

## Chapter 26

# No Evidence for ITD-Specific Adaptation in the Frequency Following Response

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**Abstract** Neurons sensitive to interaural time differences (ITDs) in the fine structure of low-frequency signals have been found in binaurally responsive auditory nuclei in a wide range of species. The present study investigated whether the frequency following response (FFR) would show evidence for neurons “tuned” to ITD in humans. The FFR is a scalp-recorded measure of sustained phase-locked brainstem activity that has been shown to follow the frequency of low-frequency tones. The magnitude of the FFR often decreases over time for tones of long duration. The present study investigated whether this adaptation effect is ITD specific.

The FFR to a 100-ms, 80-dB SPL, 504-Hz target tone was measured for ten subjects. The target was preceded by a 200-ms, 80-dB SPL, 504-Hz adaptor. The target always led by 0.5 ms in the left ear. The adaptor led either in the left ear or in the right ear by 0.5 ms. Stimuli (adaptor + target = pair) were presented in alternating polarity at a rate of 1.81 Hz. We used a “vertical” montage (+Fz, – C7, ground = Fpz) for which the FFR is assumed to reflect phase-locked neural activity from rostral generators in the brainstem. The averaged FFR waveforms for each polarity were subtracted, to enhance temporal fine structure responses. The results showed significant adaptation effects in the spectral magnitude of the FFR. However, adaptation was not larger when the adaptor had the same ITD as the target than when the ITD of the adaptor differed from that of the target. Thus, the current data provide no evidence that the spectral magnitude of the scalp-recorded FFR provides a non-invasive indicator of ITD-specific neural activation.

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## 1 Introduction

Interaural time differences (ITDs) provide a major cue for the localisation of low-frequency sounds in azimuth. Neurons sensitive to ITD in the fine structure of low-frequency signals have been found in binaurally responsive auditory nuclei in a wide range of species. However, the exact way in which ITD-sensitive neurons contribute to sound localisation is still under debate. The majority of physiological knowledge on ITD-sensitive neurons is based on animal studies. In these, electrophysiological recordings from one side of the brainstem or mid-brain (mostly from individual neurons in the inferior colliculus, IC) indicate that the peaks of the functions relating neuronal discharge rate to ITD are distributed around a mean of 200–300  $\mu$ s; for most neurons, the maximal discharge rate is found for a tone leading to the side contralateral to the recording side. There is evidence for adaptation in the IC specific to ITD that can be distinguished from adaptation in earlier monaural pathways (McAlpine et al. 2000; Ingham and McAlpine 2004). Ingham and McAlpine (2004) recorded from single IC neurons of the guinea pig. A given ITD-sensitive neuron was first adapted by a 1-s stimulus with its worst ITD, i.e. the ITD that produced the least firing. This was done so that all monaural components in the auditory pathway were adapted. When the ITD was suddenly changed to the neuron's best ITD (the ITD that produced the highest firing rate), the firing rate increased and then adapted again to a rate that was higher than the previous adapted rate. These results indicate that a change in ITD following an adaptation period can lead to an enhanced neural response in some neurons.

In humans, recording from individual neurons in the IC is rarely possible. The present study investigated whether ITD-specific adaptation would be evident in the scalp-recorded frequency following response (FFR) measured in humans. The FFR reflects sustained activity in a population of neurons that phase lock to stimulus-related periodicities (Marsh et al. 1975; Smith et al. 1975; Glaser et al. 1976). The contribution from various anatomical sources to the FFR depends on electrode positions. Here, a “vertical” electrode montage (see Sect. 2) was used. For this, the FFR is generally assumed to reflect sustained phase-locked neural activity from rostral generators in both hemispheres of the brainstem (IC and lateral lemniscus, LL). Hence, the FFR to our test sounds will have been driven by neurons with a wide range of locations throughout both ICs. Our experimental question was whether the FFR to a target sound with a given ITD would be reduced more by an adaptor that had the same, rather than a different, ITD. The rationale is based on the assumption that, as in other EEG adaptation studies (Näätänen et al. 1988), an adaptor will reduce the measured response more when it adapts those neurons responding most strongly to the target than when it adapts neurons that respond less strongly to the target.

## 2 Methods

### 2.1 Stimuli

The FFR to a 100-ms, 80-dB SPL, 504-Hz target tone was measured. The target was preceded by a 200-ms, 80-dB SPL, 504-Hz adaptor. The target always led by 0.5 ms in the left ear. The adaptor either led in the left ear (condition “LL”) or the right ear (condition “RL”) by 0.5 ms. The target followed the adaptor either immediately (“no-gap” condition) or after a silent gap corresponding to 10 cycles of the 504-Hz tone (19.841 ms; “with-gap” condition). All tone durations included 5-ms raised-cosine rise/fall times.

The target always had a starting phase of  $-0.4\pi$  (this is the phase that occurs 200 ms after the start of a 504-Hz tone starting with zero phase). A change of ITD between adaptor and target creates *within*-ear differences between the phase of the ringing on the basilar membrane (BM) after the end of the adaptor and the onset phase of the target, potentially leading to a “dip” in the response on the BM (Shailer and Moore 1987). Such a dip might affect the FFR in response to the target. To equate the dips across conditions, the starting phase of the adaptor was adjusted as follows. In condition RL, the adaptor started at zero phase in both ears (but was delayed by 0.5 ms in the left ear). In this condition, the change in ITD between adaptor and target resulted in unavoidable within-ear phase shifts at the transition between adaptor and target of  $+\theta$  and  $-\theta$  in the left and right ears, respectively;  $\theta$  was equal to  $0.504\pi$  (i.e.  $2\pi$  ITD/period of the tone). In condition LL, the starting phase of the adaptor was  $+\theta$  in both ears (but its onset was delayed by 0.5 ms in the right ear). The result was a phase shift at the transition between adaptor and target of  $-\theta$  in both ears. Thus, assuming that phase shifts of  $+\theta$  and  $-\theta$  result in similar dips in the BM response (Shailer and Moore 1987), dips were equal across conditions.

Stimuli were generated with 16-bit resolution and a sampling rate of 40 kHz. They were played out through the digital-to-analogue converter included in the evoked potentials acquisition system (Intelligent Hearing Systems-Smart-EP, IHS) and presented binaurally through mu-metal shielded Etymotic Research ER2 insert earphones.

### 2.2 Recording

The FFR was recorded differentially between gold-plated scalp electrodes positioned at the midline of the forehead at the hairline (+, Fz) and at the seventh cervical vertebra (–, C7). A third electrode placed on the mid-forehead (Fpz) served as

the common ground. Electrode impedances were less than 1 k $\Omega$  for all recordings. The FFR signal was recorded with a sampling rate of 8 kHz, amplified by a factor of 100,000, and band-pass filtered from 50 to 3,000 Hz (6 dB/octave roll-off, resistor-capacitor filter). Epochs with voltage changes exceeding 31  $\mu$ V were automatically discarded and the trial repeated. The starting polarity of the stimuli (adaptor + target) was alternated for each presentation, and alternate-polarity sweeps were recorded and averaged in separate data buffers by the SmartEP system. Stimuli were played with a repetition rate of 1.81/s. The same stimulus condition was played in blocks of 1,500 (valid) trials; two blocks were run for each condition in randomized order across subjects.

### **2.3 Analysis**

Offline processing was done using MATLAB (MathWorks, Natick, MA). First, the averaged FFR responses for original-polarity and for inverted-polarity stimuli were subtracted and the result divided by two, for each subject and condition. Subtraction of responses to alternating polarity stimuli enhances the representation of phase locking in response to temporal fine structure information and minimizes the representation of phase-locked activity to the envelope of the stimulus. The resulting waveform was high-pass and low-pass filtered at 150 and 2,000 Hz (eighth-order digital Butterworth filter; 3-dB down cutoff frequencies), respectively. The FFR was analysed and compared across five 50-ms time ranges: (1) from 12 to 62 ms after adaptor onset (A-start), (2) from 62 to 112 ms after adaptor onset (A-mid), (3) from 150 to 200 ms after adaptor onset (A-end), (4) from 12 to 62 ms after target onset (T-start), and (5) from 50 to 100 ms after target onset (T-end). For spectral analysis, for each subject, the 50-ms waveform was zero-padded symmetrically to make up a 1-s signal, and the magnitude spectrum was calculated via a Discrete Fourier Transform. The magnitude spectrum is specified in decibels re 0.01  $\mu$ V. The dependent measure for the amount of phase-locked neural activity (the FFR strength) was defined as the highest magnitude present in the spectrum within a 12-Hz range centred at 504 Hz.

### **2.4 Subjects**

Ten subjects (four male) participated in both experiments. They ranged in age from 20 to 24 years and had self-reported normal hearing. The 10 were selected from a pool of 13 subjects, because they showed clear FFR signals. The experiment was conducted in one session, lasting for about 3 h, including breaks.

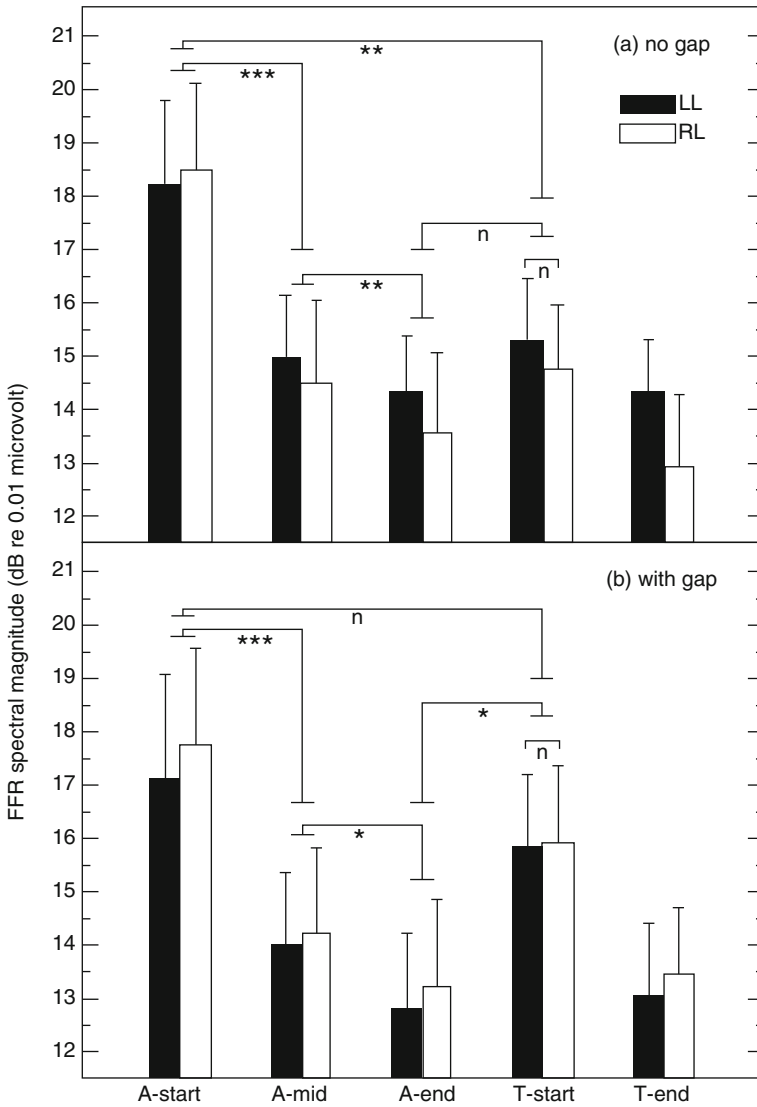
### 3 Results

The latency of the unprocessed FFRs was between 7.5 and 10 ms, estimated visually as the time point relative to stimulus onset of the first occurrence of a major amplitude excursion followed by a regular pattern in the FFR traces. This is in good agreement with the range of latencies reported in the literature for FFRs (Glaser et al. 1976; Skoe and Kraus 2010) and is consistent with a generation site at the level of the IC or LL.

Figure 26.1 shows the FFR strength (the magnitude of the peak at  $504 \pm 6$  Hz in the spectrum of the FFR) averaged across subjects and the corresponding standard error across subjects. First consider the no-gap conditions (panel (a), top). Importantly, adaptation over time is clearly visible in the FFR. To assess the significance of the reduction in FFR strength across time periods, four separate repeated measure two-way analyses of variances, ANOVAs (with factors time and adaptor ITD), were calculated. The first showed that the FFR strength was significantly larger during period A-start than during period A-mid [ $F(1,9)=42.4$ ,  $p<0.001$ ]. The second showed that the FFR strength was significantly larger during period A-mid than during period A-end [ $F(1,9)=14.93$ ,  $p<0.01$ ]. The third showed that during period T-start, the FFR strength was not significantly larger than during period A-end; the ANOVA showed no significant main effect or interaction. The fourth showed that the FFR strength was significantly larger during period A-start than during T-start [ $F(1,9)=18.80$ ,  $p<0.01$ ]. In all of these ANOVAs, the effect of adaptor ITD and its interaction with time period were both nonsignificant. The main effects of time period show that there was significant adaptation over time, which was not restricted to a short period after the onset of the stimulus and which was not abolished by the offset and onset ramps at the transition from adaptor to target.

To assess whether there was ITD-specific adaptation, the FFR strength during period T-start was compared across the conditions where the adaptor had the same ITD as the target (LL) and where it did not (RL). A paired-sample *t*-test showed no significant difference between the FFR strength for these two conditions [second group of two bars from the right;  $t(9)=1.11$ ,  $p=0.30$ ]. Thus, although the FFR response to the target was reduced due to the preceding adaptor, there was no evidence that this adaptation depended on whether the ITD of the adaptor matched that of the target.

Consider next the with-gap conditions (panel (b), bottom). Again, adaptation over time was visible in the FFR. However, the short silent gap between the adaptor and the target largely abolished the reduction in FFR strength during period T-start. The results of the ANOVAs were as follows. First, the FFR strength was significantly smaller during period A-mid than during period A-start [ $F(1,9)=28.67$ ,  $p<0.001$ ]. Second, the FFR strength was significantly smaller during period A-end than during period A-mid [ $F(1,9)=5.57$ ,  $p<0.05$ ]. Third, the FFR strength was significantly larger during period T-start than during period A-end [ $F(1,9)=7.47$ ,  $p<0.05$ ].



**Fig. 26.1** Mean FFR spectral magnitude at 504 Hz and the corresponding standard errors across ten subjects. Panel **a** shows the data for the no-gap condition. The three left-hand groups of two bars show the FFR strength during three time ranges of the stimulation with the adaptor: 12–62 ms after onset (*A-start*), 62–112 ms after onset (*A-mid*), and 150–200 ms after onset (*A-end*). The two right-hand groups of two bars show the FFR strength during two time ranges of the stimulation with the target: 12–62 ms after onset (*T-start*) and 50–100 ms after onset (*T-end*). The *black* and the *white* bars show results when the adaptor led in the left and right ears, respectively. Panel **b** is as (a), but for the with-gap condition.  $n = p > 0.05$ ;  $* = p < 0.05$ ;  $** = p < 0.01$ ;  $*** = p < 0.001$

The effect of time period indicates significant recovery from adaptation. Fourth, the FFR strength was not significantly larger during *A-start* than during *T-start* [ $F(1,9) = 2.13$ ,  $p > 0.18$ ]. In all of these ANOVAs, the effect of adaptor ITD and its

interaction with time period were both nonsignificant. Thus, while there was significant adaptation over the course of the adaptor, the larger FFR at T-start than at A-end meant that a silent gap of only ten cycles duration was sufficient to allow significant recovery from adaptation. In addition, a paired-sample *t*-test comparing FFR strength during T-start across conditions LL and LR showed no significant difference [ $t(9) = -0.26$ ,  $p = 0.80$ ]. This was not entirely surprising, as the short silent gap before T-start allowed significant recovery from adaption.

## 4 Discussion and Conclusion

The FFR strength in response to the left-leading target was not smaller when it was preceded by the left-leading adaptor than when preceded by the right-leading adaptor. Thus, the observed adaptation effect of the adaptor on the response to the target could have been dominated by the adaptation of monaural components in the auditory pathway. Several (not mutually exclusive) factors may contribute to this finding.

1. Not all neurons in the IC, and not all neurons that contribute to the FFR, are ITD sensitive. The responses of such neurons would dilute a differential adaptation effect of the two adaptors.
2. One assumption underlying our rationale was that neurons responding to the left-leading target would have responded more strongly to the adaptor in condition LL than in condition RL. In animal studies, the majority of ITD-sensitive neurons were found to have peaks in the firing rate vs. ITD function between 100 and 300  $\mu$ s; the best ITD varies across neurons. Given that we used ITDs of 500  $\mu$ s, it is possible that some ITD-sensitive neurons would not have shown a large difference in response to the adaptors in condition LL vs. RL.

A second assumption was that the FFR to the target would be reduced more when the adaptor preferentially excited neurons that were more sensitive to the target's ITD than when the adaptor preferentially excited neurons sensitive to the opposite ITD. Consider a simple model in which the FFR corresponds to the linear sum of activity from neurons tuned to left-leading and from neurons tuned to right-leading ITDs. The firing rate of neurons tuned to left-leading ITDs and responding to the left-leading target would be reduced more in condition LL than in condition RL. However, neurons tuned to right-leading ITDs may still have responded to the left-leading target, and for these neurons, the reduction in firing rate caused by the adaptor would have been greater in condition RL than in condition LL. If adaptation reduces the firing rate to the target by a certain amount (only depending on the response to the adaptor), then the two opposing effects could theoretically completely cancel each other. In practice, the fixed reduction in firing rate is limited by the fact that firing rate cannot drop below zero, and thus, complete cancellation would only occur if no or few neurons were subject to this "floor effect". Alternatively, if one assumes reduction by a certain factor (a multiplicative adaptation process), then the effects would not completely

cancel. This follows because neurons tuned to the left-leading target have (by definition) a larger unadapted response to the target than neurons tuned to the opposite ITD, and so their firing rates would be reduced by a greater amount.

3. The FFR requires averaging over several thousand trials. Therefore, stimuli were played with a repetition rate of 1.81/s, giving an inter-target interval (end of target to start of next target) of 452.5 ms. It is possible that the interval between successive targets was not sufficiently long to allow ITD-sensitive neurons firing in response to the target to fully recover from adaptation due to the previous target (Ingham and McAlpine 2004). Hence, even in condition RL, there may have been some ITD-specific adaptation from the previous targets. However, this would presumably have been substantially smaller than the ITD-specific adaptation occurring in condition LL.

In conclusion, although we observed substantial and significant adaptation of the scalp-recorded FFR in humans, we found no evidence that this adaptation was ITD specific.

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