $p = 4.2 \times 10^{-10}$). Specifically, the response in the first trial in baseline was significantly larger than the response in the first trial during stress (post hoc, $p = 7.9 \times 10^{-31}$) and the 20th trial in baseline ($p = 1.8$ x e^{-20}). NE responses under stress showed no significant difference between the first and last trial ($p = 0.88$), indicating that the reduced NE response during stress was present from the start and it did not change over the session. Finally, the last trial in baseline remained significantly larger than the last trial under stress ($p = 0.014$). All comparisons were Bonferroni-corrected for multiple comparisons. Data are presented as mean ± SEM.

(c) During baseline sessions, many ROIs had a decrease in NE response from the first to the last trial, indicating habituation (grey). Under repetitive stress (blue), this decline was markedly reduced, suggesting reduced habituation (*t*-test, $p = 2.2 \times 10^{-11}$; KS test, $p = 5.7 \times 10^{-11}$). The activity difference was calculated by subtracting the response in the initial trial from that of the final trial. Note that the y-axes differ in their maximum values across plots. The dotted lines represent the mean per condition. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

release is chronically dampened, the cortex may struggle to filter out background noise or rapidly amplify important inputs—processes crucial for attentional selection, learning of relevant auditory cues, and adaptive responses to new stimuli. At the same time, our data also reveals a diminished habituation effect to repetitive loud sounds under stress, indicating an inability to modulate noradrenergic signaling over repeated exposures appropriately. Such a failure to adapt can lead to persistent vigilance or anxiety-like states, consistent with the well-known link between repetitive stress and hypervigilance or anxiety disorders (Clancy et al., 2017; McEwen, 2017; Morris et al., 2020; Shepard et al., 2016).

Overall, our findings highlight a direct link between repetitive stress and compromised NE signaling in the auditory cortex, providing a potential mechanistic explanation for stress-induced sensory processing deficits (Bangel et al., 2017; Bisharat et al., 2025; Canlon et al., 2013; Clancy et al., 2017; Holstein et al., 2010; Mazurek et al., 2012; McGirr et al., 2020; Wu et al., 2019). Future investigations could explore whether restoring NE tone—pharmacologically or through behavioral interventions—can reverse these effects, thereby helping to preserve or regain the adaptive range essential for healthy auditory perception and learning.

4. Materials and methods

4.1. Resource availability

Data are available upon request from the corresponding author at resnikj@bgu.ac.il.

This study did not generate new unique reagents.

4.2. Experimental model and subject details

All procedures were approved by the Ben-Gurion University Animal Care and Use Committee. Data was collected from 12 adult mice (10–16 weeks postnatal; PV-Cre, JAX stock no: 017320). Nine mice contributed to the NE imaging experiments and 3 to the GCaMP imaging experiments. Mice of both sexes were used for this study. Mice were maintained on a reverse 12 h light/12 h dark cycle and were provided with ad libitum access to food and water.

4.3. Restraint stress

Before the relevant session, the mice were placed in a 50 ml tube for 30 min to achieve mild stress. This was done once a day for seven days. The imaging session started directly after the restraint (every other day).

4.4. Survival surgeries for awake, head-fixed imaging and behavior experiments

Mice were anesthetized with isoflurane in oxygen (5 % induction, 1.5 % maintenance). The dorsal surface of the mice's heads was trimmed and sterilized. ThermoStar homeothermic blanket monitoring system was used to maintain body temperature at 36.6C∘ (RWD). Lidocaine hydrochloride was administered subcutaneously to numb the scalp. The skin overlying the skull was cut with surgical scissors, reflected and the periosteum removed. The skull surface was prepped with an etchant (C&B metabond) and vetbond (3M) before affixing a custom stainless-steel headplate to the dorsal surface with dental cement (C&B metabond). At the conclusion of the headplate attachment and any additional procedures listed below, Buprenex (0.05 mg/kg) and meloxicam (0.1 mg/kg) were administered, and the animal was transferred to a warmed recovery chamber.

4.5. Virus mediated gene-delivery

Two burr holes were made in the skull over the auditory cortex (1.75–2.25 mm rostral to the lambdoid suture) of the mice. A precision injection system (Nanoject III) was used to inject 75 nL in each burr hole of AAV5.Syn.GCaMP6s.WPRE.SV40 for mice used in the GCaMP imaging experiment and of AAV9-hSyn-GRAB_NE1m (Feng et al., 2019) for mice used in the NE imaging experiments, 200–250 μm below the pial surface. Before starting the imaging sessions, we waited ~3 weeks for virus incubation.

4.6. Two-photon imaging

Three round glass coverslips (one 4 mm, two 3 mm, #1 thickness) were etched with piranha solution and bonded into a vertical stack using transparent, UV-cured adhesive. Headplate attachment, anesthesia and analgesia follow the procedure described above. A 3 mm craniotomy was made over the right ACtx using a scalpel and the coverslip stack was cemented into the craniotomy. Two-photon excitation was provided by a Ti:Sapphire-pulsed laser tuned to 920 nm. Imaging was performed with a 163/0.8NA water-immersion objective (Nikon) from a 512X512 pixel field of view at 30Hz with a Galvo-Resonant 8 kHz scanning microscope (Thorlabs). Scanning software was synchronized to the stimulus generation hardware using digital pulse trains. The microscope was rotated by 50–60 degrees off the vertical axis to obtain images from the lateral aspect of the mouse cortex while the animal was maintained in an upright head position. Imaging was performed in a light-tight, sound-attenuating chamber mounted on a floating table. Animals were monitored throughout the experiment to confirm all imaging was performed in the awake condition. Imaging was performed in layers L2/3, 200–250 μm below the pial surface. Fluorescence images were captured at 2x digital zoom, providing an imaging field of (0.42 × 0.42 mm). Raw calcium imaging data were preprocessed using Suite2P (Pachitariu et al., 2017), which included offline motion correction and initial automated detection of neuronal somata. The cell somata appeared in the FOV as dark "donut-shaped" regions due to somatic exclusion of sensor expression. Suite2P identified these putative cell bodies, and we manually curated the output to exclude blood vessels, noise, overlapping cells, and artifacts. To capture local extracellular NE signals surrounding the soma, we generated perisomatic ROIs by expanding the somatic masks (~15–20 μm in diameter) and subtracting the central region, resulting in ring-shaped ROIs that approximate the perisomatic neuropil. ROIs with overlapping regions were excluded. These ring-shaped ROIs enabled spatially resolved quantification of NE dynamics across the field of view. ΔF/F was computed as follows: (F(t)– F0)/F0, where F(t) was the raw calcium signal and F0 was the mean baseline fluorescence prior to stimulus presentation across trials. To minimize stress associated with head restraint, mice underwent a four-day habituation protocol prior to baseline imaging, including gradual increases in head-fixation duration and progressive exposure to the imaging setup (application of imaging gel on day 3 and placement of the objective on day 4).

4.7. Auditory and somatosensory stimuli for imaging experiments

Auditory stimuli were generated with a 24-bit digital-to-analog converter (National Instruments model PXI-4461) using scripts programmed in MATLAB (MathWorks) and LabVIEW (National Instruments). Speakers were calibrated for their distance from the contralateral ear (left ear) of the mouse. For imaging experiments, we presented either 1000 ms white noise bursts (generated from a Gaussian distribution) at sound intensities ranging from 30 to 90 dB SPL in 15 dB steps, or 200 ms air puffs delivered at an average of 6 PSI, producing an average sound level of 40 dB. Sound stimulus trials had a 10-s duration, and each stimulus was repeated 20 times. Air puff trials had a 25-s duration, and the stimulus was repeated 5 times.

4.8. Two-photon imaging analysis

GRAB_NE1m fluorescence reflects the binding of extracellular NE to the sensor's α2-adrenergic receptor-based extracellular domain, producing a change in fluorescence. Therefore, the signal reports local fluctuations in extracellular NE concentration in the vicinity of the sensor, shaped by endogenous release, diffusion, and reuptake. Because absolute baseline fluorescence is influenced by factors such as expression level and optical conditions, our analyses focus on stimulus-evoked relative changes in NE responses across sound intensities.

Imaging data was analyzed as ΔF/F and normalized by calculating the z-score of NE activity relative to the 2-s baseline period preceding stimulus onset. Unless otherwise noted, analyses used this z-scored activity. NE response was defined as the average z-scored NE activity during the 1-s following stimulus onset.

For the slope analysis, in Fig. 3, a linear fit was applied to the mean activity across sound levels for each ROI and session (i.e., gain). In Fig. 4, the slope reflects the transformation between the mean NE activity growth measured during the first two imaging sessions (mean baseline) and the NE activity growth observed on a given day.

For the activity difference analysis in Fig. 4, the difference was calculated for each ROI and session as the NE activity during the last trial in which 90 dB SPL noise was played minus the activity during the first such trial.

4.9. Statistical analysis

All statistical analyses were performed in MATLAB R2023a (Mathworks). Data shown in all analyses is the mean activity ±SE unless otherwise indicated. Post hoc pairwise comparisons were corrected for multiple comparisons using the Bonferroni correction. Asterisks indicate $p < 0.05$. For multiple comparisons, full statistical details are reported in the figure legends.

CRediT authorship contribution statement

Ekaterina Kaganovski: Writing – original draft, Formal analysis, Data curation. **Jennifer Resnik:** Writing – review & editing, Writing – original draft, Supervision, Funding acquisition, Conceptualization.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuropharm.2025.110676.

Data availability

Data will be made available on request.

References

Abercrombie, E.D., Jacobs, B.L., 1987. Single-unit response of noradrenergic neurons in the locus coeruleus of freely moving cats. II. Adaptation to chronically presented stressful stimuli. J. Neurosci. 7, 2844–2848. https://doi.org/10.1523/JNEUROSCI.07-09-02844.1987.

Bangel, K.A., van Buschbach, S., Smit, D.J.A., Mazaheri, A., Olff, M., 2017. Aberrant brain response after auditory deviance in PTSD compared to trauma controls: an EEG study. Sci. Rep. 7, 16596. https://doi.org/10.1038/s41598-017-16669-8.

Berridge, C.W., Waterhouse, B.D., 2003. The locus coeruleus–noradrenergic system: modulation of behavioral state and state-dependent cognitive processes. Brain Res. Rev. 42, 33–84. https://doi.org/10.1016/S0165-0173(03)00143-7.

Bisharat, G., Kaganovski, E., Sapir, H., Temnogorod, A., Levy, T., Resnik, J., 2025. Repeated stress gradually impairs auditory processing and perception. PLoS Biol. 23, e3003012. https://doi.org/10.1371/journal.pbio.3003012.

Borodovitsyna, O., Joshi, N., Chandler, D., 2018. Persistent stress-induced neuroplastic changes in the locus coeruleus/norepinephrine system. Neural Plast., 1892570 https://doi.org/10.1155/2018/1892570.

Canlon, B., Theorell, T., Hasson, D., 2013. Associations between stress and hearing problems in humans. Hear. Res. 295, 9–15. https://doi.org/10.1016/j.heares.2012.08.015.

Chandler, D.J., Jensen, P., McCall, J.G., Pickering, A.E., Schwarz, L.A., Totah, N.K., 2019. Redefining noradrenergic neuromodulation of behavior: impacts of a modular locus coeruleus architecture. J. Neurosci. 39, 8239–8249. https://doi.org/10.1523/jneurosci.1164-19.2019.

Clancy, K., Ding, M., Bernat, E., Schmidt, N.B., Li, W., 2017. Restless 'rest': intrinsic sensory hyperactivity and disinhibition in post-traumatic stress disorder. Brain 140, 2041–2050. https://doi.org/10.1093/brain/awx116.

Curtis, A.L., Pavcovich, L.A., Grigoriadis, D.E., Valentino, R.J., 1995. Previous stress alters corticotropin-releasing factor neurotransmission in the locus coeruleus. Neuroscience 65, 541–550. https://doi.org/10.1016/0306-4522(94)00496-R.

Devilbiss, D.M., Waterhouse, B.D., 2000. Norepinephrine exhibits two distinct profiles of action on sensory cortical neuron responses to excitatory synaptic stimuli. Synapse 37, 273–282. https://doi.org/10.1002/1098-2396(20000915)37:4<273::AID-SYN4>3.0.CO;2-#.

Feng, J., Zhang, C., Lischinsky, J.E., Jing, M., Zhou, J., Wang, H., Zhang, Y., Dong, A., Wu, Z., Wu, H., Chen, W., Zhang, P., Zou, J., Hires, S.A., Zhu, J.J., Cui, G., Lin, D., Du, J., Li, Y., 2019. A genetically encoded fluorescent sensor for rapid and specific *in vivo* detection of norepinephrine. Neuron 102, 745–761.e8. https://doi.org/10.1016/j.neuron.2019.02.037.

Foote, S.L., Freedman, R., Oliver, A.P., 1975. Effects of putative neurotransmitters on neuronal activity in monkey auditory cortex. Brain Res. 86, 229–242. https://doi.org/10.1016/0006-8993(75)90699-X.

Gaucher, Q., Edeline, J.-M., 2015. Stimulus-specific effects of noradrenaline in auditory cortex: implications for the discrimination of communication sounds. J. Physiol. 593, 1003–1020. https://doi.org/10.1113/jphysiol.2014.282855.

Gelbard-Sagiv, H., Magidov, E., Sharon, H., Hendler, T., Nir, Y., 2018. Noradrenaline modulates visual perception and late visually evoked activity. Curr. Biol. 28, 2239–2249.e6. https://doi.org/10.1016/j.cub.2018.05.051.

George, S.A., Knox, D., Curtis, A.L., Aldridge, J.W., Valentino, R.J., Liberzon, I., 2013. Altered locus coeruleus–norepinephrine function following single prolonged stress. Eur. J. Neurosci. 37, 901–909. https://doi.org/10.1111/ejn.12095.

Ghosh, S., Maunsell, J.H.R., 2024. Locus coeruleus norepinephrine contributes to visual-spatial attention by selectively enhancing perceptual sensitivity. Neuron 112, 2231–2240.e5. https://doi.org/10.1016/j.neuron.2024.04.001.

Glaeser-Khan, S., Savalia, N.K., Cressy, J., Feng, J., Li, Y., Kwan, A.C., Kaye, A.P., 2024. Spatiotemporal organization of prefrontal norepinephrine influences neuronal activity. eNeuro 11. https://doi.org/10.1523/ENEURO.0252-23.2024.

Hermans, E.J., Henckens, M.J.A.G., Joëls, M., Fernández, G., 2014. Dynamic adaptation of large-scale brain networks in response to acute stressors. Trends Neurosci. 37, 304–314. https://doi.org/10.1016/j.tins.2014.03.006.

Holstein, D.H., Vollenweider, F.X., Jäncke, L., Schopper, C., Csomor, P.A., 2010. P50 suppression, prepulse inhibition, and startle reactivity in the same patient cohort suffering from posttraumatic stress disorder. J. Affect. Disord. 126, 188–197. https://doi.org/10.1016/j.jad.2010.02.122.

Ikeda, Maaya, Sung, David Jeon, Cowell, Rosemary A., Remage-Healey, Luke, 2015. Norepinephrine modulates coding of complex vocalizations in the songbird auditory cortex independent of local neuroestrogen synthesis. J. Neurosci.

Isingrini, E., Perret, L., Rainer, Q., Amilhon, B., Guma, E., Tanti, A., Martin, G., Robinson, J., Moquin, L., Marti, F., Mechawar, N., Williams, S., Gratton, A., Giros, B., 2016. Resilience to chronic stress is mediated by noradrenergic regulation of dopamine neurons. Nat. Neurosci. 19, 560–563. https://doi.org/10.1038/nn.4245.

Kagiampaki, Z., Rohner, V., Kiss, C., Curreli, S., Dieter, A., Wilhelm, M., Harada, M., Duss, S.N., Dernic, J., Bhat, M.A., Zhou, X., Ravotto, L., Ziebarth, T., Wasielewski, L. M., Sönmez, L., Benke, D., Weber, B., Bohacek, J., Reiner, A., Wiegert, J.S., Fellin, T., Patriarchi, T., 2023. Sensitive multicolor indicators for monitoring norepinephrine in vivo. Nat. Methods 20, 1426–1436. https://doi.org/10.1038/s41592-023-01959-z.

Kazanovich, I., Itzhak, S., Resnik, J., 2024. Experience-driven development of decision-related representations in the auditory cortex. EMBO Rep. 26, 84–100. https://doi.org/10.1038/s44319-024-00309-0.

Keim, K.L., Sigg, E.B., 1976. Physiological and biochemical concomitants of restraint stress in rats. Pharmacol. Biochem. Behav. 4, 289–297. https://doi.org/10.1016/0091-3057(76)90244-6.

Kubitschke, M., Müller, M., Wallhorn, L., Pulin, M., Mittag, M., Pollok, S., Ziebarth, T., Bremshey, S., Gerdey, J., Claussen, K.C., Renken, K., Groß, J., Gneiße, P., Meyer, N., Wiegert, J.S., Reiner, A., Fuhrmann, M., Masseck, O.A., 2022. Next generation genetically encoded fluorescent sensors for serotonin. Nat. Commun. 13, 7525. https://doi.org/10.1038/s41467-022-35200-w.

Kvetňanský, R., Palkovits, M., Mitro, A., Torda, T., Mikulaj, L., 2008. Catecholamines in individual hypothalamic nuclei of acutely and repeatedly stressed rats. Neuroendocrinology 23, 257–267. https://doi.org/10.1159/000122673.

Latimer, K.W., Barbera, D., Sokoletsky, M., Awwad, B., Katz, Y., Nelken, I., Lampl, I., Fairhall, A.L., Priebe, N.J., 2019. Multiple timescales account for adaptive responses across sensory cortices. J. Neurosci. 39, 10019–10033. https://doi.org/10.1523/JNEUROSCI.1642-19.2019.

Lee, V., Pawlisch, B.A., Macedo-Lima, M., Remage-Healey, L., 2018. Norepinephrine enhances song responsiveness and encoding in the auditory forebrain of male zebra finches. J. Neurophysiol. 119, 209–220. https://doi.org/10.1152/jn.00251.2017.

Manunta, Y., Edeline, J.-M., 2004. Noradrenergic induction of selective plasticity in the frequency tuning of auditory cortex neurons. J. Neurophysiol. 92, 1445–1463. https://doi.org/10.1152/jn.00079.2004.

Manunta, Y., Edeline, J.-M., 1997. Effects of noradrenaline on frequency tuning of rat auditory cortex neurons. Eur. J. Neurosci. 9, 833–847. https://doi.org/10.1111/j.1460-9568.1997.tb01433.x.

Martins, A.R.O., Froemke, R.C., 2015. Coordinated forms of noradrenergic plasticity in the locus coeruleus and primary auditory cortex. Nat. Neurosci. 18, 1483–1492. https://doi.org/10.1038/nn.4090.

Mazurek, B., Haupt, H., Olze, H., Szczepek, A.J., 2012. Stress and tinnitus—from bedside to bench and back. Front. Syst. Neurosci. 6, 47. https://doi.org/10.3389/fnsys.2012.00047.

McBurney-Lin, J., Lu, J., Zuo, Y., Yang, H., 2019. Locus coeruleus-norepinephrine modulation of sensory processing and perception: a focused review. Neurosci. Biobehav. Rev. 105, 190–199. https://doi.org/10.1016/j.neubiorev.2019.06.009.

McCall, J.G., Siuda, E.R., Bhatti, D.L., Lawson, L.A., McElligott, Z.A., Stuber, G.D., Bruchas, M.R., 2017. Locus coeruleus to basolateral amygdala noradrenergic projections promote anxiety-like behavior. eLife 6, e18247. https://doi.org/10.7554/eLife.18247.

McEwen, B.S., 2017. Neurobiological and systemic effects of chronic stress. Chronic Stress 1, 2470547017692328. https://doi.org/10.1177/2470547017692328.

McGirr, A., LeDue, J., Chan, A.W., Boyd, J.D., Metzak, P.D., Murphy, T.H., 2020. Stress impacts sensory variability through cortical sensory activity motifs. Transl. Psychiatry 10, 1–14. https://doi.org/10.1038/s41398-020-0713-1.

Morris, L.S., McCall, J.G., Charney, D.S., Murrough, J.W., 2020. The role of the locus coeruleus in the generation of pathological anxiety. Brain Neurosci. Adv. 4, 2398212820930321. https://doi.org/10.1177/2398212820930321.

Pachitariu, M., Stringer, Carsen, Dipoppa, Mario, Schröder, Sylvia, Federico Rossi, L., Dalgleish, Henry, Carandini, Matteo, Harris, Kenneth D., 2017. Suite2p: beyond 10,000 neurons with standard two-photon microscopy. bioRxiv [WWW Document]. URL. https://www.biorxiv.org/content/10.1101/061507v2. accessed 9.20.23.

Patriarchi, T., Cho, J.R., Merten, K., Howe, M.W., Marley, A., Xiong, W.-H., Folk, R.W., Broussard, G.J., Liang, R., Jang, M.J., Zhong, H., Dombeck, D., von Zastrow, M., Nimmerjahn, A., Gradinaru, V., Williams, J.T., Tian, L., 2018. Ultrafast neuronal imaging of dopamine dynamics with designed genetically encoded sensors. Science 360, eaat4422. https://doi.org/10.1126/science.aat4422.

Pavcovich, L.A., Cancela, L.M., Volosin, M., Molina, V.A., Ramirez, O.A., 1990. Chronic stress-induced changes in locus coeruleus neuronal activity. Brain Res. Bull. 24, 293–296. https://doi.org/10.1016/0361-9230(90)90219-P.

Pérez-Valenzuela, C., Gárate-Pérez, M.F., Sotomayor-Zárate, R., Delano, P.H., Dagnino-Subiabre, A., 2016. Reboxetine improves auditory attention and increases norepinephrine levels in the auditory cortex of chronically stressed rats. Front. Neural Circ. 10. https://doi.org/10.3389/fncir.2016.00108.

Plappert, C.F., Pilz, P.K.D., 2005. Long-term habituation of the startle response in mice evoked by acoustic and tactile stimuli. Behav. Brain Res. 162, 307–310. https://doi.org/10.1016/j.bbr.2005.03.022.

Privitera, M., von Ziegler, L.M., Floriou-Servou, A., Duss, S.N., Zhang, R., Waag, R., Leimbacher, S., Sturman, O., Roessler, F.K., Heylen, A., Vermeiren, Y., Van Dam, D., De Deyn, P.P., Germain, P.-L., Bohacek, J., 2024. Noradrenaline release from the locus coeruleus shapes stress-induced hippocampal gene expression. eLife 12, RP88559. https://doi.org/10.7554/eLife.88559.

Qi, M., Gao, H., 2020. Acute psychological stress promotes general alertness and attentional control processes: an ERP study. Psychophysiology 57, e13521. https://doi.org/10.1111/psyp.13521.

Reyes, B.A.S., Zitnik, G., Foster, C., Bockstaele, E.J.V., Valentino, R.J., 2015. Social stress engages Neurochemically-Distinct afferents to the rat locus coeruleus depending on coping strategy. eNeuro 2. https://doi.org/10.1523/ENEURO.0042-15.2015.

Salgado, H., García-Oscos, F., Dinh, L., Atzori, M., 2011a. Dynamic modulation of short-term synaptic plasticity in the auditory cortex: the role of norepinephrine. Hearing Research, Auditory Cortex: Current Concepts in Human and Animal Research 271, 26–36. https://doi.org/10.1016/j.heares.2010.08.014.

Salgado, H., Garcia-Oscos, F., Martinolich, L., Hall, S., Restom, R., Tseng, K.Y., Atzori, M., 2012. Pre- and postsynaptic effects of norepinephrine on γ-aminobutyric acid-mediated synaptic transmission in layer 2/3 of the rat auditory cortex. Synapse 66, 20–28. https://doi.org/10.1002/syn.20979.

Salgado, H., Garcia-Oscos, F., Patel, A., Martinolich, L., Nichols, J.A., Dinh, L., Roychowdhury, S., Tseng, K.-Y., Atzori, M., 2011b. Layer-specific noradrenergic modulation of inhibition in cortical layer II/III. Cerebr. Cortex 21, 212–221. https://doi.org/10.1093/cercor/bhq081.

Sapir, H., Bisharat, G., Golan, H., Resnik, J., 2025. Impaired folate metabolism reshapes auditory response profiles and impairs loudness perception in MTHFR-deficient mice. Neurobiol. Dis. 208, 106863. https://doi.org/10.1016/j.nbd.2025.106863.

Shepard, R., Page, C.E., Coutellier, L., 2016. Sensitivity of the prefrontal GABAergic system to chronic stress in male and female mice: relevance for sex differences in stress-related disorders. Neuroscience 332, 1–12. https://doi.org/10.1016/j.neuroscience.2016.06.038.

Stone, E.A., McCarty, R., 1983. Adaptation to stress: tyrosine hydroxylase activity and catecholamine release. Neurosci. Biobehav. Rev. 7, 29–34. https://doi.org/10.1016/0149-7634(83)90005-2.

Wu, J., Feng, M., Liu, Y., Fang, H., Duan, H., 2019. The relationship between chronic perceived stress and error processing: evidence from event-related potentials. Sci. Rep. 9, 11605. https://doi.org/10.1038/s41598-019-48179-0.

Yarden, T.S., Mizrahi, A., Nelken, I., 2022. Context-dependent inhibitory control of stimulus-specific adaptation. J. Neurosci. 42, 4629–4651. https://doi.org/10.1523/JNEUROSCI.0988-21.2022.

Yarden, T.S., Nelken, I., 2017. Stimulus-specific adaptation in a recurrent network model of primary auditory cortex. PLoS Comput. Biol. 13, e1005437. https://doi.org/10.1371/journal.pcbi.1005437.