Sex differences in auditory subcortical function

Jennifer Krizman [a,b], Erika Skoe [a], Nina Kraus [a,b,c,d,*]

[a] Auditory Neuroscience Laboratory, Department of Communication Sciences, Northwestern University, Evanston, IL 60208, USA
[b] Department of Neurobiology and Physiology, Northwestern University, Evanston, IL 60208, USA
[c] Department of Otolaryngology and Northwestern University, Evanston, IL 60208, USA
[d] Northwestern University Institute of Neuroscience, Northwestern University, Evanston, IL 60208, USA

HIGHLIGHTS

- Male and female young adults have measurably different neural responses to speech; to the fast acoustic components of speech, female responses are generally earlier and more robust than male responses.
- The differences observed between males and females in the nervous system's response to speech parallel those previously reported for poor, relative to good, readers.
- These sex differences provide a baseline for interpreting the higher incidence of language impairment in males, and the neural deficits associated with these disorders.

ABSTRACT

Objective: Sex differences have been demonstrated in the peripheral auditory system as well as in higher-level cognitive processing. Here, we aimed to determine if the subcortical response to a complex auditory stimulus is encoded differently between the sexes.
Methods: Using electrophysiological techniques, we assessed the auditory brainstem response to a synthesized stop-consonant speech syllable [da] in 76 native-English speaking, young adults (38 female). Timing and frequency components of the response were compared between males and females to determine which aspects of the response are affected by sex.
Results: A dissimilarity between males and females was seen in the neural response to the components of the speech stimulus that change rapidly over time; but not in the slower changing, lower frequency information in the stimulus. We demonstrate that, in agreement with the click-evoked brainstem response, females have earlier peaks relative to males in the subcomponents of the response representing the onset of the speech sound. In contrast, the response peaks comprising the frequency-following response, which encode the fundamental frequency (F_0) of the stimulus, as well as the spectral amplitude of the response to the F_0, is not affected by sex. Notably, the higher-frequency elements of the speech syllable are encoded differently between males and females, with females having greater representation of spectrotemporal information for frequencies above the F_0.
Conclusions: Our results provide a baseline for interpreting the higher incidence of language impairment (e.g. dyslexia, autism, specific language impairment) in males, and the subcortical deficits associated with these disorders.
Significance: These results parallel the subcortical encoding patterns that are documented for good and poor readers in that poor readers differ from good readers on encoding fast but not slow components of speech. This parallel may thus help to explain the higher incidence of reading impairment in males compared to females.

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1. Introduction

Between the sexes, significant differences exist in the click-evoked auditory brainstem response (ABR), a response predominately representative of high frequency information (Eggermont and Don, 1980). This difference is reflected in the timing of the response, with females having earlier latencies (the time interval between the stimulus onset and the response peak) compared to males (Jerger and Hall, 1980). No sex differences, however, are seen in the phase-locked response to pure tones, a response termed the frequency following response (FFR) that encodes low frequency information (Batra et al., 1986; Hoormann et al., 1992). Because

* Corresponding author at: Northwestern University, 2240 Campus Drive, Evanston, IL 60208-3540, USA. Tel.: +1 847 491 3181; fax: +1 847 491 2523.
E-mail address: nkraus@northwestern.edu (N. Kraus).
URL: http://www.brainvolts.northwestern.edu (N. Kraus).

the click- and tone-evoked auditory responses represent the subcortical processing of the elemental components of more complex stimuli, namely onset and phase-locked responses to the acoustic features of speech, (Aiken and Picton, 2008; Akhoun et al., 2008; Basu et al., 2010; Chandrasekaran and Kraus, 2010; Hornickel et al., 2009a; Skoe and Kraus, 2010) we predict that a speech syllable should produce responses that show a non-uniform difference of encoding between the sexes. To address this question, we recorded speech-ABRs to the stop consonant speech-syllable [da] presented to the right ear in a normal learning, young adult population.

Stop consonant syllables, such as [da], have been shown to be difficult for certain populations to perceive, such as individuals with hearing impairments (Gordon-Salant et al., 2007; Townsend and Schwartz, 1981; Van Tasell et al., 1982) and children with specific language impairment and dyslexia (Bradlow et al., 1999; Merzenich et al., 1996; Serniclaes and Sprenger-Charolles, 2003; Tallal, 1980). To determine the biological underpinnings of these deficits, the brainstem response to the stop consonant syllable [da] has been investigated in individuals with speech in noise difficulties (Anderson and Kraus, 2010; Anderson et al., 2010a,b; Chandrasekaran et al., 2009; Hornickel et al., 2009b), normal hearing young adults (Dhar et al., 2009; Hornickel et al., 2009a; Song et al., 2010; Vander Werff and Burns, 2011), auditory experts (Kraus and Chandrasekaran, 2010; Parbery-Clark et al., 2009a,b), typically-developing children, as well as children with reading impairments (Banai et al., 2009, 2005; Chandrasekaran et al., 2009; Cunningham et al., 2001; Hornickel et al., 2009b; Russo et al., 2004; Wible et al., 2004), and children with autism spectrum disorders (Russo et al., 2010, 2008). Although males tend to have a higher prevalence of both autism and language-based learning impairments than females (Katusic et al., 2001; Rutter et al., 2004), and children with autism and language impairments demonstrate impaired subcortical encoding of auditory stimuli (Banai et al., 2009, 2005; Basu et al., 2010; McAnally and Stein, 1996), this is the first study to examine sex differences that are evident in the subcortical response to speech.

Distinct processing for fast and slow (low vs. high frequency) components of acoustic signals has been amply demonstrated (see Zatorre and Gandour, 2008 for review). Acoustic information is asymmetrically routed (Hickok and Poeppel, 2007; Poeppel, 2003) with faster cues lateralized to the left hemisphere (Abrams et al., 2006; Belin et al., 1998; Zatorre and Belin, 2001) and slower information lateralized to the right hemisphere (Abrams et al., 2008, 2006; Boemio et al., 2005). Because fast, rapid fluctuations are important for conveying linguistic meaning, speech is maximally processed by the left hemisphere (Zatorre et al., 2002). A corresponding right ear advantage (REA) has been demonstrated behaviorally for speech, although this advantage is dependent upon the temporal characteristics of the speech stimulus (Schwartz and Tallal, 1980). Subcortically, lateralization of signal processing is evident, with rapid and transient stimuli being encoded more robustly when presented to the right ear and sustained, slower information being maximally encoded when presented to the left (Ballachanda et al., 1994; Sininger and Cone-Wesson, 2006). The speech-ABR to [da] demonstrates an REA for specific features characteristic of the fast elements of speech (Hornickel et al., 2009a). These differences are also reflected in asymmetry in peripheral processing of auditory stimuli. For example, across both sexes, otoacoustic emissions generated in response to continuous tones are more robust in the left ear, whereas transient stimuli evoke larger responses in the right ear (Sininger and Cone-Wesson, 2004).

Sex differences that exist in the auditory system may interact with peripheral and hemispheric asymmetry for processing slow and fast elements of sound. Regardless of sex, right ears are more

sensitive than left to auditory stimuli and females have, on average, greater hearing sensitivity than males (see McFadden, 1998 for review). Moreover, across both sexes, spontaneous otoacoustic emissions (SOAEs) are more prevalent in right ears than left ears but females have larger and more numerous SOAEs than males (Bilger et al., 1990; Lamprecht-Dinnesen et al., 2000). OAEs evoked by transient, rapidly presented stimuli such as clicks or tone bursts (TEOAEs) are also larger in females than males and are generally larger in right than left ears (Ismail and Thornton, 2003; McFadden et al., 2009). Across both sexes, infants demonstrate larger TEOAEs in the right ear while OAEs evoked by continuous tone pairs (DPOAEs) are larger in the left ear (Sininger and Cone-Wesson, 2004). Although adults demonstrate a weak sex difference in the amplitude of DPOAEs, with females having a larger amplitude response, they do not show an ear asymmetry (McFadden et al., 2009).

Given the well-documented sex differences in the auditory system and their interaction with lateralization of auditory processing, we hypothesized that the transient (i.e., fast) aspects of the speech-ABR, like the click-ABR, would be affected by the sex of the subject. Specifically, we predicted that females would have faster response timing for the onset peaks in the speech-evoked response. Furthermore, the lack of a sex effect for the FFR to the fundamental frequency (F_0) and second harmonic (Hoormann et al., 1992) of tone burst stimuli led us to hypothesize that males and females would not differ in the encoding of the lowest frequency (i.e., slow) components of the speech syllable or the corresponding temporal interpeak intervals. Because the click-ABR is reflective of primarily high-frequency encoding, we also hypothesized that responses collected from males and females would differ in the spectral magnitude of the higher frequency (i.e., above the F_0) information in the stimulus.

2. Methods

2.1. Participants

Seventy-six subjects, 38 female, aged 22–29 years (females: mean = 24.21 years, SD = 2.02 years, males: mean = 24.65 years, SD = 2.07 years) were recruited from Northwestern University and reported no history of language impairment. Subjects were included if their air-conduction thresholds were ⩽20 dB nHL at octave frequencies between 250 and 8000 Hz. Inclusion in the study also required that the subject's wave V latency elicited by a 100-μs click (presented in rarefaction to the right ear at a presentation rate of 31.25 Hz and a level of 45 dB nHL) was within the range of normative values (mean ± 1.5 standard deviations) previously established in the lab (5.41–5.96 ms). Fig. 1 shows the average audiometric thresholds and click-evoked responses of the male and female groups.

2.2. Stimuli and recording parameters

Brainstem responses were elicited using a 40 ms speech sound, [da], presented at a rate of 10.9 Hz to the subject's right ear. This five-formant synthesized speech sound (Klatt, 1980) comprises an initial noise burst and a formant transition between the consonant and the vowel. Although the stimulus does not contain a steady-state vowel, it is still perceived as the syllable [da]. The F_0 and the first three formants (F_1, F_2, F_3) change linearly over the duration of the stimulus: F_0 from 103 to 125, F_1 from 220 to 720, F_2 from 1700 to 1240, and F_3 from 2580 to 2500 Hz. F_4 and F_5 remain constant at 3600 and 4500 Hz, respectively. The speech stimulus was presented in alternating polarity monaurally to the right ear at 80 dB SPL through an insert earphone. Responses were collected with the Bio-logic Navigator Pro System (Natus Medical Incorpo-
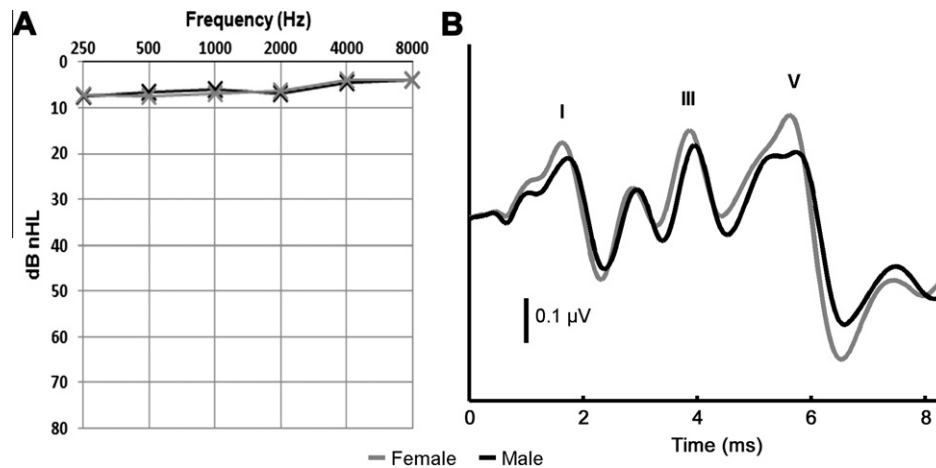
Fig. 1. Comparison of the mean audiometric thresholds and mean click-evoked auditory brainstem response between males (black) and females (gray). (A) There was no difference in the pure-tone auditory thresholds between males and females between 250 and 8000 Hz. (B) As expected, the female click-evoked response had a significantly earlier and larger amplitude peak V.

rated, San Carlos, California) using a recording procedure previously described in detail (Banai et al., 2009; Dhar et al., 2009; Hornickel et al., 2009a; Krizman et al., 2010; Song et al., 2010). During data collection, the subject was seated comfortably in a soundproof room and watched a movie of his or her choice. The left ear remained unoccluded and the movie soundtrack was set to <40 dB SPL so as to be heard at a level that would not mask the stimulus. Using Ag/AgCl electrodes, the evoked response was collected from the vertex (Cz) referenced to the ipsilateral (right) ear lobe and the forehead was used as ground. All procedures were approved by the Northwestern University Institutional Review Board. All participants gave their consent to participate and were compensated monetarily for their time.

2.3. Data analysis

For each subject, peak latencies were visually identified and corresponding amplitudes were determined for seven peaks in the brainstem response, including the onset (V and A), consonant-to-vowel transition (C), offset (O) and FFR (D, E and F) peaks. The onset peaks, V and A, have been shown to be analogous to the click-evoked response peaks V and V_n (Song et al., 2006). Therefore, criteria similar to the standard peak-picking criteria of these click-evoked peaks (Hall, 2007) were used to identify the speech-evoked onset peaks. Peak V was selected as the largest peak near 6.5 ms immediately before the negative slope, and A was specified as the first point at the bottom of this downward slope as identified by a plateau or slope reversal that lasted over three points near the expected latency range for peak A. Peaks C, D, E, F, and O were identified as the deepest troughs within the expected latency range for each peak, as determined by previously established young adult normative data (Dhar et al., 2009; Hornickel et al., 2009a). Typical latencies are: $C \sim 18.5$ ms, $D \sim 22$ ms, $E \sim 10$ ms following D, peak $F \sim 10$ ms after peak E, and O is centered around 48 ms. If two points were equivalent in amplitude within the trough, the one with the earlier latency was always chosen. If the peak was a plateau, such that multiple points ($\geqslant 3$) were of the same maximum amplitude, the center point was always chosen. Any ambiguities in peak selection in the averaged waveform (6000 trials) were resolved by comparison of the two sub-average waveforms (3000 trials each). Two experienced peak pickers, one blind to subject sex, separately identified the peak latencies in each subject's response. If the two experts could not agree on a latency, the peak was marked as "not reliable" and excluded from analyses. Additionally,

Table 1
The mean (standard deviation) latencies and amplitudes of the males and females are given for peak V of the click-evoked response and the seven peaks of the speech-ABR. Females had significantly earlier latencies at click-evoked peak V, and peaks V and A of the speech-evoked response. The slope of the onset response, and the spectral magnitude of the higher frequencies were larger in females than males. Significance ($p < 0.0033$) is indicated with asterisks. Signal-to-noise ratio (SNR) was calculated as the mean amplitude of the response divided by the mean amplitude of the pre-stimulus activity. SNR values are provided in the table and did not differ between males and females. Due to the multiple factors influencing the amplitude of individual peaks in the temporal waveform, analyses were not performed on peak amplitude differences between males and females; however, mean values are provided in the table.

	Male		Female	
Latency (ms)				
Click				
***V	5.84	(0.15)	5.72	(0.14)
Speech-ABR				
***V	6.78	(0.24)	6.60	(0.24)
***A	7.79	(0.26)	7.54	(0.34)
C	18.60	(0.69)	18.63	(0.67)
D	22.80	(0.56)	22.75	(0.81)
E	31.18	(0.46)	31.04	(0.62)
F	39.81	(0.63)	39.50	(0.45)
O	48.50	(0.51)	48.25	(0.36)
Amplitude (µV)				
Click				
V	0.19	(0.10)	0.25	(0.13)
Speech-ABR				
V	0.11	(0.05)	0.13	(0.07)
A	−0.19	(0.06)	−0.22	(0.07)
C	−0.04	(0.05)	−0.06	(0.05)
D	−0.13	(0.10)	−0.15	(0.08)
E	−0.21	(0.06)	−0.25	(0.10)
F	−0.13	(0.10)	−0.19	(0.11)
O	−0.13	(0.07)	−0.17	(0.07)
SNR	2.76	(1.08)	2.89	(0.92)
Speech-ABR onset measures				
Duration (ms)	1.01	(0.22)	0.97	(0.28)
Amplitude (µV)	0.30	(0.09)	0.35	(0.11)
**Slope (ms/µV)	−0.30	(0.10)	−0.39	(0.16)
Spectral Magnitude (µV)				
F_0	0.0615	(0.031)	0.0651	(0.023)
F_1	0.0078	(0.004)	0.0103	(0.005)
***HF	0.0033	(0.001)	0.0043	(0.001)

any peak smaller than the average amplitude of the pre-stimulus baseline activity (from −15.4 ms to 0 ms) was deemed "not
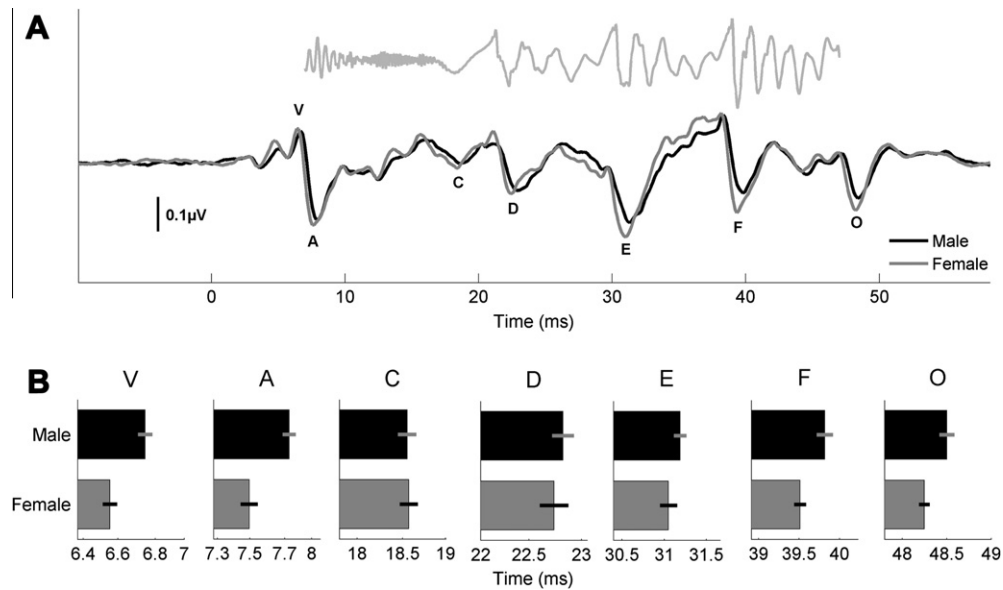
Fig. 2. Differences in the grand average auditory brainstem responses to the 40 ms speech stimulus [da] between males and females. (A) The grand average response of the males (black) and the females (gray) are plotted for comparison. The stimulus waveform is plotted above the male and female responses with a delay of 7 ms in order to emphasize the stimulus characteristics evoking the corresponding response peaks. (B) Mean latencies at each of the characteristic peaks of the speech-ABR are shown with error bars representing ±1 standard error of the mean. From these plots it is clear that not all peaks of the speech-evoked response are affected by sex. The latencies of the onset peaks, V and A, are sex dependent. At these peaks, females consistently demonstrate earlier latencies than males. In contrast, the transition peak, C the peaks of the frequency following response, peaks D, E, and F, and the offset peak O are sex invariant, with males and females having similar peak latencies at these peaks.

reliable" and excluded from analyses. Across all peaks in the waveform, peak reliability was 96%. Three composite measures of neural synchrony to the onset of the stimulus were also analyzed: V to A interpeak latency, V to A peak-to-trough amplitude, and the slope of the VA complex as calculated by the change in peak amplitude over time. Frequency encoding was analyzed using a fast Fourier analysis of the FFR (11.4–40.6 ms), a region of the response that includes peaks C, D, E and F. Three ranges, corresponding to the major frequencies of the stimulus, were analyzed: the fundamental frequency (F_0) 103–125 Hz, the first formant frequency range (F_1) 180–755 Hz, and higher frequencies (HF) 756–1130 Hz, which are between the first formant and the second formants, but still within the phase-locking capabilities of the brainstem (Liu et al., 2006). Mean values for male and female participants in the current study are presented in Table 1.

Independent sample, two-tail t-tests were used to determine significant differences in the speech-evoked response between males and females for each of the dependent variables. Results are reported with a correction for multiple comparisons ($\alpha = 0.0033$). Data processing was performed using custom routines coded in Matlab 2006b (The MathWorks, Inc., Natick, MA) and statistical analyses were performed in SPSS (SPSS Inc., Chicago, IL).

3. Results

3.1. Peak timing

Consistent with sex differences reported for the click-evoked ABR, the timing of the onset peaks of the speech-evoked response were sex dependent with females having significantly earlier peak latencies at peaks V ($t(75) = 3.496$, $p = 0.001$) and A ($t(76) = 3.326$, $p = 0.001$) compared to males (Fig. 2). Timing of the other peaks in the speech-evoked response, when correcting for multiple comparisons, was not dependent on the sex of the subject, including the transition peak C ($t(62) = -0.120$, $p = 0.905$), the FFR peaks, D ($t(73) = 0.501$, $p = 0.618$), E ($t(74) = 1.099$, $p = 0.275$) and F ($t(76) = 2.464$, $p = 0.016$), and the offset peak, O ($t(73) = 2.5$,

$p = 0.015$). The interpeak interval of the FFR peaks corresponding to the period of the fundamental frequency, D to E ($t(69) = 0.964$, $p = 0.338$) and E to F ($t(72) = 0.679$, $p = 0.499$) also did not differ significantly between males and females. This coincides with the absence of sex differences for the F_0 amplitude in the frequency domain (see Section 3.3).

3.2. Composite onset measures

The response to the onset of [da] was further analyzed using composite measures. The slope from peak V to peak A differed between males and females ($t(75) = 2.794$, $p = 0.007$), with females having steeper slopes. Neither of the measures contributing to the VA slope were significant (VA peak to trough amplitude, $t(75) = -2.351$, $p = 0.021$; interpeak interval $t(75) = 0.685$, $p = 0.495$).

3.3. Spectral magnitude

To evaluate the spectral encoding in the evoked response to the formant transition, a fast Fourier transform was performed over the 11–40 ms range of the response. Over this region, the encoding of the F_0 ($t(76) = -0.633$, $p = 0.529$), and the first formant range ($t(76) = -2.314$, $p = 0.023$) were not different between the sexes while the higher frequency response components up to 1130 Hz ($t(76) = -3.477$, $p = 0.001$) were larger in females (Fig. 3). Taken together with the differences in the timing of the onset peaks, these results support the differential encoding of the fast (i.e., onset and high frequency) elements of speech between females and males.

4. Discussion

The purpose of this study was to identify the aspects of the speech-evoked brainstem response of adult subjects that show sex differences. We hypothesized that differences would exist, with females having faster and larger responses than males, and that these differences would be restricted to the encoding of the

rapid features of the speech syllable such as the onset of the noise burst and the formant-related frequencies. Indeed, females had significantly earlier encoding of the stimulus onset and greater subcortical representation of the higher frequencies in the stimulus. As predicted, no difference was demonstrated in the encoding of the F_0 (neither spectral magnitude nor the timing between F_0-related peaks).

Behaviorally, morphologically, and physiologically, sex differences have been demonstrated to exist throughout the auditory system (Jerger and Hall, 1980; McFadden, 1993b, 1998; McFadden et al., 2009; Michalewski et al., 1980). What is of interest here, however, is that the sex differences in the evoked brainstem response to a complex speech stimulus are not pervasive in that they are not uniformly present in every aspect of the response. Aspects of the response that encode the faster elements of speech differed between males and females while slower elements, specifically the F_0, did not. As is discussed below, our findings are in agreement with selective sex differences observed for click-evoked and tone-evoked responses (Hoormann et al., 1992) as well as behavioral and cognitive processing differences in humans (Burman et al., 2008; Cahill, 2006; Camarata and Woodcock, 2006) and animals (Clark et al., 2000a,b; Fitch et al., 1993b; Herman et al., 1997). Moreover, our results parallel differences in the encoding of the fast elements of speech that is seen in the subcortical encoding of speech in good and poor readers (Banai et al., 2009).

### 4.1. Peripheral and anatomical sex differences

In the click-evoked ABR, females have, on average, earlier peak latencies than males (Jerger and Hall, 1980). An initial explanation for this latency difference was the difference in head size between males and females, with males having a larger diameter, on average, than females (Aoyagi et al., 1990; Church et al., 1984). However, others have found the functional–anatomical correlation to be too weak to be considered a valid explanation (Durrant et al., 1990; Sabo et al., 1992), especially given that latency differences persist when comparing males and females of equal head size (Trune et al., 1988). Our results support the notion that head size

is not an exclusive contributor to sex differences given that the speech-ABR sex differences are selective to specific aspects of the response.

Although gross morphological differences such as head size may not account for the subcortical dissimilitude between males and females, sexual dimorphism within the inner ear maybe a contributing factor. Indeed, males and females differ in cochlear size, with males having longer cochlear ducts than females, resulting in longer cochlear travel times in males (Bowman et al., 2000; Don et al., 1993; Sato et al., 1991). The travel time difference, likely affected by the greater stiffness of the female basilar membrane resulting from its shorter length, may contribute to females having earlier latencies relative to males in the speech-ABR. Moreover, these peripheral differences may be influenced by differential activation of the oliviocochlear system, suggesting sex differences in efferent modulation (Bilger et al., 1990; Ismail and Thornton, 2003; McFadden, 1993b; McFadden et al., 2009).

4.2. Cortical sex differences in the auditory system

In addition to the differences in the male and female peripheral hearing mechanism, behavioral and imaging studies have indicated that male and female cortices process acoustic stimuli differently. For example, fMRI studies have identified stronger activation of cortical language processing areas in females, as compared to males, throughout development (Burman et al., 2008), which may account for advantages in verbal and written language development seen in females (Bauer et al., 2002; Bornstein et al., 2000; Martin and Hoover, 1987). The planum temporal, which is important in auditory processing (Binder et al., 1996), is symmetric in females but larger in the left hemisphere of males, (Kulynych et al., 1994) and this asymmetry has been shown to be reversed or nonexistent in dyslexic males (Hynd et al., 1990). Moreover, a study looking at sex differences in cortical language processing found that males and females differ in the functional organization of the brain for phonological processing such that females showed bilateral activation during phonological processing tasks while
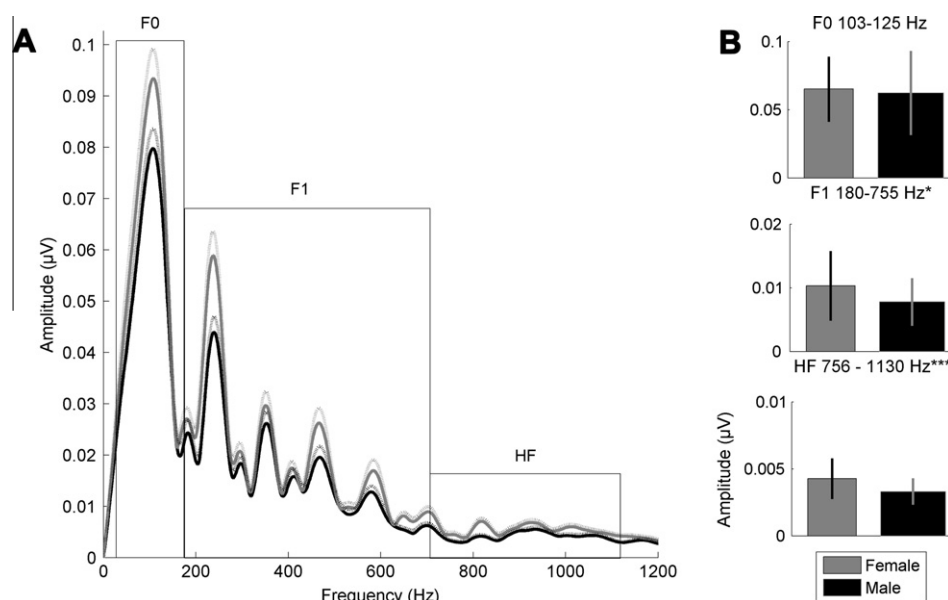
Fig. 3. A fast Fourier analysis of the frequency following response revealed no differences in the response to the fundamental frequency (F_0) and first formant (F_1) of the speech stimulus. However, compared to males (black), females (gray) had more robust spectral encoding of higher frequency (HF) information (A) Boxes outline the three frequency ranges (F_0, F_1, HF) and dashed lines represent one standard error of the mean spectral magnitude. (B) Bar graphs represent the mean spectral amplitude (±1 standard error) of the same three frequency regions for females and males.

male activation was strongest in the left hemisphere (Shaywitz et al., 1995).

Differences in hemispheric laterality during language processing tasks have been observed behaviorally as well. In a dichotic listening test, in which two different words were presented simultaneously, one to each ear, males demonstrated a significant right ear advantage (REA) for performance on the task while females performed similarly on words presented to either ear (Kimura and Harshman, 1984; Lake and Bryden, 1976). However, because slowing down or speeding up the formant transitions within a speech syllable alters the magnitude of the REA for speech (Schwartz and Tallal, 1980), this may explain why other studies have reported an REA regardless of sex (i.e., both sexes showed an REA) (Bryden, 1988). Similarly in rodents, sex differences to tone sequences have been demonstrated, with male rodents having a stronger REA than female rodents (Fitch et al., 1993a).

Additional rodent work investigating the effects of bilateral cortical lesions shortly following birth demonstrates a difficulty for early-cortical lesioned male, but not female, rodents to discriminate rapidly presented tones (<350 ms), while both sexes could reliably discriminate tones presented at longer interstimulus intervals (ISIs) (Herman et al., 1997). The cortical lesions resulted in significantly smaller cells in the medial geniculate nucleus (MGN) in early-lesioned male, but not female rodents (Herman et al., 1997).

4.3. Role of estrogen in sex differences in the auditory system

Larger and more frequent spontaneous otoacoustic emissions (Bilger et al., 1990; McFadden, 1993b) and stronger click-evoked OAEs exist in healthy, normal hearing young adult females than males (McFadden et al., 2009). Females also demonstrate more acute sound sensitivity than males (Rogers et al., 2003; Sagi et al., 2007). These differences are reduced during menopause (Hultcrantz et al., 2006; Murphy and Gates, 1997; Wharton and Church, 1990), in females taking oral contraception (McFadden, 2000), and in females who have a male twin (McFadden, 1993a; McFadden et al., 1996), which suggests a role of hormones, including estrogen, in improving auditory function in females (McFadden et al., 2009). In support of this hormonal explanation, females with Turner syndrome, a chromosomal abnormality resulting in estrogen deficiency, demonstrate longer click-ABR latencies and earlier age-related hearing loss, similar to males (Beckman et al., 2004; Güngör et al., 2000; Hultcrantz et al., 1994). It has also been suggested that auditory thresholds vary with the menstrual cycle in females. For example, in some females with Meniere's disease, auditory symptoms are exacerbated during the premenstrual phase, when estrogen levels are lowest (Andrews et al., 1992; Andrews and Honrubia, 2010).

Rodent studies have shown that when the estrogen receptor (ER-beta) is knocked out, severe and early onset presbycusis is evident (Wang et al., 2001) and that ovariectomizing female rodents results in delayed electrophysiological responses from cochlear and brainstem structures (Coleman et al., 1994). Furthermore, prenatal stress more adversely affects male rodents, resulting in cortical symmetry, similar to female rodents (Fleming et al., 1986; Power and Moore, 1986). Taken together with evidence that lesioning the MGN results in cell size reduction in male, but not female rodents, these sex-specific effects support a role of neuroendocrine systems in the development of the functional specialization of the brain (Berrebi et al., 1988; Herman et al., 1997). For these reasons, if estrogen does influence the efficacy of the auditory system, it may do so by enhancing synaptic transmission and improving neural conduction (Tremere et al., 2009; Tremere and Pinaud, 2011). These enhancements of the auditory system, in conjunction with the differences in size of the auditory periphery may contribute to the earlier and larger responses seen in the speech-ABRs of females compared to males. Additionally, the corticofugal system, which acts in tandem with peripheral (Don et al., 1993; Eggermont and Don, 1980) and likely also experience-dependent factors (Kraus and Chandrasekaran, 2010; Krishnan et al., 2005; Parbery-Clark et al., 2009a; Strait et al., 2009), is known to modify brainstem processing (Bajo et al., 2009; Gao and Suga, 1998, 2000, 2008; Ma and Suga, 2001a, b; Suga and Ma, 2003; Tzounopoulos and Kraus, 2009). Thus, the speech-ABR sex differences likely reflect an interaction between peripheral and cortical factors that are mediated by a reciprocal network of afferent and efferent synapses that are all likely influenced by estrogen activity.

4.4. Parallels with reading impaired population

Between the sexes, disparities in encoding of auditory information are apparent in the response to transient cues and rapidly presented stimuli. These differences may relate to differences in temporal encoding between normal and impaired readers. It has been demonstrated that an ISI of ~330 ms or a formant transition of ~80 ms is the behavioral discrimination threshold for individuals with language or reading disabilities (Tallal and Newcombe, 1978; Tallal and Piercy, 1973, 1974, 1975). Stop consonant speech syllables, such as [da], and rapidly changing formant transitions, which contain timing cues on the order of milliseconds, demonstrate a strong REA and are exceedingly difficult for language-impaired children to discriminate (Bradlow et al., 1999; Kraus et al., 1996; Tallal, 1976; Tallal and Piercy, 1974, 1975). The stimulus presentation rate and the length of the dynamic formant transition used here (50 ms ISI and 40 ms formant transition) fall well within the range of rates that are difficult for language-impaired children to differentiate behaviorally. Even in presumably normal males and females, differences in encoding of slow vs. fast elements of a stimulus are seen in the auditory brainstem response (Hornickel et al., 2009a; Krizman et al., 2010). Interestingly, these rate-sensitive (i.e., fast) components of the speech-ABR correspond both to the components of the response that demonstrate sex differences *and* those that are deficient in impaired readers (Banai et al., 2009). Males are significantly more likely to have a language or reading impairment, such as dyslexia (Nass, 1993) and this disability may result from a general difficulty in processing rapidly presented, dynamic stimuli (Farmer and Klein, 1995; Tallal, 1975, 1976, 1979; Temple et al., 2000). Consistent with "extreme male brain" (EMB) theory, our results suggest that dyslexia may represent an extreme form of what is observed in the typical male brain (Baron-Cohen et al., 2005).

5. Conclusions

This study demonstrated sex differences in the encoding of the fast, but not the slow elements of speech, with females having significantly faster and larger magnitude responses to only the transient aspects of the stimulus compared to males. Although we tested a normal population and cannot speak directly to language impairments, it is interesting that within this population, sex differences in the encoding of a speech stimulus are still apparent. Both the faster timing of the transient peaks and the larger spectral magnitude of the higher frequency components likely reflect more synchronous neural activity in females in response to the rapidly changing features of the acoustic stimulus. No sex differences, however, were seen in response to the slower, sustained components, indicating similar neural phase-locking between males and females to these components. The prevalence of language and reading impairments, including dyslexia, in males combined with the demonstrated disparity between males and females in the subcortical encoding of a rapidly transitioning stop-consonant speech

syllable ([da]), provide insight into the biological and genetic processes that influence language processing. This study serves as a foundation for studying sex differences in an impaired population. Future research should explore the potential of the speech-ABR to be used as a neural marker for assessing individuals with auditory-based disorders.

Acknowledgments

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