Title: Stimulus-specific processing of auditory deviants and repetitive stimulus sequences in the human brainstem

Abbreviated title: Deviance detection in human ABRs

Authors: Johannes Wetekam[1,*], Nell Gotta[1], Luciana López-Jury[2], Julio Hechavarría[1,3,□,*], Manfred Kössl[1,□]

1. Department of Neurobiology and Biological Sensors
   Institute of Cell Biology and Neuroscience, Goethe University
   Max-von-Laue-Str. 13, 60438 Frankfurt am Main, Germany
2. Max Planck Institute for Brain Research
   Max-von-Laue-Str. 4, 60438 Frankfurt am Main, Germany
3. Ernst Strüngmann Institute (ESI) for Neuroscience
   Deutschordenstraße 46, 60528 Frankfurt am Main, Germany

□ Shared last authorship

*Corresponding authors: Johannes Wetekam: wetekam@bio.uni-frankfurt.de, Julio Hechavarría: julio.hechavarria@esi-frankfurt.de

Number of pages: 26, Number of figures: 3, Number of supplementary figures: 1, Number of words Abstract: 247, Number of words Introduction: 672, Number of words Results: 962, Number of words Discussion: 1094

Acknowledgements

This work was funded by the Deutsche Forschungsgemeinschaft [KO 987/14-1].

Conflict of Interest

The authors declare no competing interests.

Abstract

Detecting unexpected events, also known as deviant stimuli, is essential for survival. Research on the neural mechanisms that underlie deviance detection has gained momentum in the last decades. One major discovery from this research is that deviance detection is not limited to high-order cortical areas but is also present in evolutionary older subcortical structures. However, most of the research studying subcortical deviance detection has so far been limited to animal experiments, with studies in humans mostly focussing on cortical effects. It is therefore still mostly unknown how and to what extend deviance detection manifests in the human brainstem. Here, we aimed to tackle this issue by measuring auditory brainstem responses (ABRs) to investigate the earliest correlates of deviance detection in the human brain. We demonstrate that the human brainstem is sensitive to auditory deviants and that the measured effects depend on the carrier frequency of the stimuli. We found the strongest and fastest deviance detection responses when low-frequency chirps occurred as deviants in a context of high-frequency stimuli. A second experiment revealed that the larger deviant ABR amplitudes can be explained by repetition suppression effects of the more frequent standard stimulus. On the contrary, high-frequency chirps did not elicit deviance detection and caused repetition enhancement instead of suppression. These results show that the human auditory brainstem is sensitive to the stimulus' probability of occurrence and can use different, stimulus-specific processing mechanisms. Our results reveal a previously unknown complexity of advanced auditory signal processing in the human brainstem.

Keywords: stimulus-specific adaptation, mismatch negativity, ABR, predictive coding, repetition suppression, repetition enhancement

1. Introduction

The ability of the brain to detect unexpected inputs in an otherwise repetitive acoustic environment is known as auditory deviance detection and has been subject to intensive research in the last decades. During this time, studies with human subjects as well as animals were able to characterise deviance detection with great detail (Escera et al., 2014; Carbajal and Malmierca, 2018; Shiramatsu and Takahashi, 2021) and human and animal research complemented each other. Nevertheless, to this date, a key difference between human and animal research is the brain areas in which deviance detection has been studied. On one hand, given the difficulties to record brain activity of subcortical structures in humans, deviance detection research has so far been mostly focused on the cortex, most prominently in the form of mismatch negativity (MMN) (Näätänen et al., 1978, 2007; Winkler, 2007; Fitzgerald and Todd, 2020). And even though recent functional magnetic resonance imaging (fMRI) studies could demonstrate that the inferior colliculus (IC) is involved in probability encoding in humans (Cacciaglia et al., 2015; Tabas et al., 2020; Tabas and Kriegstein, 2024), how and to what extent deviance detection manifests in subthalamic stations of the human auditory pathway remains poorly understood. Conversely, animal experiments allow a much more flexible investigation of deviance detection effects in different cortical and subcortical brain areas (Kraus et al., 1994a; Ulanovsky et al., 2003, 2004; Parras et al., 2017; Shiramatsu and Takahashi, 2021). This led to ample animal-data regarding deviance detection in non-cortical brain regions, both at single-unit (Malmierca et al., 2009; Antunes et al., 2010; Zhao et al., 2011) and population level (Kraus et al., 1994b; Patel et al., 2012; Duque et al., 2018; Wetekam et al., 2022, 2024). In the current study, we aim to narrow the gap of knowledge regarding subcortical deviance detection between humans and non-human animal models. To achieve this, we recorded auditory brainstem responses (ABRs) to low- and high-frequency chirp stimuli (Fig. 1a) in combination with an oddball paradigm (Fig. 1b). This allowed us to investigate early correlates of deviance detection in the auditory brainstem of humans.

It has been suggested that deviance detection can be caused by two separate neural mechanisms, namely repetition suppression and deviant enhancement (also known as prediction error) (Parras et al., 2017; Carbajal and Malmierca, 2018). On one hand, deviant enhancement describes an increased neural response to a rare stimulus that is unexpectedly perceived during a repetitive context. Importantly, it is not the rarity of the stimulus per se that is causing this increment of response strength, but the fact that it interrupts an otherwise repetitive stream of 'standard' inputs. On the other hand, repetition suppression reflects a reduction of neural responsiveness to a particular stimulus caused by the repetitive perception of that stimulus (Condon and Weinberger, 1991; Grill-Spector et al., 2006; Auksztulewicz and Friston, 2016). Evidence from previous studies suggests that the repetition suppression component decreases along the ascending auditory pathway, while the deviant enhancement component increases (Parras et al., 2017; Carbajal and Malmierca, 2018). Based on this, we hypothesized that in the lowest stations of the auditory brain, i.e. the brainstem, the dominant mechanism driving deviance detection is repetition suppression. Accordingly, in a second experiment, we examined repetition effects on the ABR by presenting the same stimuli used in the oddball paradigm (Fig. 1a), but this time in a repetitive stimulation sequence (Fig. 1c).

The results we obtained showed stimulus-specific effects regarding both the strength of deviance detection and repetition suppression / enhancement in the human brainstem. Low-frequency chirps produced the hypothesized strong novelty responses when they occurred rarely (i.e. as deviants) and elicited repetition suppression when they occurred repetitively over time. Conversely, the high-frequency chirp did not elicit deviance detection in the brainstem and instead caused a repetition enhancement effect when presented repetitively, in line with recent evidence for repetition enhancement in the mouse IC (Lesicko et al., 2022). Taken together, our results indicate that the human brainstem is sensitive to auditory deviants but also that it responds to infrequent and frequent stimuli in a frequency-specific manner.

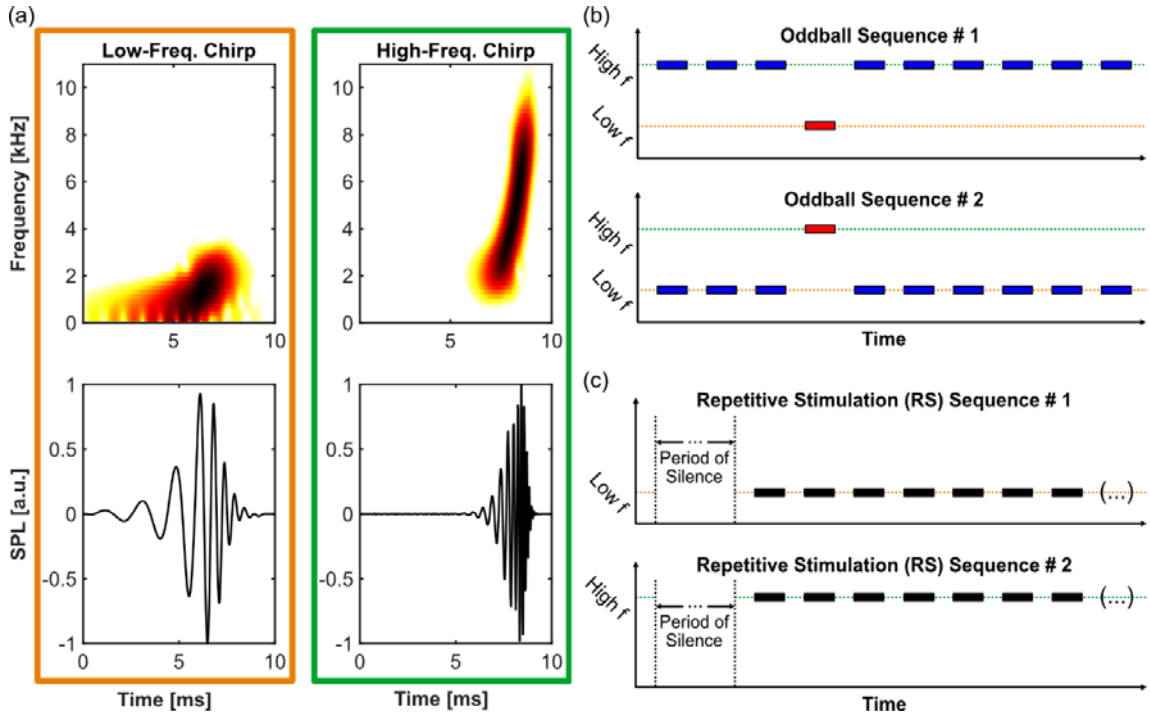

Figure 1: Used stimuli and stimulation protocols. (a) Spectrograms (top) and oscillograms (bottom) of a low-frequency chirp (orange frame) and a high-frequency chirp (green frame) that were used as stimuli in this study. (b) Schematic representation of the oddball paradigm; blue: standard, red: deviant. (c) Schematic representation of the repetitive stimulation sequence. Periods of silence and trains of repetitive stimulation were presented to the subject multiple times, in an alternating pattern.

2. Material and Methods

Participants

ABRs of 32 participants (12 males, 20 females), aged between 20 and 40 years (mean age = 26.4 years) and with normal hearing, were recorded for the current study. Informed consent was obtained from each participant before the recording and all subjects received monetary compensation for their participation. The study was approved by the ethics review board of Goethe University Frankfurt. Before the recording started, a two-alternative forced choice test was used to determine the participant's individual hearing thresholds for the stimuli used during the ABR recording.

Stimulation and recording procedure

Two artificially generated chirps, differing in their frequency composition, were used as stimuli in this study (Fig. 1a). The chirps were designed to maximise ABR amplitudes by compensating for the cochlear traveling wave delay (Fobel and Dau, 2004; Elberling et al., 2007; Elberling and Don, 2008), based on the latency-frequency function of narrowband ABR-data obtained by Don et al. 2005 (Don et al., 2005). While these chirp stimuli evoke a large wave V which increases the overall ABR amplitude, earlier ABR components (waves I-IV) are usually less pronounced compared to click-evoked ABRs. The stimuli were created with a logarithmic frequency distribution, where the low-frequency chirp ranged from 500 Hz to 2 kHz and the high-frequency chirp from 2 kHz to 8 kHz. The signals were digitally generated in custom-written Matlab (MathWorks) scripts, D/A converted by a 192 kHz Fireface UC soundcard (RME Audio) and sent to an ER-3C earphone (10 Ω, Etymotic Research), inserted into the participant's right ear.

During the first experiment, stimuli were presented to the participants in two pseudo-randomly arranged oddball sequences. In the first sequence, the high-frequency chirp was presented as high-probability (90 %, 9000 repetitions) standard while the low-frequency chirp

was presented as low-probability (10 %, 1000 repetitions) deviant. Subsequently, the same sequence was presented again, but this time with swapped roles of the deviant and standard stimulus (Fig. 1b). This resulted in two responses per stimulus, perceived as standard and as deviant, respectively. The recording was repeated with three different stimulus presentation rates of 40 Hz, 33 Hz and 20 Hz. In experiment 2, the same chirp stimuli were presented again, but this time in a repetitive stimulation sequence (Fig. 1b) instead of in an oddball paradigm. Here, only one chirp type was presented during a sequence, arranged in trains of 10 stimuli. In total, 1000 trains of a given chirp were presented to the subject, where each train was separated from the next by a period of silence. These silent periods had a duration of either 255 ms or 300 ms and gave the brainstem the chance to recover from possible repetition effects that may have occurred during the stimulation train. The recording was performed with two different stimulus presentation rates within the train, 40 Hz and 20 Hz, representing the fastest and the slowest stimulus presentation rates of experiment 1.

ABRs were differentially recoded by two Ag-AgCl electrodes, attached to the participant's skin at the vertex (Cz, active) and the ipsilateral earlobe (reference). Additionally, a third electrode at the forehead provided the ground. Impedance was reduced to < 10 kΩ and the data was collected at a sampling rate of 10 kHz. The recording took place in an electrically and sound-insulated booth where the participants were sitting comfortably in a reclining chair. They were instructed to relax, keep their eyes closed and move not more than necessary during the recording.

Data processing and statistical evaluation

All data analysis and statistical evaluation was conducted in Matlab. The recorded data was bandpass filtered with a 50-1500 Hz Butterworth filter (4th order). The processing and analysis differed between the data of experiment 1 and 2 and both procedures will be explained individually in the following. *Experiment 1 (oddball data)*: For baseline correction,

the mean response amplitude of each trial was calculated in a 1 ms time window right before ABR onset. To ensure an objective comparison between the responses to both chirps, the end of this time window was set to the time point of maximal stimulus amplitude. This was approximately 6.5 ms and 3 ms after the onset of the low- and high-frequency chirp, respectively (Fig. 1a). The mean amplitude value in this window was subsequently subtracted from the whole trial which results in a mean pre-ABR activity of 0 µV. For averaging, only those standard trials that were followed by a deviant trial were considered. Likewise, only deviants that were preceded by a standard were included in the analysis. This method allowed us to use the same number of deviant and standard trials to calculate the average response for a given participant (here between 851 and 914 trials). *Experiment 2 (repetition data)*: The same time window as in experiment 1 was used for baseline correction, but instead of a single response, one trial contained the responses to a train of 10 stimuli plus the subsequent period of silence. Averaging was performed across all trials (n = 1000), resulting in a subject-average that contains all ABRs to the 10 stimuli presented in a train. This approach allowed the evaluation of stimulus repetition effects on the ABRs within the stimulation train. For both experiments, all trials were corrected for the sound travelling delay caused by the distance between speaker and ear (26 cm). In each time-voltage graph, the x-axis value of 0 ms represents the time point when the maximal stimulus amplitude reached the ear. Stimulus amplitude peak was chosen as reference value instead of stimulus onset because of the relatively long rise times of the used chirp stimuli, compared to the commonly used click stimulus.

To evaluate the response strength, the peak-to-peak amplitude within a defined time window that contained the relevant components of the ABR was calculated. The time window ranged from 0 ms to 10 ms for the low-frequency chirp responses and from 0 ms to 8 ms for the high-frequency chirp responses. Similarly, to evaluate the timing of ABR peak V, the latency of the

maximum response value within another time window that only covered wave V was measured. This time window ranged from 5.5 ms to 9 ms for the low-frequency chirp responses and from 4.5 to 8 ms for the high-frequency chirp responses. Analysis was focussed on peak V because earlier ABR waves (I-IV) were not or only marginally represented in the chirp-evoked ABRs of this study. To compare ABR amplitudes and peak V latencies between deviant and standard response, paired two-tailed t-tests were used in combination with Cohen's *d* as a measure of effect size (Cohen, 1988). Repetition effects on ABR amplitude within the trains of experiment 2 were evaluated by fitting linear regression models to the measured data. In this case, the obtained p-value describes whether the number of stimulus repetition is associated with a change in ABR amplitude or peak V latency, respectively. The R^2-value reflects how well the regression model fits the observed data. For the linear regression analysis, only the responses to stimulus 1-9 of each train were considered since in many subjects the last (tenth) ABR was altered by a train-offset response. The data and code used for this study are freely available on G-Node (DOI: 10.12751/g-node.vjcry8).

3. Results

ABR deviance detection depends on the stimulus frequency and presentation rate

To investigate effects of deviance detection in the brainstem, ABRs were recorded to a low- and a high-frequency chirp stimulus, presented in an oddball paradigm (Fig. 1b). Since previous studies with animals revealed that subcortical deviance detection is sensitive to the stimulus presentation rate (Malmierca et al., 2009; Antunes et al., 2010; Zhao et al., 2011; Ayala and Malmierca, 2012; Patel et al., 2012), three different rates were tested: The fastest rate tested, 40 Hz, represents a commonly used stimulation rate in ABR research. Two slower rates of 33 Hz and 20 Hz were used to test whether potential effects of deviance detection are correlated with the stimulation rate. To evaluate differences in response strength between deviant and standard response to a given stimulus, the peak-to-peak amplitude within a defined time window was compared between both conditions (deviant and standard). It should be noted that the ABR shape elicited by the used chirp stimuli differs from typical click-evoked ABRs. While wave V has a large magnitude, the earlier waves I-IV are not clearly distinguishable. This makes wave V, which represents IC activity, the main contributor of all effects described in the following. The fastest repetition rate of 40 Hz resulted in a significantly increased deviant compared to standard response when the low-frequency chirp was the stimulus ($t = 2.4$, $p = 2.7 * 10^{-2}$), while no significant difference in response strength was observed for the high-frequency chirp (Fig. 2a). The same result was obtained with a repetition rate of 33 Hz. Again, only the low-frequency chirp elicited a significantly increased deviant – compared to standard – response ($t = 2.7$, $p = 1.4 * 10^{-2}$, Fig. 2b). In contrast to this, the slowest repetition rate of 20 Hz did not result in significantly different deviant versus standard ABR amplitudes for either of the tested stimuli (Fig. 2c). This demonstrates that the observed differences between deviant and standard response strength depend on the stimulation rate, where the effect decays if the repetition rate becomes too slow. Interestingly,

although the ABR amplitude to the high-frequency stimulus was never significantly different between deviant and standard, there was a trend towards an increased standard compared to deviant response. This suggests that different mechanisms modify the response strength of ABRs and that their effect is dependent on the perceived stimulus frequency. This observation will be investigated in more detail in experiment 2.

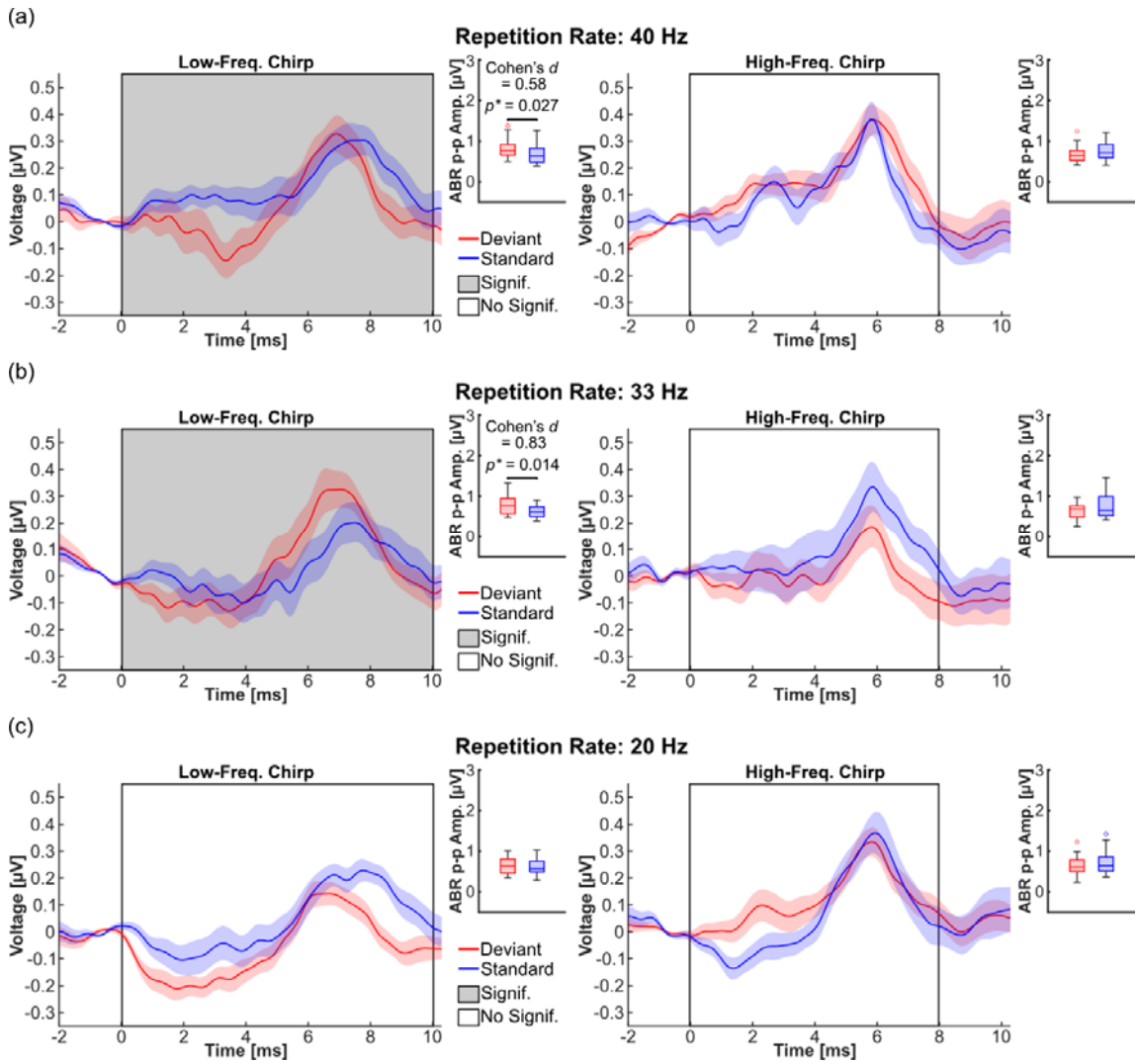

Figure 2: ABR deviance detection depends on the stimulus frequency and presentation rate (n = 20 subjects). (a) Grand averages of ABRs to a low- (left) and high-frequency (right) chirp, presented as deviant (red) and standard (blue). The stimulus presentation rate was 40 Hz. The boxes framing the responses represent the time window taken for peak-to-peak amplitude calculation, covering the whole ABR response (0-10 ms or 0-8 ms post stimulus peak, for the low- and high-frequency chirp, respectively). A grey box colour indicates a significant difference between deviant and standard response, a white colour indicates no significant difference. Shaded areas around the ABRs depict the standard error of the mean. The insets on the right to each response graph show the peak-to-peak ABR amplitudes calculated for each subject and condition. (b) As in (a) but the stimulus presentation rate was 33 Hz. (c) As in (a) but the stimulus presentation rate was 20 Hz.

Effects of deviance detection on the ABR peak V latency

Beside the response strength, ABR peak timing is another parameter that is known to be sensitive to certain stimulation parameters (Eggermont and Don, 1980; Picton et al., 1981; Picton, 2010). Additionally, it has been shown that the perception of auditory deviants can reduce the response latency of individual neurons in the inferior colliculus (IC) (Malmierca et al., 2009; Zhao et al., 2011; Ayala and Malmierca, 2012; Duque et al., 2012). Therefore, we tested whether the stimulus probability affected the latency of the most prominent ABR component, peak V, which reflects IC activity. Like the response strength, deviance detection-related effects on peak V latency were dependent on the stimulus frequency. At all tested repetition rates, the low-frequency chirp elicited significantly shorter peak V latencies when it was perceived as a deviant compared to when it was a standard (Supp. Fig. 1). The largest peak V latency difference was at 40 Hz, where the deviant response peaked on average 0.85 ms before the standard response ($t = 3.7$, $p = 1.5 * 10^{-3}$). This latency difference decreased gradually when the stimulus repetition rate was reduced. At 33 Hz, the deviant response peaked 0.68 ms earlier than the standard ($t = 2.8$, $p = 1.1 * 10^{-2}$), and at 20 Hz the average difference was 0.55 ms ($t = 3.9$, $p = 8.9 * 10^{-4}$). Conversely, no significant latency differences were observed for the high-frequency chirp, at any of the tested stimulus presentation rates. In line with the ABR amplitude data, these results indicate a strong stimulus specificity of deviance detection in the brainstem.

Low-frequency chirps elicit repetition suppression, while high-frequency chirps evoke repetition enhancement of ABRs

The data obtained in the oddball paradigm (experiment 1) revealed that different stimulus-specific effects can act on the ABR amplitude (Fig. 2). On one hand, low-frequency chirps elicited larger deviant compared to standard responses, in line with many previous observations of deviance detection in higher brain areas. On the other hand, ABRs to high-frequency chirps tended to be larger when the stimulus was a standard instead of a deviant. Two possible neural mechanisms that could explain the observed effects are repetition suppression and repetition enhancement, provided that they become active in a stimulus-specific manner. To test this hypothesis, we performed a second experiment where repetition effects of the previously used stimuli on ABRs were investigated. When the low-frequency chirp was presented at a 40 Hz repetition rate, there was a significant reduction of peak-to-peak response amplitude with increasing stimulus repetition number (Fig 3a, left). This demonstrates the presence of repetition suppression modifying the low-frequency chirp responses. In contrast, a significant increment of ABR amplitude over stimulus repetition was obtained when the high-frequency chirp was the stimulus (Fig. 3a, right). Here, ABR amplitudes were affected by repetition enhancement instead of suppression. At the lower repetition rate of 20 Hz, the repetition suppression effect caused by the low-frequency chirp disappeared (Fig. 3b, left), whereas the repetition enhancement of the high-frequency chirp responses remained virtually unchanged (Fig. 3b, right). These observations are in accordance with those of experiment 1 (Fig. 2) and suggest that the differences between deviant and standard response strengths are, at least to a large extend, caused by the underlying mechanisms of repetition suppression (in case of the low-frequency chirp responses) and repetition enhancement (in case of the high-frequency chirp responses).

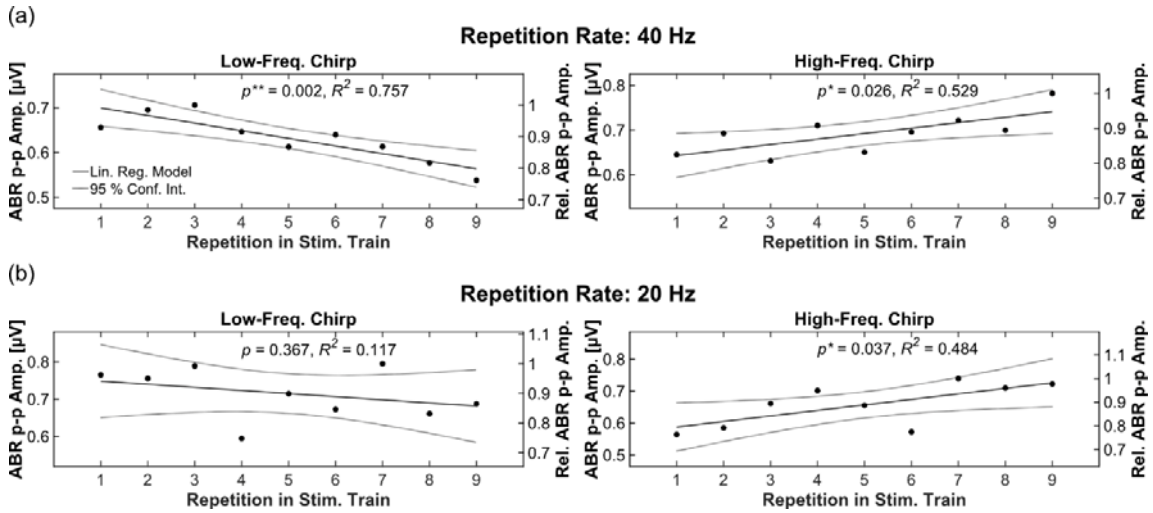

Figure 3: Low-frequency chirps elicit repetition suppression, while high-frequency chirps evoke repetition enhancement of ABRs. (a) Peak-to-peak amplitudes of ABRs to repetitively presented stimuli. The stimulus presentation rate was 40 Hz (n = 9 subjects). Peak-to-peak amplitudes were calculated for the same time windows as in the oddball experiment (0-10 ms or 0-8 ms post stimulus peak, for the low- and high-frequency chirp, respectively). The left y-axis depicts the absolute, the right y-axis the relative (to the maximum) peak-to-peak amplitude. Linear regression models were fit to the observed data and show significant repetition suppression of the low-frequency chirp responses (left) and significant repetition enhancement of the high-frequency chirp responses (right). (b) As in (a) but the stimulus repetition rate was 20 Hz (n = 8 subjects). While the repetition suppression of the low-frequency chirp responses disappeared (left), the repetition enhancement of the high-frequency chirp responses was still significant (right).

4. Discussion

This study used a low- and a high-frequency chirp stimulus to investigate auditory deviance detection in the human brainstem. Low-frequency chirps occurring as deviants elicited significantly larger and faster ABRs when compared to the same stimulus used as standard (experiment 1). In accordance with this finding, the same stimulus caused repetition suppression of the ABR when presented in a repetitive stimulation sequence at a high repetition rate (experiment 2). These findings are in line with the commonly described effects of deviance detection obtained from the human cortex and in animal experiments. At the same time, unlike the low-frequency chirp, the high-frequency chirp did not elicit significant deviance detection in the oddball paradigm. The latter hints towards different mechanisms of processing low- and high-frequency sounds in the human brainstem. Indeed, this idea is confirmed by our findings in experiment 2 (repetitive sequences), which show that repetition suppression and repetition enhancement are distinctly linked to low- and high-frequency chirps, respectively. Taken together our findings provide evidence of deviance detection in the human brainstem and indicate the existence of different neural mechanisms for processing streams of low- and high-frequency sounds in humans.

Our findings can be directly compared to previous studies. In our first experiment, the low-frequency chirp evoked larger and earlier deviant compared to standard ABRs, and the amplitude difference increased with rising stimulation rate. This finding is in line with animal research that studied stimulus-specific adaptation (SSA) at single-unit level in the IC of rats (Malmierca et al., 2009; Zhao et al., 2011). Here, the authors demonstrated that deviant stimuli evoke earlier single-neuron responses compared to standard stimuli and that SSA in the IC is weaker at lower stimulation rates. These analogies to the current results strongly suggest that both phenomena are closely related to each other. Most likely, unexpected deviant stimuli evoke stronger and earlier neural responses because in nature their perception

usually has a more important behavioural relevance for an individual, compared to the perception of a highly repetitive sound. From a mechanistic perspective, deviance detection is also a fundamental principle of the predictive coding framework that has received strong attention in the last years. The predictive coding theory describes a possible mechanism of the brain to efficiently deal with the tremendous amount of sensory input it receives. The theory proposes that the brain constantly predicts the events of the near future and compares those internal prediction with the perceived input. In the case of a mismatch between input and expectation, a prediction error is generated that is then used to update the prediction model (Friston, 2005; Winkler, 2007). Therefore, detecting unexpected events plays an essential role in the predictive coding framework and evidence for this mechanism of sensory processing has been accumulating lately (Winkler, 2007; Auksztulewicz and Friston, 2016; Parras et al., 2017; Carbajal and Malmierca, 2018; Fitzgerald and Todd, 2020; Quintela-Vega et al., 2023; Song et al., 2023; Tzovara et al., 2024).

While the effects elicited by the low-frequency chirps are well in line with previously published deviance detection data, the high-frequency chirp did not evoke significant deviance detection, neither of ABR amplitude nor peak V latency. This shows that deviance detection in the human brainstem is sensitive to the stimulus frequency and that different processing strategies are utilised in a frequency-specific way. A finding that was known previously only from animal experiments (Wetekam et al., 2022, 2024; Carbajal et al., 2024). A few studies that investigated deviance detection in the human frequency-following response (FFR) demonstrated higher neural responsiveness to the standard compared to the deviant stimulus (Chandrasekaran et al., 2009; Skoe and Kraus, 2010; Slabu et al., 2012), a trend that is also visible in the high-frequency chirp responses reported here. However, whether both findings are related to the same neural mechanisms is impossible to say at this point. The exact neural origin of the FFR has not yet been definitively determined, but it appears to be

generated by an interplay between both subcortical and cortical structures (Coffey et al., 2016, 2019).

Experiment 2 provided further evidence for stimulus-specific signal processing mechanisms in the human brainstem. Here, the low-frequency chirp elicited repetition suppression and the high-frequency chirp repetition enhancement. Repetition suppression is a commonly encountered phenomenon in the brain and has been characterised in much detail (Thornton and Coleman, 1975; Pratt and Sohmer, 1976; Junius and Dau, 2005; Grill-Spector et al., 2006; Gotts et al., 2012; Auksztulewicz and Friston, 2016). It has been discussed to reflect improved neural efficiency caused by the repetitive perception of the same stimulus. On the other hand, repetition enhancement effects are less frequently reported. Under which circumstances repetitive stimulation leads to suppression or enhancement is not fully understood yet, but former work could show that familiar stimuli lead to repetition suppression while unfamiliar stimuli tend to elicit repetition enhancement (Henson et al., 2000; Müller et al., 2013; Segaert et al., 2013). Given that the spectrum of our low-frequency chirp (500-2000 Hz) contains most of the frequencies usually encountered in a person's daily life, it may be perceived as a more familiar stimulus compared to the high-frequency chirp (2000-8000 Hz). Additionally, high-pitched sounds are associated with alarm signals (Zeskind and Collins, 1987; Haas and Edworthy, 1996; Schwartz and Gouzoules, 2019), which can gain behavioural relevance when perceived repeatedly. The primary goal of processing high-frequency stimuli may therefore not be the maximising of processing efficiency but to provide an alarm signal that builds up with increasing stimulus number. The finding of repetition enhancement in the human brainstem is in line with a recent report where the authors demonstrated that repetition enhancement is exhibited by certain neural populations in the mouse IC (Lesicko et al., 2022). Importantly, this phenomenon was only detectable in awake and not anesthetised mice which could be the reason why subthalamic repetition enhancement has not been reported more

frequently in former studies. In the same paper, by deactivating the cortico-collicular feedback, Lesicko and colleagues also demonstrated that repetition enhancement is most likely being generated in the cortex and reaches the brainstem via top-down projections. Conversely, repetition suppression was unaffected by cortico-collicular inactivation, suggesting that it is emerges *de novo* in the brainstem (Lesicko et al., 2022).

Conclusion

The data presented in this study demonstrate that human ABRs are sensitive to auditory deviants and repetitive stimulation. The reported effects are highly dependent on the stimulus frequency, showing that the brainstem is actively involved in advanced signal processing. These results bridge a gap between experiments in humans and animal models and establish human ABRs as a suitable technique to study deviance detention in subcortical brain areas.

Author contributions

Study design: Johannes Wetekam, Nell Gotta, Luciana López-Jury, Julio Hechavarría, Manfred Kössl

Experiments: Johannes Wetekam, Nell Gotta

Analysis, and original draft of the manuscript: Johannes Wetekam

Review and editing of the original draft: Johannes Wetekam, Nell Gotta, Luciana López-Jury, Julio Hechavarría, Manfred Kössl

Abbreviations

ABR:	Auditory brainstem response
FFR:	Frequency-following response
fMRI:	Functional magnetic resonance imaging
IC:	Inferior colliculus
MMN:	Mismatch negativity

References

Antunes FM, Nelken I, Covey E, Malmierca MS (2010) Stimulus-specific adaptation in the auditory thalamus of the anesthetized rat. PLoS ONE 5.

Auksztulewicz R, Friston K (2016) Repetition suppression and its contextual determinants in predictive coding. Cortex 80:125–140.

Ayala YA, Malmierca MS (2012) Stimulus-specific adaptation and deviance detection in the inferior colliculus. Frontiers in Neural Circuits 6:1–16.

Cacciaglia R, Escera C, Slabu L, Grimm S, Sanjuán A, Ventura-Campos N, Ávila C (2015) Involvement of the human midbrain and thalamus in auditory deviance detection. Neuropsychologia 68:51–58.

Carbajal GV, Casado-Román L, Malmierca MS (2024) Two Prediction Error Systems in the Nonlemniscal Inferior Colliculus: “Spectral” and “Nonspectral.” J Neurosci 44 Available at: https://www.jneurosci.org/content/44/23/e1420232024 [Accessed June 12, 2024].

Carbajal GV, Malmierca MS (2018) The Neuronal Basis of Predictive Coding Along the Auditory Pathway: From the Subcortical Roots to Cortical Deviance Detection. Trends in Hearing 22:1–33.

Chandrasekaran B, Hornickel J, Skoe E, Nicol T, Kraus N (2009) Context-Dependent Encoding in the Human Auditory Brainstem Relates to Hearing Speech in Noise: Implications for Developmental Dyslexia. Neuron 64:311–319.

Coffey EBJ, Herholz SC, Chepesiuk AMP, Baillet S, Zatorre RJ (2016) Cortical contributions to the auditory frequency-following response revealed by MEG. Nature Communications 7.

Coffey EBJ, Nicol T, White-Schwoch T, Chandrasekaran B, Krizman J, Skoe E, Zatorre RJ, Kraus N (2019) Evolving perspectives on the sources of the frequency-following response. Nature Communications 10:1–10.

Cohen J (1988) Statistical Power Analysis for the Behavioral Sciences. New York.

Condon CD, Weinberger NM (1991) Habituation produces frequency-specific plasticity of receptive fields in the auditory cortex. Behavioral Neuroscience 105:416–430.

Don M, Kwong B, Tanaka C (2005) A diagnostic test for Ménière’s disease and cochlear hydrops: Impaired high-pass noise masking of auditory brainstem responses. Otology and Neurotology 26:711–722.

Duque D, Pais R, Malmierca MS (2018) Stimulus-specific adaptation in the anesthetized mouse revealed by brainstem auditory evoked potentials. Hearing Research 370:294–301.

Duque D, Pérez-González D, Ayala YA, Palmer AR, Malmierca MS (2012) Topographic distribution, frequency, and intensity dependence of stimulus-specific adaptation in the inferior colliculus of the rat. Journal of Neuroscience 32:17762–17774.

Eggermont JJ, Don M (1980) Analysis of the click-evoked brainstem potentials in humans using high-pass noise masking. II. Effect of click intensity. J Acoust Soc Am 68:1671–1675.

Elberling C, Don M (2008) Auditory brainstem responses to a chirp stimulus designed from derived-band latencies in normal-hearing subjects. The Journal of the Acoustical Society of America 124:3022–3037.

Elberling C, Don M, Cebulla M, Stürzebecher E (2007) Auditory steady-state responses to chirp stimuli based on cochlear traveling wave delay. The Journal of the Acoustical Society of America 122:2772.

Escera C, Leung S, Grimm S (2014) Deviance detection based on regularity encoding along the auditory hierarchy: Electrophysiological evidence in humans. Brain Topography 27:527–538.

Fitzgerald K, Todd J (2020) Making Sense of Mismatch Negativity. Frontiers in Psychiatry 11:468.

Fobel O, Dau T (2004) Searching for the optimal stimulus eliciting auditory brainstem responses in humans. The Journal of the Acoustical Society of America 116:2213–2222.

Friston K (2005) A theory of cortical responses. Philosophical Transactions of the Royal Society B: Biological Sciences 360:815–836.

Gotts SJ, Chow CC, Martin A (2012) Repetition priming and repetition suppression: A case for enhanced efficiency through neural synchronization. Cognitive Neuroscience 3:227–237.

Grill-Spector K, Henson R, Martin A (2006) Repetition and the brain: neural models of stimulus-specific effects. Trends in Cognitive Sciences 10:14–23.

Haas EC, Edworthy J (1996) Designing urgency into auditory warnings using pitch, speed and loudness. Computing & Control Engineering Journal 7:193–198.

Henson R, Shallice T, Dolan R (2000) Neuroimaging Evidence for Dissociable Forms of Repetition Priming. Science 287:1269–1272.

Junius D, Dau T (2005) Influence of cochlear traveling wave and neural adaptation on auditory brainstem responses. Hearing Research 205:53–67.

Kraus N, McGee T, Carrell T, King C, Littman T, Nicol T (1994a) Discrimination of speech□like contrasts in the auditory thalamus and cortex. The Journal of the Acoustical Society of America 96:2758–2768.

Kraus N, McGee T, Littman T, Nicol T, King C (1994b) Nonprimary auditory thalamic representation of acoustic change. Journal of Neurophysiology 72:1270–1277.

Lesicko AM, Angeloni CF, Blackwell JM, De Biasi M, Geffen MN (2022) Corticofugal regulation of predictive coding Groh JM, Shinn-Cunningham BG, Groh JM, eds. eLife 11:e73289.

Malmierca MS, Cristaudo S, Pérez-González D, Covey E (2009) Stimulus-specific adaptation in the inferior colliculus of the anesthetized rat. Journal of Neuroscience 29:5483–5493.

Müller NG, Strumpf H, Scholz M, Baier B, Melloni L (2013) Repetition Suppression versus Enhancement—It's Quantity That Matters. Cerebral Cortex 23:315–322.

Näätänen R, Gaillard AWK, Mäntysalo S (1978) Early selective-attention effect on evoked potential reinterpreted. Acta Psychologica 42:313–329.

Näätänen R, Paavilainen P, Rinne T, Alho K (2007) The mismatch negativity (MMN) in basic research of central auditory processing: A review. Clinical Neurophysiology 118:2544–2590.

Parras GG, Nieto-Diego J, Carbajal GV, Valdés-Baizabal C, Escera C, Malmierca MS (2017) Neurons along the auditory pathway exhibit a hierarchical organization of prediction error. Nature Communications 8.

Patel CR, Redhead C, Cervi AL, Zhang H (2012) Neural sensitivity to novel sounds in the rat's dorsal cortex of the inferior colliculus as revealed by evoked local field potentials. Hearing Research 286:41–54.

Picton TW (2010) Auditory brainstem responses: peaks along the way. Human auditory evoked potentials:213–246.

Picton TW, Stapells DR, Campbell KB (1981) Auditory evoked potentials from the human cochlea and brainstem. J Otolaryngol Suppl 9:1–41.

Pratt H, Sohmer H (1976) Intensity and rate functions of cochlear and brainstem evoked responses to click stimuli in man. Arch Otorhinolaryngol 212:85–92.

Quintela-Vega L, Morado-Díaz CJ, Terreros G, Sánchez JS, Pérez-González D, Malmierca MS (2023) Novelty detection in an auditory oddball task on freely moving rats. Commun Biol 6:1–15.

Schwartz JW, Gouzoules H (2019) Decoding human screams: perception of emotional arousal from pitch and duration. Behaviour 156:1283–1307.

Segaert K, Weber K, de Lange FP, Petersson KM, Hagoort P (2013) The suppression of repetition enhancement: A review of fMRI studies. Neuropsychologia 51:59–66.

Shiramatsu TI, Takahashi H (2021) Mismatch-negativity (MMN) in animal models: Homology of human MMN? Hearing Research 399 Available at: https://doi.org/10.1016/j.heares.2020.107936 [Accessed May 5, 2022].

Skoe E, Kraus N (2010) Hearing It Again and Again: On-Line Subcortical Plasticity in Humans. PLOS ONE 5:e13645.

Slabu L, Grimm S, Escera C (2012) Novelty Detection in the human auditory brainstem. Journal of Neuroscience 32:1447–1452.

Song P, Zhai Y, Yu X (2023) Stimulus-specific adaptation (SSA) in the auditory system: Functional relevance and underlying mechanisms. Neuroscience & Biobehavioral Reviews 149:105190.

Tabas A, Kriegstein K von (2024) Multiple Concurrent Predictions Inform Prediction Error in the Human Auditory Pathway. J Neurosci 44 Available at: https://www.jneurosci.org/content/44/1/e2219222023 [Accessed June 12, 2024].

Tabas A, Mihai G, Kiebel S, Trampel R, von Kriegstein K (2020) Abstract rules drive adaptation in the subcortical sensory pathway Shinn-Cunningham BG, Griffiths TD, Malmierca MS, eds. eLife 9:e64501.

Thornton ARD, Coleman MJ (1975) The adaptation of cochlear and brainstem auditory evoked potentials in humans. Electroencephalography and Clinical Neurophysiology 39:399–406.

Tzovara A, Fedele T, Sarnthein J, Ledergerber D, Lin JJ, Knight RT (2024) Predictable and unpredictable deviance detection in the human hippocampus and amygdala. Cerebral Cortex:bhad532.

Ulanovsky N, Las L, Farkas D, Nelken I (2004) Multiple time scales of adaptation in auditory cortex neurons. Journal of Neuroscience 24:10440–10453.

Ulanovsky N, Las L, Nelken I (2003) Processing of low-probability sounds by cortical neurons. Nature Neuroscience 6:391–398.

Wetekam J, Hechavarría J, López-Jury L, González-Palomares E, Kössl M (2024) Deviance detection to natural stimuli in population responses of the brainstem of bats. J Neurosci:e1588232023.

Wetekam J, Hechavarría J, López-Jury L, Kössl M (2022) Correlates of deviance detection in auditory brainstem responses of bats. European Journal of Neuroscience 55:1601–1613.

Winkler I (2007) Interpreting the mismatch negativity (MMN). Journal of Psychophysiology - J PSYCHOPHYSIOL 21:147–163.

Zeskind PS, Collins V (1987) Pitch of infant crying and caregiver responses in a natural setting. Infant Behavior and Development 10:501–504.

Zhao L, Liu Y, Shen L, Feng L, Hong B (2011) Stimulus-specific adaptation and its dynamics in the inferior colliculus of rat. Neuroscience 181:163–174.

Figure legends

Figure 1: Used stimuli and stimulation protocols. (a) Spectrograms (top) and oscillograms (bottom) of a low-frequency chirp (orange frame) and a high-frequency chirp (green frame) that were used as stimuli in this study. (b) Schematic representation of the oddball paradigm; blue: standard, red: deviant. (c) Schematic representation of the repetitive stimulation sequence. Periods of silence and trains of repetitive stimulation were presented to the subject multiple times, in an alternating pattern.

Figure 2: ABR deviance detection depends on the stimulus frequency and presentation rate (n = 20 subjects). (a) Grand averages of ABRs to a low- (left) and high-frequency (right) chirp, presented as deviant (red) and standard (blue). The stimulus presentation rate was 40 Hz. The boxes framing the responses represent the time window taken for peak-to-peak amplitude calculation, covering the whole ABR response (0-10 ms or 0-8 ms post stimulus peak, for the low- and high-frequency chirp, respectively). A grey box colour indicates a significant difference between deviant and standard response, a white colour indicates no significant difference. Shaded areas around the ABRs depict the standard error of the mean. The insets on the right to each response graph show the peak-to-peak ABR amplitudes calculated for each subject and condition. (b) As in (a) but the stimulus presentation rate was 33 Hz. (c) As in (a) but the stimulus presentation rate was 20 Hz.

Figure 3: Low-frequency chirps elicit repetition suppression, high-frequency chirps repetition enhancement of ABRs. (a) Peak-to-peak amplitudes of ABRs to repetitively presented stimuli. The stimulus presentation rate was 40 Hz (n = 9 subjects). Peak-to-peak amplitudes were calculated for the same time windows as in the oddball experiment (0-10 ms or 0-8 ms post stimulus peak, for the low- and high-frequency chirp, respectively). The left y-axis depicts the absolute, the right y-axis the relative (to the maximum) peak-to-peak amplitude. Linear regression models were fit to the observed data and show significant repetition suppression of

the low-frequency chirp responses (left) and significant repetition enhancement of the high-frequency chirp responses (right). (b) As in (a) but the stimulus repetition rate was 20 Hz (n = 8 subjects). While the repetition suppression of the low-frequency chirp responses disappeared (left), the repetition enhancement of the high-frequency chirp responses was still significant (right).

Supp. Fig. 1: Effects of deviance detection on the ABR peak V latency (n = 20 subjects). (a) Grand averages of ABRs to a low- (left) and high-frequency (right) chirp, presented as deviant (red) and standard (blue). The stimulus presentation rate was 40 Hz. The boxes framing the responses represent the time window taken for peak latency calculation, covering ABR peak V (5.5-9 ms or 4.5-8 ms post stimulus peak, for the low- and high-frequency chirp, respectively). A grey box colour indicates a significant difference between deviant and standard response, a white colour indicates no significant difference. Shaded areas around the ABRs depict the standard error of the mean. The insets on the right to each response graph show the ABR peak V latencies calculated for each subject and condition. (b) As in (a) but the stimulus presentation rate was 33 Hz. (c) As in (a) but the stimulus presentation rate was 20 Hz.