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Diphthong stimuli for fast assessment of envelope and fine-structure information encoding in the newborn FFR: A test in the adult population

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The encoding of voice pitch variations and vowel formant structure changes plays an important role in speech comprehension since the early stages of life. However, to the best of our knowledge, no study up to date has investigated the ability to encode both elements of speech in newborns, mostly due to experimental time constraints. Moreover, research on formant transitions classically used consonant-vowel stimuli, with formant changes occurring at high frequency ranges difficult to be observed in the newborn frequency-following response (FFR). Thus, our aim was to assess the feasibility of using a single short diphthong stimulus with a rising pitch ending (/oa/) to reveal both pitch tracking and low-frequency formant encoding accuracy within the time constraints of a newborn FFR recording setup.

As a first step, we tested the diphthong /oa/ in fourteen normal-hearing adult participants (10 females; 4 males) recruited from the University of Barcelona. Because single polarity stimuli (either rarefaction or condensation) are shown to elicit an FFR that contains both envelope and fine structure information, improving the characterization of the response within a short recording time, and due to the increasing number of studies that examine the FFR by using stimuli with a single polarity, we decided to test the advantages of using a single polarity stimulus vs. averaging and subtracting both stimulus polarities. The diphthong /oa/ was presented in blocks of 2000 single polarity stimuli (condensation or rarefaction; randomized block order across participants), until a total of 4000 artifact-free sweeps were obtained for each one.

Our results showed that the FFR elicited by any single polarity (4000 sweeps) exhibited both envelope (F0 peak; pitch tracking) and fine structure information (differences in F1 and F2 between /o/ and /a/ segments), but with large differences between polarities in all measures and large inter- individual variability. On the other hand, averaging both polarities (2000x2 sweeps) highlighted envelope information, while subtracting them highlighted formant structure encoding.

Given the impossibility to know beforehand which polarity will elicit the best response in each participant, our data suggests that it is safer to use alternating polarity stimuli. Moreover, we demonstrated the feasibility to record pitch and low-frequency formant structure changes with a single stimulus and within a short recording time (~30’), which makes the diphthong /oa/ with rising pitch a good candidate for use in newborn FFR research.

Exploring simultaneous assessment of cortical and subcortical entrainment to ongoing speech

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Human speech processing relies on fine temporal coding at the level of the auditory brainstem as well as at cortical stages. Tonal languages in particular rely on accurate coding of pitch, and speakers of tonal languages may have specialized pitch-related processing at both cortical and subcortical levels. However, responses at these two stages are typically investigated separately, and using different stimuli. Subcortical responses are traditionally assessed with repetitions of short, simple stimuli such as single syllables, while cortical processes can be probed with ongoing speech. Recent studies have shown that subcortical responses can also be measured with ongoing speech stimuli, using regularized regression or cross-correlation approaches. This suggests the prospect of simultaneously observing the processing of the same ongoing speech stimuli at cortical and brainstem level. The present study explores this possibility, with the perspective of examining how temporal cues in tonal languages are processed along the auditory pathway, and how this may be affected by hearing loss.

Neural processing of speech in children with sensorineural hearing loss

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Although the primary damage associated with sensorineural hearing loss lies in the cochlea, its consequences extend throughout the entire auditory pathway. Despite having significant residual hearing, children with mild (21-40 dB HL) to moderate (41-70 dB HL) sensorineural hearing loss (MMHL) experience deficits with general auditory processing, which puts them at risk of encountering language difficulties. Here, I will present two studies aimed at better understanding the neural consequence of partial degradation of the auditory input in children with MMHL. The first study examines the developmental effects of childhood MMHL on auditory discrimination of speech, "speech-like" and "nonspeech" stimuli, using the Mismatch Negativity (MMN). We tested 46 children with MMHL and 44 normally-hearing chronological age-matched controls (CA). Children were divided into two age groups: "younger" (8-11 years) and "older" (12-16 years). Our main result indicated that, while present in younger children with MMHL, there was no significant MMN in older MMHL children, whatever the condition. In an attempt to replicate this finding, fourteen children from the initial younger group participated in a longitudinal follow-up study again 6 years later (age range: 14-17 years). Although this group had a significant MMN when they were aged 7-11 years, this was only the case for speech when they reached 14-17 years. Our findings suggest that even a mild or moderate levels of hearing loss during childhood may entail a persistent damage of auditory cortical functioning. A second study was conducted to evaluate the benefit of hearing aid amplification at various levels of the auditory pathway in children with MMHL. The frequency following response (FFR) was used as an index of speech processing at the subcortical level. Both the MMN and the intra-class correlation (ICC) coefficients were used to index processing of sounds at the cortical level. The results suggest that, as a group, children with MMHL have smaller ICC coefficients than NH controls in both unamplified and amplified conditions, and do not show an MMN. In contrast, at the subcortical level, they show an FFR that was smaller than that of NH controls in the unamplified condition only. With simulated amplification, children with MMHL demonstrate an FFR that was comparable to that observed in NH controls. Our findings suggest that the neural processing of unamplified speech may be impaired at both subcortical and cortical levels in children with MMHL. Results will be discussed with respect to the existing literature on profoundly deaf children with cochlear implant and animal studies, which highlight long-term consequences of MMHL on the neural processing of sounds.

Acknowledgments

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Lexical prediction errors affect the FFR

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Modern neuroscience views the brain as a predictive machine. Due to the intrinsic temporal unfolding of acoustic information, inferences about the continuation of sensory objects lay at the heart of audition. We here exploited the inherently predictive nature of speech to study the hierarchical dynamics of prediction errors (PE) generated to unexpected word endings. That is, where, and when, is a lexical PE generated? Can it alter the encoding of speech information at low levels of the processing hierarchy? We designed a paradigm in which we recorded our participants' EEG activity while passively listening to a random series of different Spanish words ending in the phonemes /a/ or /o/, swapping those phonemes in 50% of the words to create unexpected endings. Our results on Long Latency Responses show a prototypical left-lateralized mismatch response (MMR) to unexpected endings, plus a later highly left-lateralized potential. Moreover, we extracted the Frequency-Following Response (FFR) to the pitch of the vowel as a measure of low-level feature encoding. The integrity of the FFR evoked to unexpected endings was briefly compromised at a slightly later time than that of the MMR. Our results thus suggest that 1) high-level lexical PEs are generated first in higher information processing stages; 2) the update of the predictive model leaks upstream, disturbing the low-level encoding of sound; and 3) once the error is explained (unexpected ending discovered), the increase in confidence in the updated predictive model (e.g. vowel /a/ in a non-word) restores the integrity of sound feature encoding.

Investigating cochlear synaptopathy with envelope following responses

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The healthy auditory system is capable to enable communication in challenging situations with high levels of background noise. Despite normal sensitivity to pure-tones, many listeners complain about having difficulties in such situations. Recent animal studies demonstrated that noise over-exposure that produces temporary threshold shifts can cause the loss of auditory nerve (AN) fiber synapses (i.e., cochlear synaptopathy, CS), assumed to be predominant for medium- and low-spontaneous rate (SR) fibers. In the present study, envelope following response (EFR) magnitude-level functions were recorded in normal-hearing (NH) threshold and mildly hearing-impaired (HI) listeners with threshold elevation at frequencies above 3 kHz. EFRs were elicited by sinusoidally amplitude modulated (SAM) tones presented in quiet with a carrier frequency of 2 kHz, modulated at 93 Hz, and at modulation depths of 85% (strong) and 25% (shallow). While EFR magnitude-level functions for strongly modulated tones were similar for all listeners regardless of sensitivity thresholds, EFR magnitude-level functions for shallowly modulated tones were reduced at medium stimulation levels in some NH threshold listeners and saturated for the whole level range in the HI listeners. A phenomenological model of the AN was used to systematically investigate up to which extent IHC and OHC dysfunction and additional postulated CS could explain the trends observed in the EFR data. The effects of high frequency (beyond 8 kHz) hair-cell dysfunction, the effects of AN off-frequency contributions (i.e., away from the characteristic place of the stimulus) and the differential loss of different AN fiber types on EFR magnitude-level functions were analyzed within the model framework. The model simulations suggested, when using SAM tones in quiet as stimulus, that: (1) EFRs are dominated at all stimulus intensities by the activity of high-SR fibers, and (2) EFRs at medium-to-high stimulus levels are dominated by off-frequency contributions. Measured pure-tone audiometric threshold elevation (up to 8 kHz) and postulated hair-cell dysfunction at frequencies above 8 kHz was not sufficient to account for the recorded EFR data. Additional CS was needed to obtain simulated EFRs that could better account for the recorded EFR data, but a loss of all types of AN fibers had to be considered within the model framework.

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Emerging of prediction errors along the auditory hierarchy: a study in humans with the frequency-following response and the mismatch negativity

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Animal studies of auditory stimulus-specific adaptation (SSA) have revealed that prediction errors emerge gradually along the auditory hierarchy, from non-lemniscal inferior colliculus to non-lemniscal thalamus and primary auditory cortex, whereas repetition suppression –the attenuation of neuronal responses to stimulus repetitions—is present at very low anatomical levels, even at the lemniscal inferior colliculus (Parras et al. 2017, *Nature Comm*, 8:2148). In humans, auditory predictions errors have been extensively associated with the mismatch negativity (MMN) cortical auditory evoked potential. Yet, many studies lacked the appropriate controls to disentangle sensory adaptation from prediction errors. Furthermore, only very few studies since the seminal report of Slabu et al. (2012, *J Neurosci*, 32:1447) have addressed subcortical prediction errors in humans through recordings of the frequency-following response (FFR). The present study aimed at investigating the emergence of prediction errors along the auditory hierarchy in humans through combined recordings of the FFR and the MMN and the use of appropriate controls to disentangle prediction error from sensory adaptation. "Oddball" sequences of pure tones featuring repeated "standard" stimuli (269 Hz; p=0.8) and rare "deviant" stimuli (p=0.2; of 289, 329 and 409 Hz delivered in separated blocks to test "deviance magnitude" effects) were delivered to N=19 healthy young participants while watching silent movies. "Reversed" oddball sequences (where standard and deviant tones swapped their roles) were presented allowing comparison of responses to same physical stimuli as a function of functional role (i.e., standard, deviant). Critically, control sequences featuring five equiprobable tones (p=0.2) allowed to dissociate sensory adaptation from prediction error. Results revealed that the MMN amplitude increased as a function of deviance, yet displayed the same amplitude when retrieved against the control sequences, confirming previous results. FFRs showed a clear sensory adaptation effect across all frequencies repetition, as supported by larger spectral amplitude to standard than to control stimuli, but this not reveal subcortical prediction errors, as deviant FFRs where similar to control FFRs. This pattern of results provides insights into the human prediction error system in audition.

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Relationship between electric and acoustic stimulation (EAS) benefit from preserved acoustic hearing in the implanted ear and frequency following response (FFR)

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Considerable research and clinical attention has recently been placed on preservation of acoustic hearing with minimally traumatic cochlear implantation allowing a cochlear implant (CI) recipient to use combined electric and acoustic stimulation (EAS). By adding residual acoustic hearing in the CI ear to the bimodal hearing configuration (CI plus contralateral hearing aid (HA)), CI recipients can derive nonlinear, additive gains in speech understanding and basic auditory function. However, EAS benefit varies greatly between individuals and is not necessarily related to unaided audiometric thresholds in the CI ear. As such, clinical decision-making regarding amplification of low-frequency hearing in an implanted ear is not evidence based. The frequency following response (FFR) is an auditory-evoked neural potential containing periodicity and temporal fine structure (TFS) information from an acoustic stimulus. Studies have documented significant correlations between FFR spectral amplitudes and speech recognition for adults with normal hearing (Anderson et al., 2011; Parbery-Clark et al., 2009; Song et al., 2011); however, no studies have utilized FFR as a means of quantifying auditory neural processing for preserved acoustic hearing in an implanted ear and how that ear may contribute to EAS benefit for speech recognition in complex listening environments. We have theorized that EAS benefit is derived by access to periodicity and/or temporal fine structure from low-frequency acoustic hearing in the implanted ear (e.g., Gifford et al., 2014). As such, our hypothesis was that EAS benefit for speech recognition in complex noise would be significantly correlated with FFR spectral amplitude for fundamental frequency (F0) and temporal fine structure (F1). At the time of abstract preparation, we had recruited 5 adult CI recipients with hearing preservation in the implanted ear, with 1 participant having bilateral implants and bilateral hearing preservation. Participants completed speech recognition in noise with the CI alone, the bimodal condition (CI + HA), and best-aided EAS (CIHA+HA or CIHA+CIHA) as well as FFR for a 170-ms /da/ stimulus at 90 dB SPL presented to the acoustic hearing implanted ears without the use of the CI. Preliminary findings revealed a correlation ($r = 0.5$) between FFR F0 amplitude in the CI ear and degree of EAS benefit. Due to the participants' hearing configurations, there was no reliable neural representation of TFS in the FFR response. In summary, FFR holds potential as an objective tool that may help predict degree of benefit obtained by adding acoustic hearing from the CI ear for speech recognition in noise.

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Anatomical sources of the frequency-following response elicited to low and high pitch stimuli: a magnetoencephalographic (MEG) study.

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The auditory frequency-following response (FFR) to periodic complex sounds provides a non-invasive measure of the neural transcription of sounds, as well as how auditory experiences transform these neural representations. Although it has been considered as a correlate of subcortical sound encoding, the single study so far using magnetoencephalography (MEG) to locate the sources of the FFR challenged this assumption, demonstrating that FFR receives major contribution from the right auditory cortex. Based on frequency-specific phase-locking capabilities along the auditory hierarchy, we hypothesized that FFRs to higher frequencies would receive less cortical contribution than those to lower frequencies, hence supporting subcortical involvement in the encoding of these high-frequency sounds. We recorded simultaneously electroencephalographic (EEG) and MEG FFRs to pure tones of 89 and 333 Hz. FFRs elicited to high and low frequency sounds were observable on both MEG and EEG recordings. By using distributed source modeling, midbrain, thalamic, and cortical contribution to FFR was analyzed and described. Our results showed that the FFR to low frequency stimuli had neural contributors throughout the entire auditory hierarchy, from the cochlear nucleus to the primary auditory cortex. On the other hand, the high frequency FFR, elicited to sounds of 333 Hz, disclosed only subcortical neural generators contributing to it, specifically only the activity coming from the inferior colliculi, and no cortical contribution could be observed. These results reveal that the frequency of the eliciting stimulation is a key factor in determining the involvement of the auditory hierarchy in the generation of the FFR, so that sounds of high frequencies (~300 Hz) engage subcortical generators only. Hence, the FFR can still be used as a window into subcortical sound encoding when using the appropriate stimulus parameters.

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FFR to very low-frequency and infrasound tones

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Complaints about environmental infrasound have increased in recent years, but little is known about its perceptual mechanisms. To compare the brain's response to tones inside and outside the audible range, the frequency-following response (FFR) to monaural infrasound (11 Hz) and low-frequency (88 Hz) sinusoidal stimulation was recorded from the human scalp using multichannel EEG. There was huge variability amongst subjects. But for some subjects, FFRs to 11-Hz were measurable down to ~0 phon and saturated often already above ~20 phon. In contrast, the 88- levels of the 88 Hz tone had to be well above detection threshold to elicit an FFR.

We developed a vector display based on the electrode map of the EEG cap to illustrate the phase relationship of the of the FFR response at each electrode in relation to the stimulus phase. The length of the vectors relate to the SNR of the FFR and the significance of the phase-coherence (Rayleigh test) at each electrode is coded as colour.

We used a 64-channel Biosemi system with active common mode rejection and a traditional EEG system with 16 channels based on a Pentusa Tucker-Davis-signal processor. The FFR response map appeared to depend on the system, and also the choice of reference electrodes had a large effect on the display. We will discuss how we think the topology of the response phase could be utilised for analysing multichannel FFR recordings.

Periodicity Pitch Recognition in Complex Harmonies on EEG Timeline Data

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During the hearing process in ear and brain, an acoustic stimulus, e.g. a musical harmony, is transformed in a highly non-linear way. We study this by comparing the frequency spectrum of an input stimulus and its response spectrum in the auditory processing stream using the frequency following response (FFR).

Aims. The goal is to develop a model how the human brain perceives and processes musical sounds. Using EEG, where three different harmonies (triads) are presented, we investigate whether the periodicity pitches of complex harmonies [3] (related to their missing fundamentals) are added in the auditory brain stem by analyzing the FFR [1]. We use three-tone stimuli (common triads) because of their musical significance.

Methods. While watching a muted nature documentary, 17 healthy adult participants (7 male, 10 female) hear synthetic classic piano triads and single tones. Their responses are recorded by an EEG system using a sample rate of 5kHz. All stimuli consist of 300ms stimulus and 100ms interstimulus interval and are presented by loudspeakers in a soundproof Faraday cage with an incoming volume around 67dB. Note that the sought-for periodicity pitch frequencies do not physically exist in the frequency spectra of the stimuli.

Results. The EEG response is bandpass-filtered in the range 20–700Hz. After selecting the trials with good signal-to-noise ratio, a Fast Fourier Transformation is performed on 50ms parts, starting 50ms after stimulus onset [1]. The evaluation of the frequency spectra of the EEG response shows, that the periodicity pitch frequency calculated beforehand according to [3] as well as its double occurs with an accuracy of +/-3Hz in every 50ms section. Figure 1 illustrates the frequency spectrum of the G major chord – the most dominant frequencies belong to the fourth and third partial. Figure 2 shows the spectral characteristics of the response to that G major chord at the time intervals 50–100ms, 100–150ms and 150–200ms after stimulus onset. At the frequencies ~49Hz and ~98Hz the desired peaks are detected. The dominant frequencies of the stimulus spectrum do thereby only slightly result in more dominant periodicity pitch frequencies.

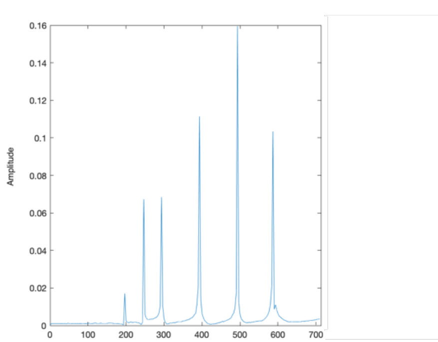

Fig.1 Frequency spectrum of the G chord stimulus.

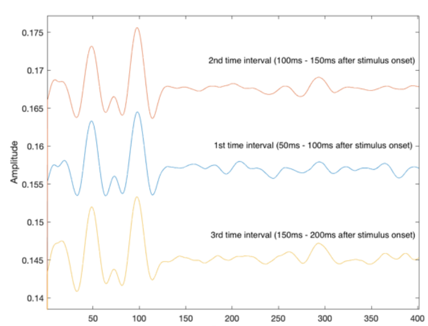

Fig.2 Response spectrum of the G major chord major for three different time intervals.

Conclusions. Although the auditory brain stem shows low-pass characteristics [2], our experiments suggest that higher frequencies and complex harmonic sounds (triads) result in the appearance of the periodicity pitch in the auditory brain stem response.

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Decoding of selective attention to continuous speech from the human auditory brainstem response

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The auditory brainstem responds to the fundamental frequency of a short speech signal (Skoe & Kraus, 2010). A recent study by some of the authors showed that the brainstem response to continuous, non-repetitive speech can be measured as well and that this neural activity is influenced by selective attention to one of two competing speakers (Forte et al., 2017). Here we sought to develop a statistical model to detect the auditory brainstem to continuous speech from high-density EEG recordings and use it to decode the auditory attention in an 'on-line' fashion from only short time segments.
To this end, the brainstem response to two competing speakers was measured via high-density electroencephalography (EEG). We employed regularized linear regression to map a fundamental waveform, that oscillates at the fundamental frequency of the voiced parts of speech, to the multichannel EEG signal at different delays. The estimated latency of 9 ms and the topography of the detected brainstem responses were consistent with previous studies that employed short, repeated speech stimuli.
To decode attention to one of two competing speakers through the detected brainstem response a classifier was trained based on the accuracies of the waveform reconstructions. The decoding performance was computed for subject-specific as well as population-average models, for a few channels of EEG, as well as for a fundamental waveform obtained from simple band-pass filtering which can run in real time. In all cases, a few seconds of data yielded the decoding of selective attention that was significantly better than chance.
We showed that it is possible to detect the auditory brainstem response to natural speech from high-density EEG recordings. This allows to measure the response of the auditory brainstem as well as of cortical responses to continuous speech simultaneously. The decoding of a subject's attentional focus from short segments of EEG data demonstrates that attention can be assessed fast and effectively from the auditory brainstem response to continuous speech. The accurate classification obtained with only few EEG channels makes the method computationally light and therefore promising for potential applications in mobile devices such as hearing aids.

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Probing the potential of ABR latency shift in noise as a proxy for hidden hearing loss

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A surprisingly large number of individuals report difficulties in challenging listening conditions despite having audiometric thresholds within normal limits. It is believed that such "hidden hearing loss" is caused by cochlear synaptopathy. In an earlier study, Mehraei et al. (2016) proposed that the shift of the ABR wave-V latency in increasing levels of background noise can serve as a marker of hidden hearing loss. Importantly, listeners with smaller ABR wave-V latency shifts showed poorer fine temporal coding precision (i.e., higher thresholds for envelope interaural time differences; ITD). In the present study, we probed the potential of the ABR wave-V latency shift as a marker of hidden hearing loss in N = 60 audiometrically normal listeners from a broad age range (20-70 years). As Mehraei et al., we assessed the latency of the click-evoked ABR wave-V in different levels of broadband noise as well as individual thresholds for envelope ITDs. Additionally, we used a battery of questionnaires to assess listeners' noise sensitivity, their hearing abilities as well as their perceived loudness and avoidance of everyday sounds. In a subgroup of listeners (N = 40; age range: 40-70 years), we also tested their performance in a challenging dichotic listening task and how much they benefited from spatial and semantic cues in this task (Tune et al., 2019). Crucially, we were unable to replicate the findings from Mehraei et al.: the ABR wave-V shift did not correlate with either ABR wave-V shift or ITD thresholds. However, we found ABR latency shifts to be positively correlated with noise sensitivity and negatively correlated with the benefit from semantic cues in dichotic listening. Furthermore, ITD thresholds were positively correlated with the benefit from spatial cues in dichotic listening. While our findings call into question the potential clinical use of the ABR wave-V shift as a marker of hidden hearing loss, they suggest that ABR latency shift in noise can serve as a reliable predictor for both lab-based and real-life listening challenges.

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A high-density EEG and structural MRI source analysis of the frequency following response to pitch-shifted stimuli

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Pitch is a perceptual rather than physical phenomenon, important for spoken language use, musical communication, and other aspects of everyday life. The frequency of pitch has a complex relationship with the sounds that evoke it, in many cases being non-obvious. Auditory stimuli can be designed to probe the relationship between perception and physiological responses to pitch-evoking stimuli. One of the more popular techniques for measuring physiological responses to pitch-evoking stimuli is the freqency following response (FFR). The FFR is an electroencephalographic (EEG) response to periodic auditory stimuli, measured from one or more active electrodes on the scalp. A direct question about the EEG correlates of pitch perception is whether the pitch frequency is always present in the spectrum of the FFR, even when the stimulus spectrum does not contain the pitch frequency. This question has been asked in the literature to mixed results, with more recent conclusions in the negative. Whether or not the FFR contains the pitch frequency itself is debated, but what is agreed upon is that it contains nonlinearities not present in the stimuli, including correlates of the amplitude envelope of the stimulus; however these nonlinearities also remain undercharacterized. Part of the reason that the FFR and its relationship to auditory stimuli are not fully understood is that the FFR is a composite response reflecting multiple neural and peripheral generators, and their contributions to the scalp-recorded FFR vary in ill-understood ways depending on the electrode montage, stimulus, and imaging technique. The FFR is typically assumed to be generated in the auditory brainstem, and there has also been evidence both for and against a cortical contribution to the FFR. Here we used an exacting methodology to examine the FFR correlates of pitch and the generators of the FFR to stimuli with different pitches. Novel stimuli were designed to tease apart direct biological correlates of pitch and amplitude envelope. FFRs were recorded with 256-electrode EEG nets, in contrast to a typical FFR setup which only contains a single active electrode. EEG electrode locations were localized using a photogrammetry system and structural MRI scans were obtained for each participant to co-register with the electrodes and constrain a source localization algorithm. The results of this localization shed light on the generating mechanisms of the FFR, including both cortical and subcortical sources. This is the first study to use EEG and MRI in this way with respect to the FFR.

Auditory cortex inhibition and the Frequency-Following Response: a combined EEG-TMS study

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The frequency-following response (FFR) is an auditory evoked potential recorded throughout electroencephalography (EEG) that reproduces the periodic characteristics of the eliciting sound. FFR measures have proven to be sensitive to cognitive function, including language, learning and attention, as well as to several clinical conditions, such as autism spectrum disorder and dyslexia. Despite being a widely studied biosignal in auditory neuroscience, the neural underpinnings of the FFR are still unclear. Traditionally, FFR has been associated with subcortical activity originating in the auditory midbrain, but recent evidence revealed a major cortical contribution, at least for stimuli of fundamental frequency around 100 Hz. In the present study, we combined EEG with an inhibitory Transcranial Magnetic Stimulation (TMS) protocol, the continuous Theta Burst Stimulation (cTBS), to disentangle the cortical contribution to the FFR elicited to stimuli of high and low frequency. We recorded FFR to the syllable /ba/ at two fundamental frequencies (low: 113 Hz; high: 317 Hz) in healthy participants. FFR, Long-Latency Response (LLR) and Auditory Brainstem Response (ABR) were recorded before and after cTBS applied to the right auditory cortex. Results failed to reveal any effect of the transient inhibition of the right auditory cortex on the FFR signal, neither for that elicited to low or to high frequency stimulation. As expected, no significant effects were found for ABR. However, cTBS did not affect also the cortical components of LLR, possibly indicating a lack of effects of cTBS on our target auditory sensory area.

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Modulation of phase-locked neural responses to speech during different arousal states is age-dependent

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Phase-locked responses are vital for auditory perception and they may vary with participants' arousal state and age. Two phase-locked neural responses that reflect fine-grained acoustic properties of speech were examined in the current study: the frequency-following response (FFR) to the speech fundamental frequency (F0), which originates primarily from the auditory brainstem, and the theta-band phase-locked response (θ-PLV) to the speech envelope that originates from the auditory cortices. The ways these responses were affected by arousal in adults across a wide age-range (19–75 years) were examined. Extracts from electroencephalographic (EEG) responses to repeated syllables were classified into either high or low arousal state based on the occurrence of sleep spindles. The magnitudes of both FFRs and θ-PLVs were statistically greater in the high, than in the low, arousal state. The difference in θ-PLV between the two arousal states was significantly associated with sleep spindle density in the young, but not the older, adults. The results show that (1) arousal affects phase-locked processing of speech at cortical/sub-cortical sensory levels; and that (2) there is an interplay between aging and arousal state which indicates that sleep spindles have an age-dependent neuro-regulatory role on cortical processes. The results lay the grounds for studying how cognitive states affect early-stage neural activity in the auditory system across the lifespan.

Age-dependent changes in frequency-following responses as a potential marker of cochlear synaptopathy in humans

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Cochlear synaptopathy occurs as a consequence of noise exposure and aging but diagnostic measures in humans are missing. With synaptopathy, a reduction of the number of auditory nerve fibers may degrade processing of fine temporal cues relying on synchronous activity of many nerve fibers. The frequency following response (FFR) is believed to reflect synchronous neural activity phase locked to the stimulus temporal fine structure. At higher stimulus levels, the spread of excitation makes the FFR to pure tone stimuli a fairly broad band response reflecting synchronous activity of many nerve fibers. A reduced FFR for pure tone stimuli at high levels may thus reflect degraded neuronal synchrony due to loss of nerve fibers, even for FFR carrier frequencies at which there is no loss of sensitivity. Here, we investigated age-related changes in FFRs to pure tone stimuli elicited at high frequencies (703 Hz) and at high levels (85 dB SPL). Consistent with our hypotheses, results suggest a reduction in the FFR amplitude with age. Additionally, we used FFRs evoked by pure tone frequency sweeps to investigate phase locked activity at different carrier frequencies. Finally, we investigated the influence of background noise on the FFR response since animal models of envelope-following responses at high modulation frequencies have demonstrated age-dependent and possibly synaptopathy-related effects.

The frequency-following response (FFR) to speech stimuli: A normative dataset in healthy newborns

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The frequency-following response (FFR) is a non-invasive electrophysiological correlate of the encoding the temporal and spectral characteristics of the complex evoking sound in a cortico-subcortical auditory network. Abnormal FFRs are found in children with auditory processing disorders, dyslexia and autism suggesting the possibility to find in the FFR a neurophysiological marker of the efficient encoding of speech sounds. The FFR as a potential predictor of communication skills has been shown in school-aged children and in infants aged 3-10 months. The possibility to improve the FFR after a short music and language training have been demonstrated, suggesting the importance to record the FFR early when the cerebral plasticity is optimal. However, little is known about the neural transcription of speech sounds in newborns. The possibility to record the FFR in neonates has been suggested in few studies. Nevertheless, before the FFR can be used in the clinics, normative values need to be established.
The aim of this study was to provide a normative database depicting the standard variability found in different parameters extracted from the newborn FFR. The FFR was recorded from 50 neonates aged 12-144 hours to syllables /da/ and /ga/ (170 ms long; F_0=113 Hz; intensity: 55 dB SPL, 2000 sweeps, delivered with alternating polarities) and seven parameters were retrieved in the time and frequency domains. Newborns were tested after passing the universal hearing screening. Four subjects were excluded from the analysis because wave V could not be identified. Our study confirms the feasibility of recording the FFR at the maternity unit from the very onset of life and provides normative data from a sample of 46 newborns. Detecting an abnormal FFR in a newborn could lead to an early intervention that, given the plasticity of the underlying neurophysiological machinery, could promote an improvement in the encoding of speech sounds during the first years of life.

Auditory brainstem response to continuous speech

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Understanding speech in noisy backgrounds requires selective attention to a particular speaker. Humans excel at this challenging task, while current speech recognition technology still struggles when background noise is loud. The neural mechanisms by which we attend selectively to a particular speech signal remain, however, poorly understood, not least due to the complexity of natural speech. Here I present recent work on the role of the auditory brainstem in speech-in-noise listening. I show how the response of the auditory brainstem at the fundamental frequency of continuous, non-repetitive speech can be measured from scalp electrodes. I further demonstrate that this response is modulated by selective attention, that the scalp-recorded brainstem response can allow to decode attention in near real time, and that it relates to an individual's ability to understand speech in noise. These findings evidence a neural mechanisms of speech-in-noise comprehension, and may be applied in smart hearing aids that automatically adjust speech processing to assist a user.

Selective attention in the brainstem and speech-in-noise comprehension

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Cochlear synaptopathy can be caused by noise exposure and ageing. It refers to the damage of higher-threshold auditory-nerve fibers and may account for the differences in the ability of normal hearing threshold listeners when communicating in challenging environments (Bharadwaj et al., 2014). However, it remains unclear if the condition actually occurs in humans, how it can be best diagnosed, and how exactly it impacts speech-in-noise processing.

Recently we proposed a method for measuring the brainstem's response to natural non-repetitive speech and employed it to show that the auditory brainstem already plays a role in selective attention to speech (Forte et al., 2017). We thereby observed individual differences in the modulation of the brainstem response by selective attention: some subjects showed large attentional modulation while others exhibited only little modulation. We therefore wondered if the strength of the attentional modulation correlates with hearing ability and if it relates to cochlear synaptopathy.

We approached this issue through a computational model and experimental measurements. First, we developed a realistic computational model of the auditory-brainstem response (ABR) to speech based on an existing model (Zilany et al., 2014). We employed it to investigate the neural response to continuous speech at different stages in the brainstem, and to explore the effects of cochlear synaptopathy. We found significant responses and characteristic latencies for neural signals generated at the level of the auditory- nerve fibres, the cochlear nuclei and the inferior colliculus (IC). The latency of the response of the IC matched the latency that we found experimentally, suggesting that the scalp-recorded brainstem response to speech is dominated by the IC.

Secondly, we assessed young healthy listeners for speech-in-noise comprehension, lifetime noise exposure, the middle ear muscle reflex, binaural hearing and different brainstem measures, including the brainstem response to continuous speech and its modulation by selective attention. We found that there was considerable variability in all measures across the participants. The tests showed only scant evidence for cochlear synaptopathy among the volunteers and we did not find indication that neither the variability in attentional modulation nor the variation in speech-in-noise perception relates with the synaptopathy. However, we show that the attentional modulation of the speech-evoked brainstem activity can partly explain a subject's ability to understand speech in noise.

Effects of ageing and noise exposure on the FFR - implications for speech in noise

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A common complaint among (older) adults, even those without hearing loss, is poor speech perception in noisy environments. These difficulties may to some extent be due to cochlear synaptopathy, that is, the loss of synapses between inner hair cells and the auditory nerve, which can arise as a result of noise exposure and/or ageing. I will present results from two studies which investigated the incidence of cochlear synaptopathy in humans and examined the potential consequences of synaptopathy for speech perception in noise. Study 1 focused on older adults (60-72 years old) with clinically normal hearing. Study 2 focused on middle-aged adults (45-60 years old) with self-reported noise exposure history and normal audiograms. The data in both studies were compared to a young control group (18-29 years old).

We measured frequency following responses (FFRs) to assess cochlear synaptopathy. In Study 1 FFRs were elicited in response to the vowel /ɑ/ in quiet, and in steady-state and amplitude-modulated noise. In Study 2 the stimulus was a 2.8 kHz transposed tone amplitude modulated at 176 Hz at one of three different modulation depths (0, -4, and -8 dB). To examine the potential effects of cochlear synaptopathy on speech perception in noise, we measured speech reception thresholds (SRTs) using different types of background noise. In Study 1, SRTs were measured to sentences in steady-state and amplitude-modulated speech-shaped noise, as well as two-talker babble. In Study 2, SRTs were measured for both consonants (VCVs) and sentences at two different levels (40 and 80 dB SPL) and in two conditions, one where both the target and background noise were diotic (N_0S_0), and another where the target signal was inverted in polarity in one ear (N_0S_π), leading to a phase disparity across the ears. We computed the binaural intelligibility level difference (BILD) by taking the difference between the N_0S_0 and N_0S_π conditions. Of particular interest is the relationship between our electrophysiological measures of cochlear synaptopathy and our behavioural speech-in-noise measures.

The FFRs of the older adults were less robust compared to the younger participants in quiet, steady-state and amplitude-modulated noise. However, these declines, which may be indicative of synaptopathy, were not necessarily associated with impaired perception of speech in noise in normal-hearing older adults (aged 60+). Data collection for Study 2 is ongoing. We predict that the middle-aged noise-exposed group will show less robust FFRs compared to the young controls. In addition, we expect that they will perform more poorly on the speech-in-noise tasks, particularly at higher stimulus levels.

The FFR and second language learning in adulthood

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In a globalized world, a growing number of people are moving to a new country and attempting to learn a second language (L2) in adulthood. However, L2 acquisition is characterized by large individual differences, with some people achieving near-native performance with ease while others produce heavily accented speech, struggle to comprehend speech, and display less grammatical and lexical knowledge. The auditory system is the primary route by which most language learners are exposed to language, and auditory patterns provide cues to language structure on multiple levels, from phonemes to syntax. However, there exist large individual differences in auditory processing, even in typically developing adults, and this variability could have consequences for the speed of second language learning. In this talk I will present data from native speakers of Mandarin and Polish who recently moved to London, showing that impaired auditory processing, as measured via both psychophysical thresholds and the FFR, is linked to impaired second language learning, including acquisition of phonemic and syntactic knowledge. This suggests that tests of language learning aptitude should include assessments of sound perception, and that a brief course of auditory training might help some individuals benefit more from their language learning experiences.

Exploring the effect of stimulus complexity, frequency and intonation on the FFR

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Frequency following responses (FFRs) can be evoked by a wide range of stimuli. As a result, studies often use different stimuli, complicating the comparison of their results. Besides, it is not very clear which stimuli provide the largest response SNRs, which is important information in the context of clinical applications. To bring some clarity to this matter, we explore the parameter space of three important stimulus parameters and studied the effect on the SNR of the FFR in normal hearing individuals. The first parameter incorporated in the study is the complexity of the stimulus, i.e. from simple modulated tones, over Klatt synthesized vowels, to natural vowels. In the first case, we study the FFR in response to the modulation frequency. For the other two, we study the FFR to the fundamental frequency of the voice. Second, we compare response SNRs across different frequency ranges, i.e. around 100, 150 or 200 Hz. Third, we study how intonation, i.e. the direction of variation of the fundamental frequency, affects the response SNR. We considered three cases: upward, flat, or downward intonation. FFRs are measured with 64 channel EEG and processed with a Fourier Analyzer. Data collection for this study is ongoing and preliminary results will be presented at the conference.

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Bridging the Gap between Supra-threshold Markers of Sensorineural Hearing Loss: Subcortical Envelope-Following Response and Speech Audiometry

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Sensorineural hearing loss (SNHL) underlies many self-reported cases of hearing decline, but not all SNHL aspects can be diagnosed by pure-tone audiograms or standard threshold measures. Recent histological studies reveal progressive cochlear deafferentation with age, noise-exposure or due to ototoxicity. It was suggested that the observed loss of synapses between inner hair cells (IHC) and auditory nerve (AN) fibers precedes permanent elevation of hearing thresholds and affects supra-threshold performance especially in complex sound environments. Animal studies report a relation between the number of intact IHC-AN synapses and subcortical auditory-evoked potentials (AEP) in response to supra-threshold stimulation. However, the application of AEPs for non-invasive diagnostics in humans and their relationship to sound perception are not straightforward.

The present study focuses on the evaluation of different methods to extract the periodic neural component of the AEP that is phase locked to the stimulus envelope (envelope-following response; EFR) as a potential proxy measure for cochlear synaptopathy. The resulting metrics were compared to the supra-threshold speech audiometry measures as a psychoacoustic marker of impaired hearing.

Two 95%-amplitude-modulated (120 Hz) stimuli with 4-kHz pure-tone carrier and (I) sinusoidal, (II) 25% duty-cycle square-wave envelopes were presented with the same peak-to-peak values as (I) at 70 dB SPL. Speech reception thresholds (SRTs) were obtained using the German Oldenburg Sentence Test (OLSA) with constant noise (70 dB SPL) and adaptive speech levels. Three speech and noise conditions were considered: unfiltered, 1.5-kHz low- and 1.65-kHz high-pass filtered material. Psychoacoustic and EEG data were recorded from young normal-hearing participants (yNH), older listeners with normal audiometric thresholds (oNH) and impaired audiometric profiles (oHI).

Results show monotonically increasing correlations between SRTs and EFRs calculated based on (I) one spectral component of the sustained AEP corresponding to the fundamental frequency of the modulator F0, (II) F0 corrected by the individual noise floor and (III) trigonometric sum of F0 and all available harmonics corrected by the noise floor value. High-pass filtered speech-in-noise (SiN) material targets similar cochlear frequency region as the 4-kHz carrier and results in a stronger correlation with the EFRs compared to the low-pass or unfiltered SiN conditions. The strongest correlation was observed between high-pass SiN and EFRs evoked by the square-wave envelope stimulus with a shorter duty-cycle (II).

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