1   **Title:** Case studies in neuroscience: Subcortical origins of the frequency-following response
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3   **Running title:** Subcortical origins of the FFR
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45 **Abstract:** The auditory frequency-following response (FFR) reflects synchronized and phase-

46 locked activity along the auditory pathway in response to sound. While historically thought to

47 reflect subcortical activity, recent evidence suggests an auditory cortex contribution as well.

48 Here we present electrophysiological evidence for the FFR's origins from two cases: a patient

49 with bilateral auditory cortex lesions and a patient with auditory neuropathy, a condition of

50 subcortical origin. The patient with auditory cortex lesions had robust and replicable FFRs, but

51 no cortical responses. In contrast, the patient with auditory neuropathy had no FFR despite

52 robust and replicable cortical responses. This double dissociation shows that subcortical

53 synchrony is necessary and sufficient to generate an FFR.

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74 **Introduction**

75   The FFR has emerged in neuroscience as a means to understand auditory behaviors such

76 as speech and music perception, real-world listening, and experience-dependent plasticity in

77 auditory processing. FFRs have long been thought to originate primarily in subcortical auditory

78 nuclei, with the inferior colliculus of the auditory midbrain serving a chief role; indeed FFRs

79 recorded directly from the midbrain strongly resemble those recorded at the scalp (White-

80 Schwoch et al. 2017) and cooling the inferior colliculus eliminates FFRs (Smith et al. 1975). This

81 hypothesis is also supported by evidence in humans. Sohmer and Pratt (1977) showed that FFRs

82 were absent in 9 patients with brainstem lesions. Bidelman (2015, 2018) recorded FFRs with

83 high-density, multichannel EEG and used source modeling to show that FFRs reflect sustained

84 auditory midbrain activity.

85   Recent MEG evidence indicates a role for the right hemisphere auditory cortex in

86 generating FFRs to the fundamental frequency (F0), along with contributions from the

87 brainstem, midbrain, and thalamus (Coffey et al. 2016) (see (Zhao and Kuhl 2018) for additional

88 MEG evidence pointing to subcortical sources of the FFR). Some authors have suggested these

89 MEG results should be considered when interpreting EEG FFRs (Coffey et al. 2016, 2017;

90 Holmes and Herrmann 2017; but see Bidelman 2018), the prevailing approach for recording

91 FFRs. This raises the question: is the auditory midbrain necessary and sufficient to generate an

92 FFR?

93   To provide clarity to the origins of the scalp-recorded FFR, we conducted a dual case

94 study. Specifically, we conducted an electrophysiological test battery in two patients who

95 provide rare opportunities to test multiple hypotheses about the origins of the FFR.

96   **Materials and Methods**

97   This study compares auditory-neurophysiological responses in two patients: NR, who

98   has bilateral auditory cortex lesions, and IT, who has auditory neuropathy. Details on their case

99   histories are presented in the results section, but both have essentially normal cochlear

100   function (see Figs. 1 and 2). Both patients provided written consent to participate in the project,

101   and procedures were approved by the Institutional Review Board of Northwestern University.

102   Auditory brainstem responses (ABRs), FFRs, and cortical potentials were recorded in

103   both patients.

104   The stimulus for ABRs was a 100 µs click presented at 80 dB SPL and 31.1 Hz and

105   recorded with a Bio-Logic NavPro system. Clicks were presented in rarefaction (and, for IT, also

106   condensation) polarity, and 2,000 artifact-free responses were recorded. Responses were

107   averaged from 100-1,500 Hz online. We also have records of an ABR latency-intensity function

108   for NR (see Fig. 1c), which used rarefaction clicks at 13.3 Hz with similar filtering, and also on a

109   Bio-Logic NavPro.

110   The stimulus for FFRs and cortical potentials was a 170-ms [da] used in previous studies

111   (Anderson et al. 2012). In addition to the [da] collected in quiet, we presented it in background

112   noise, a six-talker babble track (timed to avoid phase synchrony with the [da]). We wanted a

113   second, more challenging stimulus condition to compare to responses in quiet. This would let

114   us test both whether responses are absent or present, and test for changes in response

115   morphology as a function of listening condition (cf. White-Schwoch et al. 2015). We chose noise

116   given evidence that patients with neuropathy have significant difficulties understanding speech

117   in noise (Kraus et al. 2000).

118   For FFRs, the [da] was presented at 3.9 Hz at 80 dB SPL in alternating polarities; 6000

119   artifact-free responses were collected in the quiet and background noise conditions from Cz,

120   filtered from 70-2000 Hz, and epoched from 0-210 ms re stimulus onset. The SNR for the noise

121   condition was +10 dB. NR's FFRs were recorded in a Neuroscan SynAmps system and IT's FFRs

122   were recorded in a Biosemi Active2 system.

123   Spectra were computed via fast Fourier transforms. For cortical responses, the [da] was

124   presented at 1 Hz at 80 dB SPL in alternating polarity; 500 artifact-free responses were

125   collected in each condition from Cz, filtered from 1-40 Hz, and epoched from -100-500 ms re

126   stimulus onset. Similar to the FFR, the SNR for the noise condition was +10 dB. Both responses

127   were recorded in a Neuroscan SynAmps system; NR's responses were recorded with a 32-

128   channel cap and IT's with a single channel at Cz.

129   **Results**

130   The first case, NR, is a 28-year-old male with bilateral auditory cortex lesions following

131   treatment for acute lymphoblastic leukemia. His treatment included a breathing tube that was

132   dislodged, causing hypoxia, followed by a medically induced coma, multiple rounds of

133   chemotherapy, and a bone marrow transplant. Following his treatment he experienced hearing

134   difficulties. His medical team conducted an MRI and the radiologist's report identified bilateral

135   temporal lobe lesions.

136   NR is cortically deaf: he lacks awareness of sounds and cannot understand speech or

137   music. He also exhibits signs of mild visual agnosia. Cognitive abilities were otherwise normal.

138   Due to his poor ability to detect sounds, NR could not complete a behavioral audiogram. But,

139   NR had normal distortion product otoacoustic emissions (DPOAEs; see Fig. 1a for a DP-gram)

140   and auditory brainstem responses (ABRs; Fig. 1b/1c), indicating an origin central to the auditory

141   midbrain for his deafness. Consistent with the diagnosis of cortical deafness, NR had absent

142   cortical auditory evoked potentials (Fig. P1/N1; Fig. 2e).

143   Yet, NR had robust and highly replicable FFRs (Fig. 1a). Latencies and amplitudes were

144   within normal limits and similar to healthy, age-matched controls (Anderson et al. 2012). NR

145   had robust responses to the fundamental frequency in both quiet and background noise (Fig.

146   1b), which is noteworthy because MEG source modeling ascribes the FFR to the 100-Hz F0 of

147   this stimulus, at least in part, to the auditory cortex (Coffey et al. 2016). NR's robust response to

148   the F0 suggests that multiple sources can contribute to the F0 component of the FFR, consistent

149   with MEG source analysis (Coffey et al. 2016)—and NR's response shows that cortex is not

150   necessary for generating low frequency components of the FFR. NR's case is consistent with

151   studies in cats that were lesioned in either the IC or auditory cortex, and showed that IC was

152   necessary and sufficient to generate FFRs (Kiren et al. 1994).

153   The second case, IT, is a 41-year-old woman with auditory neuropathy, meaning she has

154   intact outer hair cell function in the cochlea but an absent auditory brainstem response due to

155   dyssynchronous subcortical firing (Starr et al. 1996). IT has tremendous difficulty understanding

156   speech in adverse listening conditions, such as noisy environments, but has normal speech

157   perception in quiet. She also reports some difficulty with sound awareness, albeit not to the

158   extent of NR, and difficulty understanding unfamiliar accents. IT had a normal audiogram (Fig.

159   2a) and normal DPOAEs (Fig. 2, inset) but an absent ABR bilaterally (Fig. 2b/c). Additionally, and

160   consistent with her absent ABR, IT had no FFR (Fig. 3b, 3d).

161   Yet, she had robust and highly replicable cortical responses (Fig. 3f). Her response in

162   quiet was somewhat larger than typically observed in adults (cf. Cunningham et al. 2000), albeit

163   later, and her response in noise was particularly delayed. This may reflect cortical-subcortical

164   interactions, particularly for coding speech features in noise. Her cortical response is also

165   evocative of that found in older adults, where larger responses are thought to reflect

166   compensatory mechanisms (Bidelman et al. 2014; Roque et al. 2019). Moreover, her response

167   likely lacks normal brainstem inhibitory processes. It is noteworthy that her response in noise is

168   especially delayed given her difficulties understanding speech in noise. Cortical-subcortical

169   interactions may partially drive cortical responses to speech in noise. Still, overall, her case is

170   consistent with the notion that a functioning auditory cortex is not sufficient to generate an

171   FFR.

172   **Discussion**

173   Together, NR and IT show a double dissociation: auditory cortex is necessary for cortical

174   responses but unnecessary for FFRs. Highly precise subcortical synchrony is necessary for FFRs

175   but unnecessary for cortical responses. The auditory midbrain and cortex may specialize to fill

176   distinct roles in auditory perception. If the cortex does not receive synchronous input from the

177   midbrain, the signal will be temporally smeared such that the cortex will not be able to

178   reconstruct it. Indeed, listeners with neuropathy exhibit profound deficits with fast temporal

179   processing (Kraus et al. 2000; Starr et al. 1996; Zeng et al. 1999). In contrast, NR's case shows

180   that this fine temporal resolution can be intact but is insufficient for speech communication or

181   music perception.

182   One drawback of this study is that we do not have detailed anatomical information

183   about NR's lesions. We have the radiologist's report, which indicates bilateral temporal lobe

184   lesions but does not provide detailed information about the possibility of residual auditory

185   fields. We note the complete absence of a cortical evoked potential, which is consistent with

186   auditory cortex lesions (Özdamar et al. 1982). Nevertheless, with our current data we cannot

187   rule out the possibility of residual cortical contributions to his FFR, although we think it unlikely

188   that such a contribution would contribute to the FFR but *not* generate any cortical evoked

189   potential (i.e. consist only of 100 Hz phaselocking).

190   In IT's case we similarly do not have a precise localization of the "site of lesion" – her

191   neuropathy may be pre- and/or post-synaptic. We note evidence of an MLR visible in her FFR

192   tracings (in the 25-75 ms rage; see Fig. 3b) consistent with functioning thalamic and

193   corticothalamic pathways (Kraus et al. 1982, 1988) and reinforces evidence of a subcortical

194   neuropathy. Still, a number of subcortical insults and lesions can produce the auditory

195   neuropathy phenotype (Kraus et al. 1984; Starr et al. 1996, 2003).

196   This is neither to gainsay cortical contributions to healthy subjects' FFRs, nor to

197   undermine the strong, long-term influence of cortical processing on subcortical auditory

198   function. As with any case study, our results depend on rare circumstances that may not

199   generalize to all subjects. Noteworthy, however, is their consistency with early FFR work in

200   humans (Sohmer et al. 1977), recent source modeling work (Bidelman 2015, 2018), and lesion

201   studies in animals (Kiren et al. 1994). When considered in tandem with previous work, these

202   case studies show that accurate and synchronous encoding of the auditory midbrain is

203   necessary and sufficient to generate an electrophysiological FFR.

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208   **Competing Interests:** The authors declare no competing interests.
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271   **Figure Captions**

272   **Figure 1:** Results from NR's audiology testing. (A) Distortion product otoacoustic emission

273   results for the right (red) and left (blue) ears from 516-10,008 Hz. Plotted is the SNR of the

274   emission (distortion product minus noise floor, DP-NF). Overall NR has normal cochlear

275   function, with a possible notch noted in the right ear. He may have a mild sensorineural hearing

276   loss from chemotherapy. (B) ABRs collected in the Auditory Neuroscience Laboratory in

277   response to a rarefaction click presented at 31.1 Hz and 80 dB SPL. Thin lines show two runs of

278   the click ABR with the bold line showing their average. While the morphology is somewhat

279   idiosyncratic, the response is reliable. (C) ABR latency-intensity study provided to us by NR's

280   audiologist. Both ears show normal responses to changes in intensity (note this click was

281   delivered at 13.3 Hz).

282   **Figure 2:** Results from IT's audiology testing. (A) Audiogram shows normal hearing thresholds.

283   Right ear is shown in red, left ear in blue, and bone-conduction testing in grey. The inset shows

284   DPOAEs in the right and left ears, which are robust. (B/C) ABRs were elicited at 31.1 Hz and 80

285   dB SPL in rarefaction (bright colors) and condensation (duller colors) in the right and left ears,

286   respectively. Consistent with her diagnosis of auditory neuropathy, IT had absent ABRs.

287   **Figure 3:** Subcortical and cortical responses are shown for both NR and IT. Each panel is

288   organized analogously. The top two rows shows FFRs to "da" in quiet (black) and noise (purple)

289   in the time and frequency domains, respectively. NR has robust responses in both conditions,

290   including to the F0 at 100 Hz, which were within normal limits (Anderson et al. 2012). IT has no

291   FFR. The bottom row shows cortical responses to the same stimuli. NR has no cortical response

292   but IT has a robust P1/N1 response both in quiet and noise.

DP-Gram

ABR (31.1 Hz, 80 dB SPL)

ABR Latency-Intensity Function (13.3 Hz)

Audigram

Frequency (Hz)

DPOAEs

ABR-Right

ABR-Left