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Research report

Sensory gating functions of the auditory thalamus: Adaptation and modulations through noise-exposure and high-frequency stimulation in rats

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ABSTRACT

The medial geniculate body (MGB) of the thalamus is an obligatory relay for auditory processing. A breakdown of adaptive filtering and sensory gating at this level may lead to multiple auditory dysfunctions, while high-frequency stimulation (HFS) of the MGB might mitigate aberrant sensory gating. To further investigate the sensory gating functions of the MGB, this study (i) recorded electrophysiological evoked potentials in response to continuous auditory stimulation, and (ii) assessed the effect of MGB HFS on these responses in noise-exposed and control animals. Pure-tone sequences were presented to assess differential sensory gating functions associated with stimulus pitch, grouping (pairing), and temporal regularity. Evoked potentials were recorded from the MGB and acquired before and after HFS (100 Hz). All animals (unexposed and noise-exposed, pre- and post-HFS) showed gating for pitch and grouping. Unexposed animals also showed gating for temporal regularity not found in noise-exposed animals. Moreover, only noise-exposed animals showed restoration comparable to the typical EP amplitude suppression following MGB HFS. The current findings confirm adaptive thalamic sensory gating based on different sound characteristics and provide evidence that temporal regularity affects MGB auditory signaling.

1. Introduction

Our everyday listening environment is highly complex, with many sounds arriving at the same time. This rich auditory environment requires efficient filtering to select relevant information. One of these filtering mechanisms is sensory gating (SG), defined as the adaptive filtering of changing-stimulus features (gating in) relative to repetitive-stimulus features (gating out) [1,2]. Thus, SG leads to differential neural activity in response to unpredictable and predictable stimulus characteristics. This basic distinction allows efficient allocation of neural and cognitive resources, while dysfunctional SG might affect the listening experience in healthy aging and factor into various psychiatric and neurological conditions such as schizophrenia and tinnitus [3].

However, SG describes a broad spectrum and although globally referring to adaptive filtering, it implies several operational levels [4]. For example, at the single neuron level, SG might result from stimulus-specific adaptation, while more complex adaptation might impact cognitive or circuit levels [4]. Accordingly, manifestations of

Abbreviations: MGB, medial geniculate body; EP, evoked potentials; DBS, deep brain stimulation; HFS, high-frequency stimulation; LMEM, linear mixed-effects model; SG, sensory gating.

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altered SG might include less efficient resource allocation during aging or in hearing disorders but also the generation of phantom perceptions such as tinnitus [1,2,5]. These different manifestations of SG might share a common denominator, namely aberrant functioning of a sensory-perceptual filtering or "noise canceling system" that is located in or at least involves brain structures that signal auditory information from the periphery to cortical targets.

The medial geniculate body (MGB) of the thalamus is a major relay between the midbrain and the auditory cortices (AC) that acts as a gatekeeper for auditory signals [6]. This makes the MGB and associated circuitry likely candidates for a neural correlate of (dys-) functional SG, although the exact function of the thalamic gate and its modulation remain poorly understood [5,7]. Accurate temporal coding of complex sounds, such as speech, in the central auditory system relies heavily on the inhibitory neurotransmitter GABA and its synaptic receptors ($GABA_ARs$) [8]. There are three primary sources of GABAergic inhibitory input: from interneurons (reduced in rodents) [9], IC [10,11], and TRN [12] that shape MGB response properties. Within the MGB, fast phasic and slow tonic inhibition are mediated by synaptic and extrasynaptic $GABA_ARs$. These mechanisms regulate the excitability and firing modes of MGB neurons and engage thalamocortical oscillations that shape the coding and gating of auditory signals. Moreover, tegmental cholinergic afferents that project to the MGB also modulate auditory coding properties. This modulation might potentially improve attention and facilitate the disambiguation of difficult or novel sounds.

These GABAergic feedback loops might thus instantiate the filter mechanisms that suppress responses to predictable sensory input. In turn, alteration of these GABAergic inhibitory properties might result in unsuppressed input or even in phantom perception. However, there are competing hypotheses on whether reduced disinhibition from midbrain structures or altered interaction with cortical regions (thalamocortical dysrhythmia) causally contribute to the tinnitus sensation [7,13].

In addition to several operational levels, SG might relate to different sound characteristics, i.e., spectral and temporal information. The latter is defined by the duration and arrangement of sounds into groups and patterns. These sound characteristics might be used independently or combined to tune adaptive filtering.

As the thalamus is located centrally in the vertebrate brain, deep brain stimulation (DBS) can be used to exert modulation of auditory SG. Although the exact working mechanisms of DBS remain elusive, complex inhibitory and distant excitatory effects have been described [14,15].

Here, we tested the hypothesis that different SG operations can be observed at the level of the MGB of the thalamus. Considering prior reported positive effects of high frequency stimulation (HFS) of the MGB, we further hypothesized that HFS of the MGB modulates thalamic SG. More specifically, HFS was expected to restore a dysfunctional "noise canceling system" by counteracting aberrant filtering of sensory input at the level of the MGB [14].

To this end, we investigated auditory SG in the MGB in control and noise-exposed rats and explored the effect of HFS. Lasting effects of noise-exposure were assessed by means of the gap-prepulse inhibition of the acoustic startle (GPIAS). In line with previous surface EEG findings in humans, we expected to observe a more suppressed EP amplitude for predictable than unpredictable stimulus features [16]. EP recordings were conducted in anesthetized animals using two continuous paired stimulus "oddball" sequences that were each composed of two pure tones differing in pitch. Presentations of these sequences manipulated pitch (frequently presented lower pitch standard tones and pseudorandomly interspersed infrequently presented higher pitch deviant tones), sequential order (position within a tone pair) and global sequence regularity (temporally regular [isochronous] and irregular [randomized] sequence inter-stimulus-intervals), before and after MGB HFS was applied. Thus, the experimental design allowed the assessment of different stimulus features that might impact the tuning of the SG filter mechanism, i.e., pitch (repetition of low and high pitch), grouping (first and second position), and temporal regularity (regular and irregular timing of presentation) before and after MGB HFS.

2. Materials and methods

2.1. Subjects

The experimental group tested here has been described previously (see van Zwieten et al., 2021 for further detail) [17]. Rats were seven weeks old at the beginning of the experiment and weighed approximately 250 g. Thirteen male Sprague Dawley rats were divided into two groups: i) noise-exposed (n = 8) and ii) unexposed controls (n = 5). Rats were individually housed in standard Makrolon™ cages, with food and water ad libitum. Conditions in the room were kept constant, with a temperature of 20–22 ℃ and humidity of 60–70%. The light-dark cycle was reversed, and experiments were conducted within the dark period. The study was approved by the Animal Experiments and Ethics Committee at Maastricht University, the Netherlands.

2.2. Study design

The overall design of the study comprised four main parts: GPIAS, noise exposure, repeated GPIAS, and recording of EPs and HFS. The following readout parameters were used: the dependent variable was the amplitude of the EP (mV) in response to the stimulus onset. The independent variables were noise exposure (noise-exposed, unexposed; between-subjects), tone position (first, second; within-subjects), timing (regular, irregular; within-subjects), and HFS phase (pre-HFS, post-HFS; within-subjects). Noise exposure, GPIAS, surgical and deep brain stimulation procedures have also been described in detail elsewhere [17,18].

2.3. Noise exposure

All animals were anesthetized using Ketamine and Xylazine. Only the subjects in the noise-exposed group were exposed unilaterally to a 16 kHz octave-band noise at 115 dB for 90 min (Ultrasonic Power Amplifier, Ultrasonic Dynamic Speaker Vifa, Avisoft Bioacoustics, Berlin Germany), while the contralateral ear was blocked with molding clay [17]. Unexposed control rats were only anesthetized.

2.4. Gap prepulse inhibition of the acoustic startle

The behavioral setup allowed the testing of animals with the DBS construct mounted on the skull [17,18]. The advantage of this setup is that it allows the animals to freely move during GPIAS testing to not harm the DBS electrodes. A potential disadvantage of the setup is the increased variability in startle amplitudes between animals and that this setup has not been validated to compare z-scores. Considering the increased variability in the startle response, we opted to not use gap ratio values to assess tinnitus-like behavior at the individual subject level. Instead, behavioral evidence of lasting effects of noise-exposure at the group level was assessed before and three weeks after noise or sham exposure by GPIAS, as previously described in detail [17].

Freely moving rats were placed in a cylinder, on a piezo sensor. Gap and no-gap trials were alternately presented with 20 repetitions per background frequency (10 kHz, 16 kHz and 20 kHz at 75 dB). The startle stimulus consisted of a click sound of 105 dB intensity with 20 ms duration. In gap trials, a gap of 50 ms was added to the background sound, 100 ms prior to the startle stimulus. Prior to each session, the animals were acclimatized for 5 min and habituated to the startle sound by presenting 10 no-gap trials. To habituate the animals to the testing procedure, one complete session was performed at the beginning of the experiment. Two complete sessions per condition were conducted, each on separate testing days. The gap/no-gap ratio was calculated by dividing the amplitude per gap-startle by the mean of all startle-only trials [19].

2.5. Surgical procedure

Rats were anesthetized by intraperitoneal administration of urethane (7.5 ml/kg loading dose and 0.3 ml repetitive dose for maintenance) from a 20% of weight urethane solution (Sigma-Aldrich / Merck KGaA, Darmstadt, Germany). The level of anesthesia was monitored by checking whisker and pedal reflexes. Body temperature was controlled and maintained at 37 °C by means of a heating pad (ATC1000, World Precision Instruments, Sarasota, Florida). Rats were mounted on a stereotaxic apparatus (Stoelting Co, Illinois, USA) using hollow ear bars to allow presentation of sound stimuli. A craniotomy was performed to access the left MGB, i.e., the side contralateral to the noise (or sham) exposed ear. To record local field potentials, a bipolar electrode was inserted into the MGB (craniocaudal −5.5 mm, mediolateral +3.6 mm, dorsoventral −6 mm) according to Paxinos rat brain atlas [20]. The electrode was a custom-made platinum-iridium bipolar electrode with a shaft diameter of 250 μm and tip diameter of 50 μm, and a distance between the cathode and anode of 50 μm (Technomed, Beek, the Netherlands)[21].

2.6. Acquisition of evoked potentials and the auditory stimulation paradigm

Electrophysiological recordings were performed four weeks after noise exposure. The electrode was connected to a data acquisition system (PowerLab 8/35, New South Wales, Australia), filtered (0.1 Hz-1KHz online, further offline filtering detailed below) and sampled at 20KHz, using the LabChart Pro 7 software package (ADInstruments, Castle Hill, Australia). Sound stimuli were presented via a PC audio interface (0204 USB Audio Interface, E-MU systems, Dublin, Ireland), using custom-made MATLAB scripts. Stimuli were amplified and presented with an Ultrasonic Dynamic Speaker (Vifa, Avisoft Bioacoustics, Berlin, Germany), calibrated with a modular precision sound level meter (Bruel and Kjaer 2231, San Diego, USA) and a free-field microphone (Bruel and Kjaer type 4191, San Diego, USA). The contralateral ear was sealed with a plug of clay to block external auditory perception.

To establish compatibility with prior human research, the stimulus sequences consisted of two pure tones differing in pitch, with a 600 Hz tone serving as the frequently presented standard and a 660 Hz tone as the infrequently presented deviant (Fig. 1) [16]. The stimulus sequences consisted of six blocks of binary grouped tones. Each block consisted of 60 stimulus pairs and lasted for 1 min. The six blocks were presented without interruption for a total of six minutes, once with regular inter-stimulus intervals and once with irregular (jittered) intervals. Occurrence of the deviant tones was balanced across the two positions of each pair. Each stimulus lasted for 70 ms, including 10 ms rise and fall times. The standard-to-deviant ratio was 4:1. These stimuli were organized into two separate sequences, one generating regular (predictable) and one an irregular (less predictable) timing condition. The latter was realized via random variation of both the interval within (intra-chunk) and the interval between consecutive pairs (inter-chunk interval). The pairs consequently either consisted of two standard tones (S1S2), a standard followed by a deviant tone (S1D2), or a deviant followed by a standard tone (D1S2). Each rat received initial auditory stimulation with the regular and irregular sequence, both before and directly after HFS in counterbalanced order. This setup allowed assessment of SG functions associated with pitch (stimulus type: standard or deviant), grouping (position in a pair: first or second), and temporal regularity (timing: regular or irregular).

2.7. Deep brain stimulation

MGB HFS was applied for a period of five minutes with the same bipolar electrode as used for the EP recordings. HFS (100 Hz, 60 μs, 100 μA, bipolar, monophasic square-wave pulses) was applied with a stimulator (DS8000, World Precision Instruments, Sarasota, Florida) connected to a constant-current isolator (DLS100, WPI, Sarasota, Florida). These stimulation parameters were based on previous experiments [18] and selected to achieve current densities that are similar to human studies [21]. Regular and irregular external sound sequences were repeated, each being preceded by HFS, again using a counterbalanced design.

2.8. Electrode localization

To check for correct electrode tip placement, the rats were euthanized by decapitation while still being under general anesthesia. The brains were quickly removed and frozen in − 40°C 2-methyl-butane (isopentane). The tissue was serially cut by cryostat (Leica CM3050S, Wetzlar, Germany). Hematoxylin-Eosin staining was performed to confirm appropriate electrode placement. Most electrodes were positioned in the ventral portion or situated at the border of the ventral and dorsal MGB subdivisions. Two rats were excluded from the LFP analysis due to incorrect positioning and hardware failure. A schematic representation of all local field potential (LFP) electrode positions in the medial geniculate body (MGB) are presented in Fig. 2 [17].

2.9. Data processing

Analyses were performed using the 'Letswave' toolbox [22] running in MATLAB®. The researcher was blind during the analysis in respect to the conditions. To select the appropriate LFP signal, data were bandpass filtered using a software filter to include frequencies between 5 and 30 Hz to select the appropriate LFPs. After baseline correction, outliers were removed for a maximum of 5 epochs (from a total of 72) in the deviant group and a maximum of 20 in the standard group (from a total of 288). Data were then averaged across each event code (S1, S2, D1, D2). The first peak amplitude following the trigger onset was selected and used for statistical comparisons (Fig. 3). The data that support the findings of this study are openly available in "figshare" http://doi.org/10.6084/m9.figshare.14811804 [23].

2.10. Statistical analysis

EP peak amplitudes were not normally distributed and, consequently, log-transformed prior to analysis. Some outliers were excluded

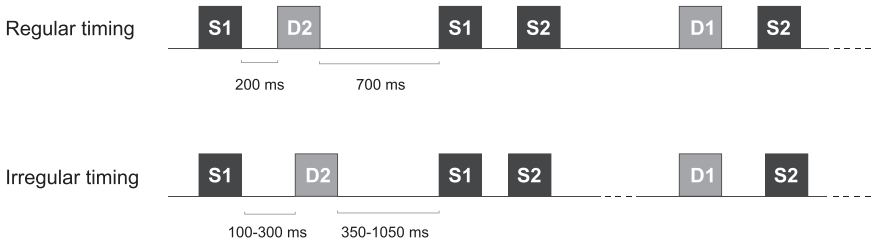

Fig. 1. Exemplary sequence of standard and deviant tones, with interval durations for the regular and irregular timing conditions. The respective interval range is indicated for the irregular sequence. S = standard tone (600 Hz), D = deviant tone (660 Hz).

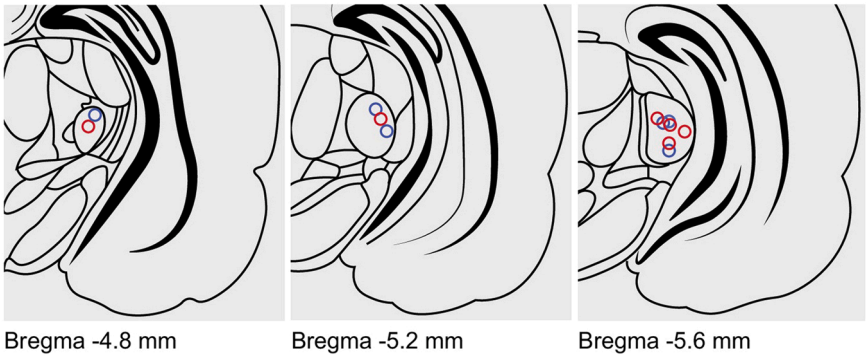

Fig. 2. Schematic representation of all local field potential (LFP) electrode locations in the medial geniculate body (MGB). Two subjects (electrode locations not in figure) were excluded from analysis due to incorrect positioning and hardware failure. Noise exposed in red, unexposed control in blue.
Adopted from van Zwieten et al., 2021[17].

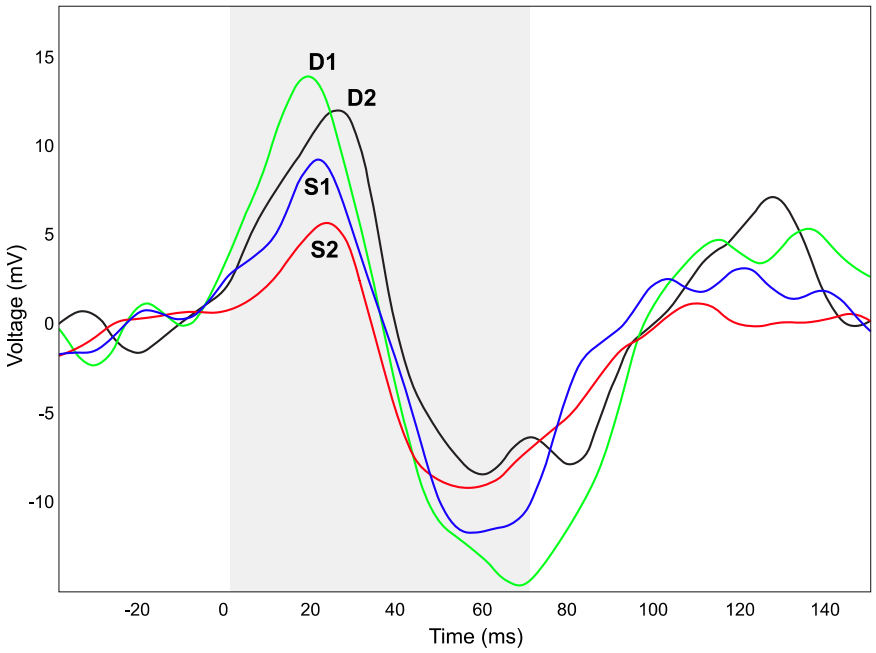

Fig. 3. Representative mean evoked potentials from a control rat at pre-HFS phase during the regular timing condition. The auditory stimuli (D1, D2, S1, S2) lead to different peak amplitudes. The gray area indicates 70 ms stimulus duration.

based on visual inspection, specifically values outside the range + /− 1 (logarithmic). The log-transformed amplitudes were fitted to a *linear mixed-effects model (LMEM)* with the following fixed factors: Stimulus Type (2; Standard, Deviant), Position (2; First, Second), Timing (2; Regular, Irregular), Noise-exposure (2; Unexposed, Noise-exposed), HFS phase (2; Pre-HFS, Post-HFS), and the following random effects: RatID, Block, and Trial, where Trial was nested in Block, and Block was nested in RatID. Models were selected based on the lowest *Akaike's Information Criteria (AIC)* value when including the interaction term or only main effects between the fixed factors. Data were analyzed using the *lmer* function in the *lme4* package [24] for R software [25]. Effect sizes were measured as generalized *eta squared* (η^2_G) using the *aov_car* function in the *afex* package [26]. Pairwise comparisons were calculated as *Tukey's Honestly Significant Difference (HSD)* using the *multcomp* package [27]. To determine evidence for the null hypothesis, *Bayes Factor t*-tests were performed using the *ttestBF* function of the *BayesFactor* package [28]. Following Jeffreys [29] *Bayes Factor* values were interpreted as follows: values around 1 indicate no evidence, 1–3 indicate anecdotal evidence, 3–10 indicate moderate evidence, 10–30 indicate strong evidence, 30–100 indicate very strong evidence, and greater than 100 indicates extreme evidence.

3. Results

3.1. Gap prepulse inhibition of acoustic startles

The effect of noise exposure was assessed through GPIAS where the gap/no-gap ratios increased following noise exposure for 20 kHz and 16 kHz ($p < 0.01$) but not 10 kHz ($p = 0.21$) background sound; unexposed rats showed no significant changes ($p > 0.14$). Group level effects are presented as the experimental setup did not allow conclusions at the individual level. The obtained GPIAS results are comparable to previous studies using this setup, indicating presence of tinnitus-like behavior in the noise-exposed group [19,30].

3.2. Evoked potentials

The peak EP amplitude up to 70 ms after tone onset was used to perform the analysis. The *LMEM* with the best model fit contained main effects of Stimulus Type and Position, and interactions between the

other variables. Fig. 4 shows full factorial results with all possible combinations. To facilitate the interpretation of the main effects and interactions, Fig. 5 shows the outcomes for each main effect and interaction. We present the significant main effects that were not implicated in interactions in Figs. 5A and 5B, and the significant interactions between Noise, HFS, and Timing in Fig. 5 C.

There were significant main effects of Stimulus Type [F (1, 37256) = 4.20, $p = 0.04$), η^2_G= 0.001; Fig. 5 A], Position [F (1, 37255) = 10.86, $p < 0.001$; Fig. 5B], η^2_G= 0.001], and Timing [F (1, 37256) = 12.79, $p < 0.001$), η^2_G= 0.002]. Further, there was a significant two-way interaction between Noise and Timing [F (1, 37256) = 21.83, $p < 0.001$), η^2_G= 0.003], and a significant three-way interaction between HFS phase, Timing, and Noise [F (1, 37256) = 12.67, $p < 0.001$), η^2_G = 0.002]. No other main effects or interactions reached significance ($p > 0.21$). As shown in Fig. 5 A, deviant tones elicited significantly larger amplitudes than standard tones, supporting the hypothesis that habituation occurs for stimuli that are more predictable and occur more often. Similarly, amplitudes were smaller for the second stimulus in a pair compared to the first, suggesting that auditory SG occurs for the second stimulus in a pair of temporally proximal tones (Fig. 5B).

Pairwise comparisons investigating the three-way interaction between HFS phase, Timing, and Noise indicated that only the noise-exposed rats displayed a significant amplitude decrease, comparing the pre-HFS phase to the post-HFS phase, in both timing conditions ($p < 0.001$). In contrast, the control group did not show significant changes ($p > 0.14$; Fig. 5 C). The control group showed significantly larger peak amplitudes for irregular timing compared to regular timing both pre- and post-HFS ($p < 0.001$). The noise-exposed group, however, did not show significant differences between timing conditions pre- or post-HFS ($p > 0.20$). Finally, amplitudes were significantly larger for the noise-exposed group compared to the control group in both timing conditions in the pre-HFS phase ($p < 0.007$). The noise-exposed group only showed larger amplitudes than controls for the post-HFS phase in the regular timing condition ($p = 0.006$) but not the irregular timing condition ($p = 0.47$). To test the hypothesis that HFS restores sensitivity in noise-exposed rats to levels similar to or better than that of controls, we performed a one-tailed Bayes factor t test, which indicated extreme evidence that amplitudes were not larger for noise-exposed rats compared to controls post-HFS in the irregular timing condition (*BF01*=151.4 ± 0.01%). For clarity we summarized the results in appendix 1.

4. Discussion

The current study investigated SG in the MGB of the thalamus in unexposed and noise-exposed animals and the effects of HFS on SG. The results indicate adaptive filtering of auditory signals at the MGB level, reflecting the predictability of two stimulus characteristics (pitch and position in a pair). Further, larger EP amplitudes were found in noise-exposed animals in most conditions. HFS of the MGB resulted in decreased EP amplitudes in noise-exposed animals only. However, HFS did not change SG based on regular stimulus timing back to normal in noise-exposed animals. An overview and roundup of main findings is presented in Table 1.

4.1. Auditory filtering capacities of MGB

Previous studies had investigated stimulus-specific adaptation in the MGB [31,32]. The current findings confirm and extend these previous results regarding the filtering capacities of the MGB. Responses to deviant tones were significantly enhanced compared to standard tones across all conditions (Fig. 5 A). Furthermore, responses to the second tone of a pair were significantly smaller than those to the first tone (Fig. 5B). In control animals, EP amplitudes in the irregular timing condition were significantly larger than in the regular timing condition (Fig. 5 C). The larger EP amplitude response to a deviant tone is comparable to a mismatch response seen in human EEG recordings [33]. A previous study in anesthetized rats showed an enhanced EP response to deviant tones across different sleep states (including REM and non-REM sleep) in the auditory cortex [34]. Other studies reported the sensitivity of EPs to deviant tones in primary auditory cortex [35] and subcortical structures [31]. Hence, filtering occurs either at the MGB or even at preceding processing levels. Considering the current MGB level results, these might reflect such earlier responses. However, this observed adaptive filtering involves the position, pitch, and temporal regularity of the tones.

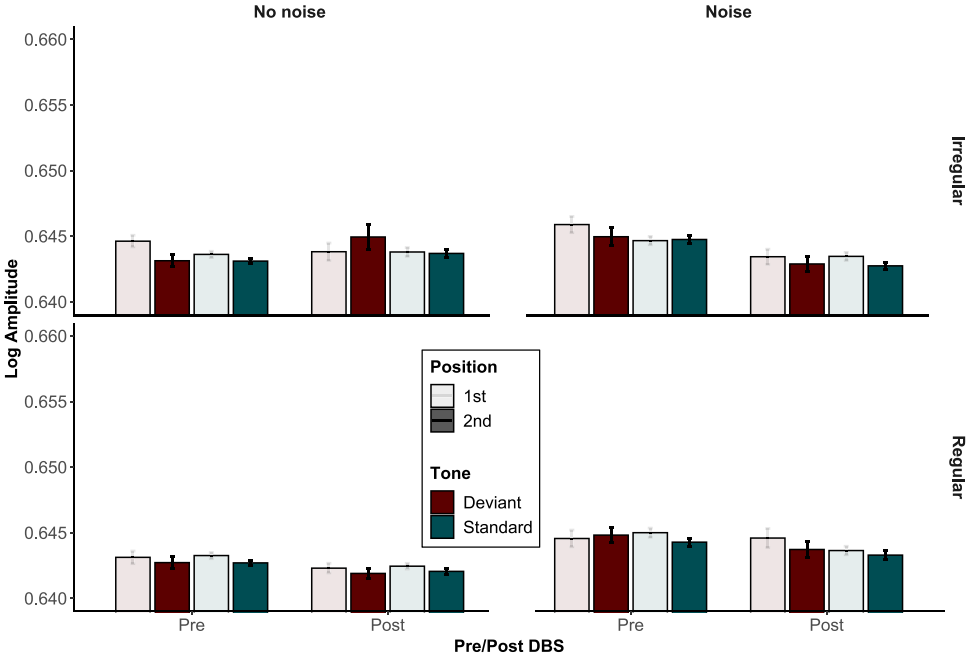

Fig. 4. Full factorial results with all possible combinations.

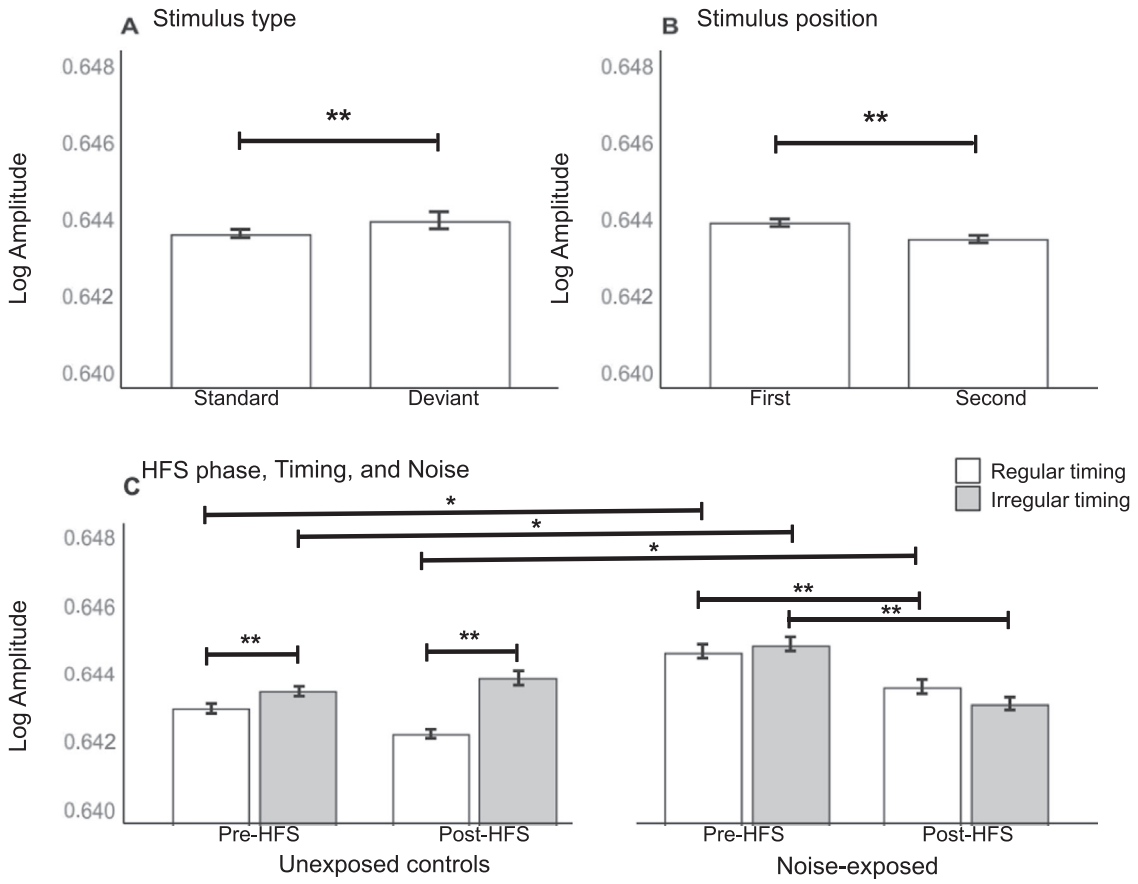

Fig. 5. Main effects and interactions. A and B show the main effects for pitch or tone position across all conditions, including unexposed and noise-exposed groups, pre- and post-HFS. These effects did not show interactions. Means (+/- standard error of the means) of EP amplitudes depict the main effects of Stimulus type (A) and Stimulus position (B). C shows the three-way interaction between Timing (temporal regularity), HFS Phase, and Noise. Pairwise comparisons exploring this interaction indicated that only the noise-exposed rats showed a significant decrease in amplitude, comparing the Pre-HFS phase to the Post-HFS phase, in both timing conditions ($p < 0.001$). In contrast, the control group did not show significant changes. * : $p < 0.05$, * *: $p < 0.005$. Abbreviations: EP evoked potentials, HFS high frequency stimulation. Full summary statistics are available in Appendix 1.

Table 1
The table aims to answer two yes-no questions:

A: Does sensory gating based on a particular factor (pitch, pair position or temporal regularity) occur in a particular condition (control versus noise-exposed groups and before or after HFS)?.

	control		noise-exposed	
	before HFS	after HFS	before HFS	after HFS
pitch	✓	✓	✓	✓
pair position	✓	✓	✓	✓
temporal regularity	✓	✓	×	×

✓: Yes. ×: no.

B: Does a particular condition (noise exposure or HFS) influence sensory gating based on a particular factor (pitch, pair position or temporal regularity) ?

	noise-exposure	HFS
pitch	×	×
pair position	×	×
temporal regularity	✓[1]	×[2]

✓: Yes. ×: no.

1: negatively influences gating (disturbs sensory gating).
2: fails to restore the disturbed gating back to normal.
Note: To clarify the terminology, depending on the context throughout the manuscript, these phrases are used interchangeably: 'pitch' as stimulus type, 'pair position' as repetition or binary grouping, and 'temporal regularity' as timing.

4.2. Sensory gating after noise exposure

The assessment of noise-exposure effects using GPIAS confirmed that gap/no gap ratios were increased in the noise-exposed group [17]. The main effects of pitch and position in a pair across all conditions (unexposed and noise-exposed groups, pre- and post-HFS) could imply that noise exposure or HFS have no effect on the SG capacities of MGB regarding pitch and pair position. However, only unexposed control rats exhibited higher MGB amplitude responses for irregular than regular timing, both before and after HFS. This indicates that adaptive timing mechanisms (e.g., entrainment of neuronal oscillations) may already operate or influence auditory processing at the subcortical level. That noise-exposed animals did not display differences between regular or irregular timing conditions before or after HFS might be due to aberrant neurophysiological activity of individual MGB neurons. At the neuronal population level, this might be reflected by the inability to distinguish regular and irregular timing in the noise-exposed animals, and consequently failure to benefit from temporal predictability in a regular stimulus sequence to a similar degree as previously observed in humans [16]. Thus, MGB responses in noise-exposed animals fail to distinguish temporal regularity in auditory stimulus sequences. These results suggest that entrainment involves SG and low-level sensory processing but fail to indicate that it can be restored via MGB HFS. Entrainment to regular stimulus timing might therefore rely on bottom-up processes that can be perturbed by dysfunctional thalamic SG. This corroborates similar findings of dysfunctional sensory gating based on stimulus regularity in patients with basal ganglia lesions, potentially indicating

recruitment of a wider brain network [5,36].

We further found a significantly larger EP amplitude in noise-exposed than in control animals across all conditions except for the irregular stimulation group in the post-HFS phase. This might be due to the increased synchronization of neural firing in subcortical auditory centers in noise-exposed animals [37]. MGB neurons in noise-exposed animals might become more sensitive to external stimulation, also known as neuronal hypersensitivity. Various studies confirmed alterations in burst patterns in the MGB of rats with acoustic trauma that might affect the EP amplitudes of animals that show tinnitus-like behavior [38,39]. Recent evidence points to tinnitus as a condition where impaired SG plays a significant role. Correlations between tinnitus severity and decreased SG via the Pa component of cortical auditory evoked potentials and an increased SG via the N1 component have been described in humans [40]. SG is also influenced by state changes of the organism [4]. For example, a case-control study showed that SG relates to behavioral aspects of tinnitus as assessed with the tinnitus handicap and sensory gating inventories [41]. The undisputed link between tinnitus, hearing loss, and hyperacusis is a major challenge in the field of tinnitus research [42]. These symptoms often co-exist and share similar neuropathologic pathways. It has been suggested that there is a certain degree of hearing loss in almost all tinnitus cases, which is sometimes undetectable by audiograms or auditory brainstem responses [43,44]. Previous studies show that only a fraction of rats exposed to loud sounds develop tinnitus-like deficits [45]. The current behavioral setup did not allow differentiation of tinnitus positive or negative animals at an individual level [17]. Therefore, we link the EP results to noise trauma and not necessarily to tinnitus. This setup also did not allow correcting for hyperacusis and hearing loss on SG. Noise exposure is known to induce (temporary) hearing loss and hyperacusis. Hyperacusis often coexists with tinnitus and both conditions might be a result of increased synchronized electrophysiological activity that could lead to elevated auditory EP responses [42]. For these reasons, it remains speculative whether elevated EP amplitudes in the noise-exposed animal group are related to tinnitus or other aberrancies. The use of anesthesia at the time of noise exposure is another potential limitation of the current study. Follow-up studies are therefore needed to disentangle effects of tinnitus, hyperacusis, cochlear trauma, and hearing loss on thalamic SG functions. The respective experimental designs should enable separating individual animals that show hyperacusis, tinnitus-like behavior and/or hearing loss or a combination of these.

4.3. *Effect of high-frequency stimulation on evoked potentials*

DBS has recently emerged as a promising treatment option for tinnitus [15,46,47]. HFS applied to the auditory pathway has been shown to effectively reduce tinnitus-like behavior in rats [18,19,30,48,49]. This has informed and allowed initiating a first MGB DBS study in humans to assess the safety and effect of MGB DBS [50]. Therefore, it is of high interest if HFS of the MGB modulates SG. The three-way interaction between HFS phase, Timing, and Noise showed a significantly suppressing effect of HFS on EP amplitudes in noise-exposed animals, but not in unexposed controls (Fig. 5 C). Currently, disrupted signaling as a working mechanism of HFS is the key premise of most hypotheses regarding the restoration of the neuronal physiology in a number of different pathologies [51]. HFS induces action potentials and causes neurons to lose their ability to transmit information [52]. This way, pathological oscillations can be reduced or even eliminated, and neural firing patterns can be normalized [53,54]. The current findings lend preliminary support for this hypothesis. EP hyperactivity, a potential neural correlate of tinnitus [38] was normalized after HFS, except for stimulus-timing effects. This normalization might also result from a disruption of pathological oscillations in the thalamocortical loop, known as thalamocortical dysrhythmia [13]. This effect was not found in non-exposed control animals. These results may indicate the specific influence of HFS on aberrant neuronal firing. However, HFS could not restore SG with respect to temporal regularity in noise exposed animals.

Most electrodes were positioned within the ventral portion of the MGB. The stimulus amplitude used has a current density that is within the normal range in rat studies [55,56]. However, we cannot exclude the possibility that current spreads to the dorsal and medial portions of the MGB. This could have been the case in those animals where electrodes were placed at the border of the ventral and dorsal MGB. While the main effect of HFS was expected to engage the ventral portion of the MGB. One should also consider the differences between a rat model and humans as such differences impact the translation of basic research results to the clinic. A major difference is the substantially lower number of interneurons in rats [9]. The effects of HFS (on SG) might thus be different in humans.

5. Conclusions

The results of the current study support the notion that the MGB acts as a filtering relay station in auditory stimulus processing. This includes filtering based on pitch, position, and temporal regularity of input. Auditory responses in noise-exposed animals did not distinguish temporal stimulus regularity. Furthermore, they showed an overall increase in EP activity in the MGB compared to unexposed controls. HFS can suppress the increased EP amplitudes towards normal levels, and thus can potentially ameliorate manifestations of the noise trauma. However, HFS did not restore SG for temporal regularity in the noise-exposed animals.

CRediT authorship contribution statement

Aryo Zare: Formal analysis, Writing – original draft, Writing – review & editing, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Gusta van Zwieten:** Methodology, Writing – review & editing. **Sonja A. Kotz:** Conceptualization, Validation, Writing – review & editing, Supervision. **Yasin Temel:** Resources, Supervision. **Faris Almasabi:** Methodology. **Benjamin G. Schultz:** Writing – review & editing, Formal analysis. **Michael Schwartze:** Conceptualization,Validation, Writing – review & editing, Supervision. **Marcus L.F. Janssen:** Conceptualization, Project administration, Resources, Supervision, Validation, Writing - review & editing.

Declaration of Competing interest

No conflicts of interest to report.

Data Availability

The raw data is available at figshare: http://doi.org/10.6084/m9.figshare.14811804.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.bbr.2023.114498.

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